

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-180**

**MEDICAL REVIEW(S)**

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA 22-180/N000-0022

Sponsor: AMAG Pharmaceuticals

Drug name: Ferumoxytol

Indication: Treatment of iron deficiency anemia in patients with chronic kidney disease

Route of administration: Intravenous Injection

Submission: Resubmission

Date submitted: October 30, 2008

Review completed: December 17, 2008

Reviewer: Min Lu, M.D., M.P.H.

**Background and Rationale**

The sponsor submitted the original NDA submission for Ferumoxytol for the treatment of iron deficiency anemia in patients with chronic kidney disease on December 18, 2007. A Complete Response letter was issued by the Division on October 17, 2008 requiring the sponsor to provide chemistry, manufacturing and clinical data to address a raised concern of similarity between Ferumoxytol and iron dextran products. The Division also required the sponsor to provide analyses of timing of ferumoxytol administration in relation to the performance of hemodialysis and its impact on safety of ferumoxytol. The Division also requested the sponsor to address the issues raised in clinical site and facility inspections.

In this resubmission, the sponsor provided responses to the Division's requests. The following are the summary of the sponsor's responses followed by this reviewer's comments.

**Difference between Ferumoxytol and iron dextran products**

The sponsor provided the comparison between the Ferumoxytol and iron dextran products in chemistry, manufacturing process, product specification and biological characterization. These data will be evaluated by CMC reviewers. No clinical data were submitted to compare Ferumoxytol and iron dextran product directly from clinical trials. The sponsor provided literature review on hypersensitivity reactions for iron dextran products. Based on literature reports, the rate of anaphylactic/anaphylactoid reactions

ranged from 0.6% to 3.5 % for iron dextran products. The sponsor claimed the rate of an anaphylactoid reaction of Ferumoxytol is much lower (  $\frac{3}{1726}$ , in clinical trial) than those of iron dextran products reported from literature, which could support a difference between Ferumoxytol and iron dextran products.

b(4)

**Reviewer's comments:**

*It will be difficult to make any valid comparison regarding to hypersensitivity reactions between Ferumoxytol and iron dextran product without direct comparison data from clinical trials.*

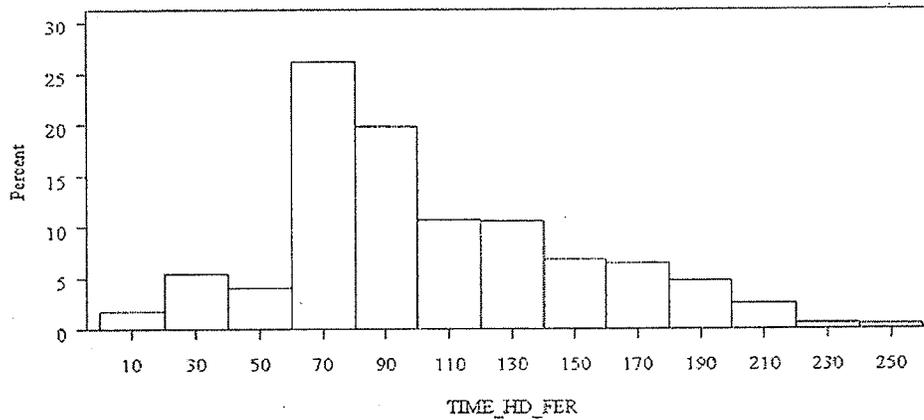
*Furthermore, in Ferumoxytol clinical trials, in addition to one anaphylaxis/anaphylactoid reaction, 2 additional hypotension SAEs with other symptoms that occurred within 5 minutes of the Ferumoxytol injection were reported. These two events should also be considered as possible hypersensitivity reactions. Therefore, the incidence of serious hypersensitivity reaction should be 0.2% (3/1726) for Ferumoxytol based on clinical trials. Overall, a total of 3.7% of adverse events potentially associated with hypersensitivity were reported in clinical trials for Ferumoxytol.*

*Due to the limited clinical information available, the difference between Ferumoxytol and iron dextran products should be based on the available data in chemistry and manufacturing process.*

**Timing of Ferumoxytol administration in relation to performance of hemodialysis (HD)**

In phase 3 clinical trials, ferumoxytol was targeted to be administered as an IV injection when the subject was stable after the initiation of dialysis. Once stable blood pressure was obtained one hour after the initiation of HD, ferumoxytol was to be administered 15 minutes later. The following Figure shows the timing of administration of ferumoxytol relative to the initiation of HD. Ferumoxytol was administered a mean ( $\pm$ SD) of 102.5 ( $\pm$ 46.8) minutes following the initiation of the HD with a median time of 90 minutes; the 25<sup>th</sup> and 75<sup>th</sup> percentile were 75 and 130 minutes, respectively.

**Figure 11: Administration Timing of Ferumoxytol Relative to the Initiation of Hemodialysis**

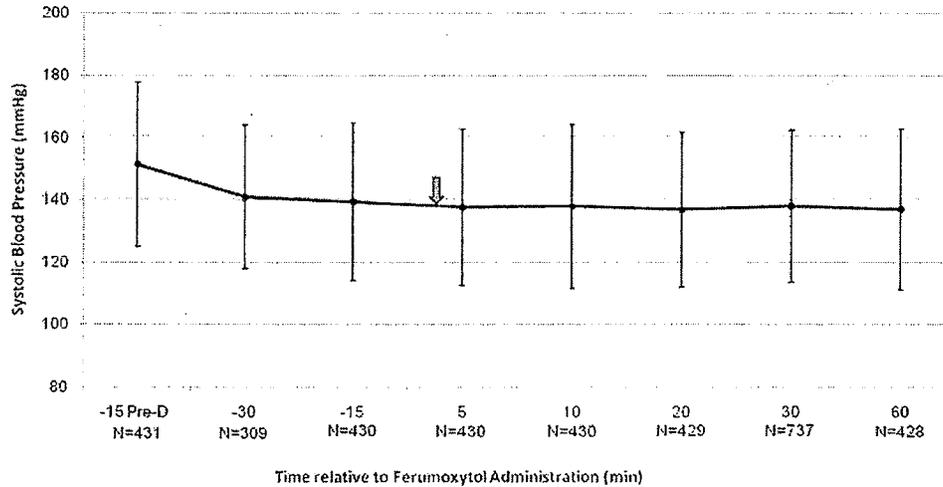


The following Figures show the mean systolic blood pressure following Ferumoxytol administration in hemodialysis and non-hemodialysis patients in clinical trials. The sponsor indicated that the expected decrease in mean systolic blood pressure from baseline during the first hour of HD was observed and following ferumoxytol administration, the mean systolic blood pressure was stable. A similar plot of mean systolic blood pressure following the administration of ferumoxytol was seen in subjects with Non-HD CKD.

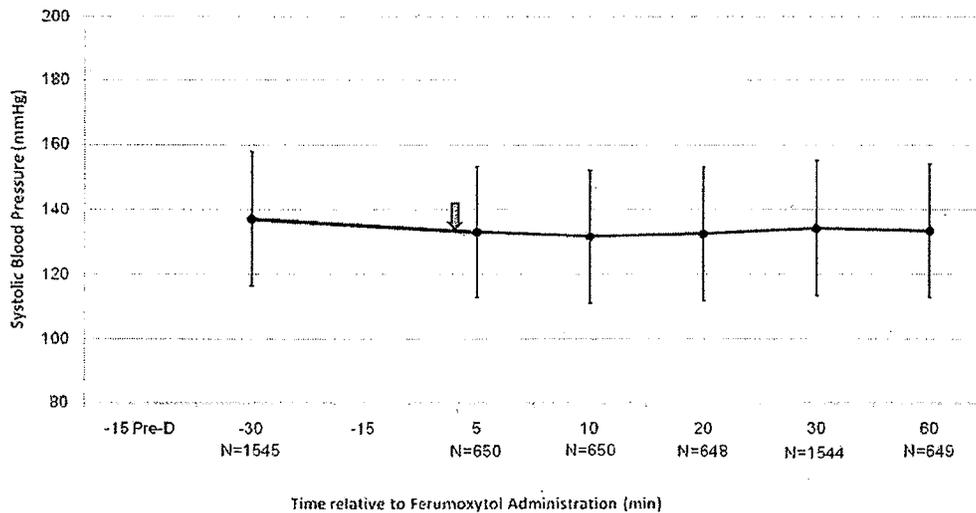
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**Figure 12. Mean Systolic Blood Pressure Measurements at Different Time Intervals Following Administration of Ferumoxytol (510 mg) to CKD Subjects on Hemodialysis (HD) (A); and Non-Hemodialysis Dependent Subjects (Non-HD) (B) in Phase III Studies**

**Figure 12A: Systolic Blood Pressure after Ferumoxytol Administration for HD**

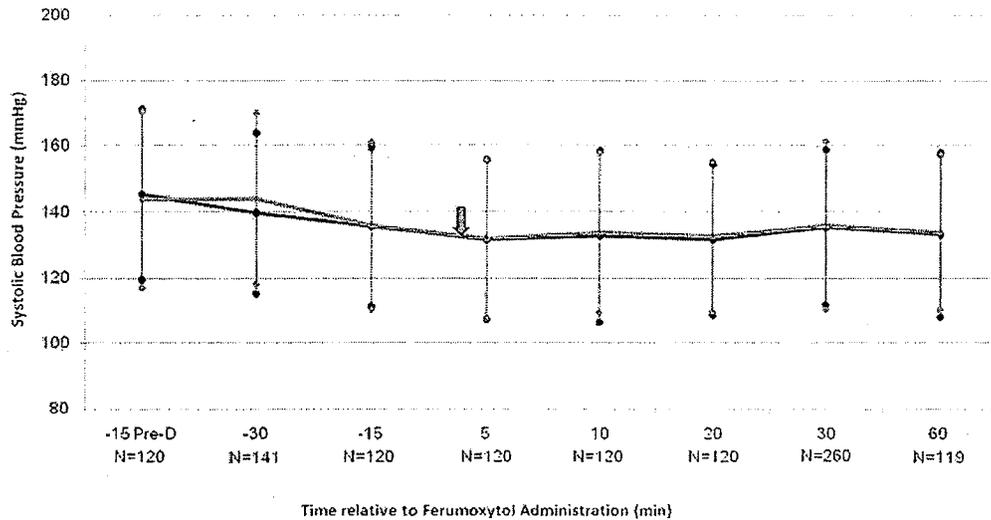


**Figure 12B: Systolic Blood Pressure after Ferumoxytol Administration for Non-HD**



The following Figure shows the mean systolic blood pressure following Ferumoxytol or Placebo administration in hemodialysis patients in cross-over Phase 3 safety study. The sponsor indicated that blood pressures following administration of ferumoxytol or placebo are stable and essentially superimposable.

**Figure 13. Mean Systolic Blood Pressure Measurements at Different Time Intervals Following Administration of Ferumoxytol (510 mg) (black) or Placebo (red) to CKD Subjects on Hemodialysis in Phase III Studies Subjects**



The following table shows the reported adverse event by relative timing to Ferumoxytol administration in hemodialysis patients. The impact of the timing of ferumoxytol 510 mg administration relative to hemodialysis initiation on adverse events was assessed in two groups, i.e., those receiving ferumoxytol administration up to 90 minutes post the start of dialysis, and those receiving it after 90 minutes. The sponsor reported that the overall rate of adverse events was similar in subjects who received ferumoxytol injections  $\leq 90$  minutes (41.4%) or  $>90$  minutes (38.2%) after dialysis initiation. The overall rate of serious adverse events was also similar in these subject cohorts, 5.5% for those in the  $\leq 90$  minute group compared with 5.6% for those in the  $>90$  minute group. There was no consistent pattern of either adverse events or serious adverse events being reported with a greater or lesser frequency following ferumoxytol injections given  $\leq 90$  minutes or  $>90$  minutes after dialysis initiation.

**Table 6: Adverse Events by System Organ Class among Subjects with CKD Stage 5D on Hemodialysis by Timing of Ferumoxytol Administration Relative to Dialysis Initiation**

System Organ Class	≤90 minutes N = 379*	>90 minutes N= 359*
	Events n (%)	Events n (%)
All Adverse Events	157 (41.4)	137 (38.2)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)
Cardiac disorders	7 (1.8)	10 (2.8)
Ear and labyrinth disorders	0 (0.0)	1 (0.3)
Eye disorders	3 (0.8)	0 (0.0)
Gastrointestinal disorders	29 (7.7)	23 (6.4)
General disorders and administration site conditions	18 (4.7)	13 (3.6)
Hepatobiliary disorders	1 (0.3)	0 (0.0)
Infections and infestations	20 (5.3)	16 (4.5)
Injury, poisoning and procedural complications	17 (4.5)	15 (4.2)
Investigations	5 (1.3)	2 (0.6)
Metabolism and nutrition disorders	2 (0.5)	3 (0.8)
Musculoskeletal and connective tissue disorders	12 (3.2)	6 (1.7)
Nervous system disorders	9 (2.4)	13 (3.6)
Psychiatric disorders	3 (0.8)	3 (0.8)
Renal and urinary disorders	1 (0.3)	2 (0.6)
Respiratory, thoracic and mediastinal disorders	13 (3.4)	15 (4.2)
Skin and subcutaneous tissue disorders	6 (1.6)	6 (1.7)
Surgical and medical procedures	3 (0.8)	0 (0.0)
Vascular disorders	8 (2.1)	8 (2.2)

\*N= number of administrations

**Table 7: Serious Adverse Events by System Organ Class among Subjects with CKD Stage 5D on Hemodialysis, by Timing of Ferumoxytol Administration Relative to Dialysis Initiation**

System Organ Class	≤90 minutes N = 379*	>90 minutes N= 359*
	Events n (%)	Events n (%)
ALL SAES	21 (5.5)	20 (5.6)
Cardiac disorders	5 (1.3)	6 (1.7)
Gastrointestinal disorders	1 (0.3)	2 (0.6)
General disorders and administration site conditions	1 (0.3)	1 (0.3)
Hepatobiliary disorders	1 (0.3)	0 (0.0)
Infections and infestations	4 (1.1)	4 (1.1)
Injury, poisoning and procedural complications	2 (0.5)	1 (0.3)
Investigations	1 (0.3)	0 (0.0)
Nervous system disorders	1 (0.3)	2 (0.6)
Psychiatric disorders	1 (0.3)	0 (0.0)
Renal and urinary disorders	1 (0.3)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	1 (0.3)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.3)
Vascular disorders	2 (0.5)	1 (0.3)

\*N= number of administrations

The sponsor reported that hypotension events were 1.3% and 1.7% for ≤90 minutes and >90 minutes after dialysis initiation, respectively. On the day of dosing, hypotension was reported at 0.8% and 1.1% for ≤90 minutes and >90 minutes after dialysis initiation, respectively. Examination of blood pressure data during the 60 minute post dosing observation period revealed no difference in the incidence of hypotension per protocol definition (systolic blood pressure decrease by ≥20 and to <90 mmHg) by timing of ferumoxytol injection, 1.2% for both injections given ≤90 minutes and >90 minutes after dialysis initiation. There was similarly no pattern related to timing of administration of ferumoxytol relative to dialysis initiation for other adverse events reported on the day of dosing.

**Reviewer's comments:**

*The sponsor did not propose any instruction on the timing of ferumoxytol administration in relation to the performance of hemodialysis in the labeling based on the submitted data. However, in clinical trials, ferumoxytol was to be administered one hour after the initiation of HD once stable blood pressure was obtained. According to the submitted data, only about 10% of hemodialysis patients received ferumoxytol within one hour of initiation of hemodialysis and 90% of patients received ferumoxytol after 1 hour on*

*hemodialysis. The majority of patients received the ferumoxytol during the second hour of hemodialysis. The submitted data also show a decrease in blood pressure in the first hour of hemodialysis. Although it appears that no significant difference in the frequency of adverse events was observed between ferumoxytol injection  $\leq 90$  minutes and  $> 90$  minutes after dialysis initiation the majority of patients in the  $\leq 90$  minutes group may have received the injection after 60 minutes following initiation of hemodialysis. Therefore, the similar instruction on the timing of ferumoxytol injection as in the study protocol should be provided to hemodialysis patients in the labeling to minimize the hypotension risk.*

#### **Adverse Events impacted by Rate of Ferumoxytol Administration**

In clinical trials ferumoxytol was planned to be administered at a rate of 1 mL/second, or 17 seconds for the 510 mg dose. The following table shows the adverse events following administration of first dose (510 mg) of ferumoxytol by rates of Ferumoxytol administration. The sponsor indicated that there was no pattern suggestive of an increased frequency of adverse events or serious adverse events by duration of injection among subjects with CKD on HD or Non-HD CKD.

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**Table 8: Adverse Events by System Organ Class in Subjects with CKD Stage 5D on Hemodialysis (HD) and CKD Stages 1-5 and 5D on Peritoneal Dialysis (Non-HD) by Injection Duration**

System Organ Class	CKD Stage 5D on HD N = 739*			CKD Stages 1-5 and 5D on PD N = 1542*		
	≤17 secs n=168* n (%)	>17-30 secs n=324* n (%)	>30 secs n=247* n (%)	≤17 secs n=293* n (%)	>17-30 secs n=691* n (%)	>30 secs n=558* n (%)
All Adverse Events	48 (28.6)	153 (47.2)	93 (37.7)	91 (31.1)	290 (42.0)	291 (52.2)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.0)	1 (0.1)	1 (0.2)
Cardiac disorders	4 (2.4)	8 (2.5)	5 (2.0)	3 (1.0)	14 (2.0)	3 (0.5)
Ear and labyrinth disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)
Eye disorders	1 (0.6)	1 (0.3)	1 (0.4)	2 (0.7)	5 (0.7)	4 (0.7)
Gastrointestinal disorders	12 (7.1)	27 (8.3)	13 (5.3)	17 (5.8)	43 (6.2)	53 (9.5)
General disorders/administrative site conditions	6 (3.6)	15 (4.6)	10 (4.0)	8 (2.7)	45 (6.5)	43 (7.7)
Hepatobiliary disorders	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)	3 (0.5)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)
Infections and infestations	5 (3.0)	14 (4.3)	17 (6.9)	3 (1.0)	23 (3.3)	26 (4.7)
Injury, poisoning and procedural complications	5 (3.0)	16 (4.9)	11 (4.5)	6 (2.0)	7 (1.0)	5 (0.9)
Investigations	1 (0.6)	6 (1.9)	0 (0.0)	1 (0.3)	7 (1.0)	11 (2.0)
Metabolism and nutrition disorders	1 (0.6)	3 (0.9)	1 (0.4)	6 (2.0)	15 (2.2)	16 (2.9)
Musculoskeletal and connective tissue disorder	2 (1.2)	10 (3.1)	6 (2.4)	8 (2.7)	15 (2.2)	24 (4.3)
Neoplasms benign, malignant and unspecified	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.2)

System Organ Class	CKD Stage 5D on HD N = 739*			CKD Stages 1-5 and 5D on PD N = 1542*		
	≤17 secs n=168* n (%)	>17-30 secs n=324* n (%)	>30 secs n=247* n (%)	≤17 secs n=293* n (%)	>17-30 secs n=691* n (%)	>30 secs n=558* n (%)
Nervous system disorders	3 (1.8)	11 (3.4)	8 (3.2)	8 (2.7)	39 (5.6)	24 (4.3)
Psychiatric disorders	0 (0.0)	6 (1.9)	0 (0.0)	0 (0.0)	4 (0.6)	2 (0.4)
Renal and urinary disorders	0 (0.0)	1 (0.3)	2 (0.8)	1 (0.3)	5 (0.7)	3 (0.5)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	5 (3.0)	16 (4.9)	7 (2.8)	6 (2.0)	25 (3.6)	25 (4.5)
Skin and subcutaneous tissue disorders	0 (0.0)	8 (2.5)	4 (1.6)	13 (4.4)	14 (2.0)	20 (3.6)
Surgical and medical procedures	0 (0.0)	0 (0.0)	3 (1.2)	2 (0.7)	1 (0.1)	3 (0.5)
Vascular disorders	3 (1.8)	9 (2.8)	4 (1.6)	3 (1.0)	23 (3.3)	16 (2.9)

\*N= Number of administrations

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**Table 9: Serious Adverse Events by System Organ Class Among Subjects with CKD Stage 5D on Hemodialysis and CKD Stages 1-5 and 5D on Peritoneal Dialysis, by Injection Duration**

System Organ Class	CKD Stage 5D on HD N = 739*			CKD Stages 1-5 and 5D on PD N = 1542*		
	≤17 sec n=168* n (%)	>17-30 sec n=324* n (%)	>30 sec n=247* n (%)	≤17 sec n=293* n (%)	>17-30 sec n=691* n (%)	>30 sec n=558* n (%)
All SAEs	7 (4.2)	23 (7.1)	11 (4.5)	10 (3.4)	34 (4.9)	28 (5.0)
Cardiac disorders	3 (1.8)	4 (1.2)	4 (1.6)	3 (1.0)	11 (1.6)	3 (0.5)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Gastrointestinal disorders	1 (0.6)	1 (0.3)	1 (0.4)	0 (0.0)	0 (0.0)	5 (0.9)
General disorders and administration site conditions	1 (0.6)	0 (0.0)	1 (0.4)	0 (0.0)	2 (0.3)	2 (0.4)
Hepatobiliary disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Infections and infestations	1 (0.6)	5 (1.5)	2 (0.8)	2 (0.7)	5 (0.7)	3 (0.5)
Injury, poisoning and procedural complications	0 (0.0)	3 (0.9)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Investigations	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	3 (0.4)	3 (0.5)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.2)
Nervous system disorders	0 (0.0)	3 (0.9)	0 (0.0)	0 (0.0)	4 (0.6)	2 (0.4)
Psychiatric disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.3)	1 (0.4)	0 (0.0)	2 (0.3)	1 (0.2)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)	1 (0.4)	1 (0.3)	1 (0.1)	2 (0.4)

System Organ Class	CKD Stage 5D on HD N = 739*			CKD Stages 1-5 and 5D on PD N = 1542*		
	≤17 sec n=168* n (%)	>17-30 sec n=324* n (%)	>30 sec n=247* n (%)	≤17 sec n=293* n (%)	>17-30 sec n=691* n (%)	>30 sec n=558* n (%)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	0 (0.0)	2 (0.6)	1 (0.4)	0 (0.0)	2 (0.3)	3 (0.5)

\*N= Number of administrations

**Reviewer's comments:**

*According to the study protocols, ferumoxytol was to be administered at a rate of 1mL/second, or 17 seconds for the 510 mg dose. Based on the submitted data, only 20% of ferumoxytol 510 mg injections were administered within 17 seconds. The majority of patients received ferumoxytol 510 mg injection more than 17 seconds; 45% received injection over 18-30 seconds and 35% received more than 30 seconds. Although it appears that no significant difference in the frequency of AEs was reported among the three groups with different durations of administration the number of patients was very limited. The labeling should reflect the rate of ferumoxytol administration in clinical trials.*

**Clinical site inspection**

Clinical site inspection by the Agency revealed an unreported event of non-serious hypotension in one subject and inaccuracies in drug disposition records in 4 subjects at one site (Site 139 in Study 62745-5).

The sponsor explained that the episode of hypotension was not reported as an adverse event by the site because it was not considered to be either a new event or a worsening of a previous condition. The sponsor indicated that the subject's medical history CRF includes a clinically significant history of orthostatic hypotension beginning in 2005. In addition, hypotension is recorded on the "History of Symptoms Relating to the Patient's Kidney Disease/Dialysis" CRF with a frequency rated as "3" (indicating hypotension occurring frequently at least once per week) and severity rated as a "3" (meaning "severe"). For these reasons, this specific occurrence of hypotension may have been considered an existing medical condition rather than a new adverse event or worsening of a pre-existing condition.

For the inaccuracies identified on the Drug Accountability Log, the sponsor explained that the inaccuracies actually applied to two subjects only; one subject (655- —) who is being counted twice because a prior screening number was entered into the Drug Accountability Log, and a second subject (626- —) who had an inaccurately recorded subject number, the first three numeric digits of which were shared with another uninvolved subject (622- —), although each subject had unique subject initials.

b(6)

The following are the sponsor's summary for each involved subject.

**Observation 1- Subject 655.** —: The site correctly recorded this subject's initials, dispensed the correct study drug (oral iron), and correctly recorded the information on the subject's CRF Dose Administration page, but incorrectly entered the subject's prior screening number on the Drug Accountability Log. **b(6)**

**Observation 2- Subject 626.** — The site correctly recorded the subject's initials, dispensed the correct study drug (ferumoxytol), and correctly recorded the information on the subject's CRF Dose Administration page, but made an error in entering the last digit of the subject number as a 2 instead of a 6; i.e., 622- —. The dates and vial numbers for ferumoxytol on the Drug Accountability Log exactly match the subject's CRF. **b(6)**

**Subject 622.** —: was not actually involved, and had no errors on the Drug Accountability Log. This subject was randomized to oral iron, had their number and initials correctly recorded on the Drug Accountability Log, received the correct study drug (oral iron), and had the correct information recorded on their CRF and Dose Administration page. Since there was no subject 622- — at the site (Observation 2), and this subject's number shared the same first three numeric digits, the subject appears to have been mistakenly involved in this Observation 2. **b(6)**

The sponsor indicated that all subjects received the appropriate study medication as randomized and had the correct information entered on their CRFs. The sponsor argued that the data integrity was not in question and the clinical data from these subjects should not be eliminated as recommended by the Agency's inspection team.

**Reviewer's comments:**

*Based on the sponsor's responses, the inaccuracies in drug disposition records occurred in 2 subjects only (one each in the ferumoxytol and oral iron groups) and both subjects received the correct study drug. In that case, the clinical data may not be impacted significantly by these patients. However, the DSI should provide comments for the sponsor's responses and additional inspection may be required if needed.*

**Facility Inspection**

The Agency has identified serious issues in the sponsor's manufacturing facility inspection. The issues have not been currently resolved.

**Safety Update**

No subjects have been enrolled in sponsor's clinical studies since the NDA's submission. There are four ongoing clinical studies being conducted under IND \_\_\_\_\_

\_\_\_\_\_. The Investigator-sponsor reported two new serious adverse events (SAEs) not related to ferumoxytol that occurred in Protocol #2753 under IND \_\_\_\_\_. **b(4)**

One subject last received ferumoxytol on 7/25/07 without complications. The subject was admitted to hospital on [redacted] with a perforated bowel (This is [redacted] days post ferumoxytol). The Principal Investigator does not feel that this SAE is related to the study drug, ferumoxytol. The subject has been on steroids since his craniotomy in April, he also received Avastin and Irinotecan on [redacted]. He was admitted [redacted] after receiving Avastin and Irinotecan with a ruptured bowel.

Another subject died 17 days after the second dose of ferumoxytol. This 61-year-old female (Patient ID 05 [redacted]) with biopsy proven Glioblastoma multiforme Grade IV and recent history of pulmonary embolus, was enrolled in Oregon Health and Sciences University (OSHU) study on 09 Jul 2008. Past medical history included near gross total resection of Glioblastoma multiforme on 28 May 2008, hypertension, diabetes, and GERD. Per protocol the subject was to receive four separate doses of ferumoxytol in conjunction with four different imaging procedures. The subject received her first dose of ferumoxytol injection (188 mg; 2 mg/kg) on 09 Jul 2008 and was started on chemoradiation with temozolomide 75mg/m2 on 10 Jul 2008. She received her second and last ferumoxytol injection (184 mg; 2 mg/kg) on 05 Aug 2008. The subject did not report any complications or side effects following either ferumoxytol dose. The chemoradiation was completed on [redacted] after one course of radiotherapy. During the afternoon of [redacted], the nurse spoke with the patient, who had no complaints other than being a little tired. Later that same evening of [redacted], the subject was found deceased at home in bed holding her cell phone. This subject had been admitted to the hospital on [redacted] for a pulmonary embolism. She was treated with heparin and warfarin for the pulmonary embolism. On [redacted], the subject was noted to have a very high INR (6.6) after which her 5mg daily dose of warfarin was held for three days. There are no reported INR results between [redacted]. On [redacted]; the subject was found to be inadequately anticoagulated with an INR of 1.3. The primary care physician increased the subject's warfarin dose to 10 mg on [redacted] and decreased it to 5 mg on [redacted]. However, the subject remained inadequately anticoagulated on [redacted] with an unchanged INR of 1.3. No autopsy was performed. The investigator considered this death is not related to ferumoxytol, but most likely the result of the subject's malignancy, thrombosis or PE.

b(6)

### Postmarketing Studies

The Division requested the sponsor to propose post-marketing studies [redacted]

[redacted]

[redacted]

[redacted]

b(4)

b(4)

*Reviewer's comments:*

b(5)

**Conclusions and Recommendations**

This reviewer recommends Ferumoxytol injection be approved after the manufacturing facility issues have been resolved.

For labeling, an instruction on the timing of ferumoxytol administration in hemodialysis patients should be added and the rate of Ferumoxytol administration in the labeling should reflect the data from clinical trials.

b(5)

See CMC review for the evaluation of the difference between Ferumoxytol and iron dextran products in chemistry and manufacturing process.

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Min Lu  
12/18/2008 02:02:21 PM  
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Kathy Robie-Suh  
12/18/2008 03:46:14 PM  
MEDICAL OFFICER

## CLINICAL REVIEW

Application Type NDA  
Submission Number 22-180  
Submission Code 000

Letter Date 18-Dec-2007  
Stamp Date 19-Dec-2007  
PDUFA Goal Date 19-Oct-2008

Reviewer Name Min Lu, M.D., M.P.H.  
Review Completion Date 09-Sep-2008

Established Name Ferumoxytol  
(Proposed) Trade Name [pending]  
Therapeutic Class Intravenous Iron Injection  
Applicant AMAG Pharmaceuticals, Inc.

Priority Designation S

Formulation Solution for injection  
Dosing Regimen 510 mg for 2 doses  
Indication Treatment of iron deficiency anemia  
Intended Population Patients with chronic kidney disease  
(CKD).

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### LIST OF ABBREVIATIONS

AA	Angiotensin converting enzyme inhibitors/angiotensin receptor blocker
ACE	Angiotensin converting enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BID	Twice Daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
b.w.	Body weight
CABG	Coronary artery bypass graft
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CHr	Reticulocyte Hemoglobin
CKD	Chronic Kidney Disease
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed concentration
CMH	Cochran-Mantel-Hansel
CPK	Creatine phosphokinase
CrCl	Creatinine Clearance
CRF	Case report form
CTCAE	Common Toxicity Criteria for Adverse Event
DBP	Diastolic Blood Pressure
DL	Deciliter
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent(s)
ESRD	End Stage Renal Disease
Fe	Iron
FeSO4	Ferrous Sulfate
G	Gram
GI	Gastrointestinal
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B Antigen
Hct	Hematocrit
HD	Hemodialysis
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IDA	Iron Deficiency Anemia
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-To-Treat

IV	Intravenous
IVRS	Interactive Voice Response System
K/DOQI	Kidney Disease Outcomes Quality Initiative
L	Liter
LFT	Liver function test
LOCF	Last Observation Carried Forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
MITT	Modified Intent to Treat
mL	Milliliter
N, n	Number
NaCl	Sodium chloride
Ng	Nanogram
NS	Normal Saline
NYHA	New York Heart Association
PD	Peritoneal Dialysis
PP	Per Protocol
PT	Prothrombin time
RBC	Red blood cell
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard Deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TIBC	Total iron binding capacity
TID	Three times daily
TSAT	Transferrin saturation
ULN	Upper Limit of Normal
WBC	White Blood Cell

## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

From a clinical perspective, ferumoxytol should be approved for the proposed indication for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

### **1.2 Risk Benefit Assessment**

The current application has demonstrated that ferumoxytol increased hemoglobin level in CKD patients with iron deficiency anemia in three randomized, open-label, oral iron-controlled clinical trials. The differences in mean increase in hemoglobin level from baseline between ferumoxytol treatment (ranged from 0.82 g/dL to 1.22 g/dL on Day 35) and oral iron (ranged from 0.16 g/dl to 0.52 g/dL on Day 35) were statistically significant ( $p < 0.01$ ) in all three trials. The improvement of clinical signs/symptoms relevant to iron deficiency anemia was not assessed in clinical trials.

The major risks of ferumoxytol treatment are hypersensitivity and hypotension reactions and possible iron overload. The incidence of hypersensitivity reactions was 3.7% with ferumoxytol treatment, 3.4% with oral iron, and 2.1% with placebo based on available clinical data. Hypotension was reported in 1.9% of the ferumoxytol-treated patients as compared to 0.3% of the oral iron-treated patients, and 0.8% in the placebo-treated patients. For the proposed dosing regimen of ferumoxytol 510 mg for 2 doses, 4.9% of patients had serum ferritin  $\geq 800$  ng/mL and TSAT  $\geq 50\%$  during the post-treatment period.

The overall benefit of ferumoxytol treatment is considered to outweigh the risk in the intended population.

### **1.3 Recommendations for Postmarketing Risk Management Activities**

The product labeling should include WARNINGS AND PRECAUTIONS for hypersensitivity, hypotension reactions and iron overload associated with ferumoxytol treatment. Because there is no market experience and a limited clinical database for evaluating hypersensitivity reactions in patients receiving ferumoxytol, the risk of hypersensitivity reactions under WARNINGS and PRECAUTIONS should be highlighted in bold and in capital letters.

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### **1.4 Recommendations for other Post Marketing Study Commitments**

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## 2 Introduction and Regulatory Background

### 2.1 Product Information

Ferumoxytol is a superparamagnetic iron oxide nanoparticle coated with polyglucose sorbitol carboxymethylether formulated with mannitol. The average particle size is less than ~~—~~ nanometers. Ferumoxytol is a sterile aqueous colloidal solution that contains 30 mg/mL of elemental iron and 44 mg of mannitol, with low bleomycin-detectable iron. Ferumoxytol is intended for intravenous use. The drug product is provided in single use vials containing 510 mg, 255 mg, or 127.5 mg of elemental iron.

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Drug established name: Ferumoxytol Injection

Proposed trade name: Pending

Chemical class: Intravenous iron products

Pharmaceutical class: Anti-anemia products

Proposed indication: Treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

### 2.2 Tables of Currently Available Treatments for Proposed Indications

Current available treatment for iron deficiency anemia includes oral iron products and intravenous iron products. Currently approved intravenous iron products in the U.S. for patients with chronic kidney disease include INFed, Ferrlecit and Venofer. The approved indications, dose regimens and main safety concerns for these intravenous iron products are shown in the table below.

**Currently approved intravenous iron products in US**

Chemical name	Iron Dextran (INFeD, Dexferrum, Proferdex)	Sodium Ferric gluconate complex (Ferlecit)	Iron Sucrose (Venofer)
Year of first U.S. approval	1974	1999 (marketed in Europe since 1950's)	2000 (marketed in Europe since 1950's)
Indication	Documented iron deficiency in patients in whom oral iron administration is unsatisfactory or impossible	Iron deficiency anemia in patients undergoing chronic hemodialysis and receiving EPO	Iron deficiency anemia in CKD patients including pre-dialysis, peritoneal dialysis and hemodialysis
Safety	Black box warning for anaphylactic reaction	Warning for hypersensitivity reactions	Warning for hypersensitivity reactions
Population	Adults and Pediatrics	Adults	Adults
Dose regimen	<p>100 mg (2 mL) may be given on a daily basis until the calculated total amount required has been reached. It is given undiluted at a slow gradual rate not to exceed 50 mg per minute.</p> <p>Adults and Children over 15 kg (33 lbs):            Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × LBW (kg) + (0.26 × LBW)</p> <p>Children 5-15 kg (11-33 lbs):            Total amount (mL) = 0.0442 (Desired Hb-Observed Hb) × W (kg) + (0.26 × W)</p> <p>Each mL contains 50 mg of elemental iron.</p> <p>A test dose (0.5 mL) is required before the dosing.</p>	<p>125 mg of elemental iron intravenously (at a rate of up to 12.5 mg/min) over 8 sessions at sequential dialysis by slow injection or infusion over 1 hour diluted in 100 mL of 0.9% sodium chloride.</p>	<p>Hemodialysis:            100 mg as slow IV injection or as an infusion diluted in a 100mL of 0.9% NaCl over at least 15 minutes over 10 consecutive dialysis session for a total cumulative dose of 1,000 mg.</p> <p>Non-Dialysis Dependent-Chronic Kidney Disease:            200 mg as slow IV injection on 5 occasions within the 14 day period for a total cumulative dose of 1,000 mg. There is limited experience with administration of an infusion of 500 mg diluted in 250 mL of 0.9% NaCl over a period of 3.5-4 hours on day 1 and day 14; hypotension occurred in 2 of 30 patients treated.</p> <p>Peritoneal Dialysis:            2 infusions of 300 mg over 1.5 hours 14 days apart followed by one 400 mg infusion over 2.5 hours 14 days later for a total cumulative dose of 1,000 mg within a 28 day period. The Venofer® dose should be diluted in a maximum of 250mL of 0.9% NaCl.</p>

Reviewer's table

### **2.3 Availability of Proposed Active Ingredient in the United States**

This product has not been approved in the U.S. or other countries. There are three intravenous iron products available in the U.S. as mentioned above.

### **2.4 Important Safety Issues With Consideration to Related Drugs**

Intravenous iron products have been associated with anaphylaxis/anaphylactoid reactions. InFed (iron dextran) has a black boxed warning for anaphylactic-type reactions. Ferrlecit and Venofer have warnings for hypersensitivity reactions.

### **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The initial IND (62,745) for treatment of iron deficiency anemia was submitted June 13, 2001 and a separate IND for use in medical imaging was filed early in May 1999 (IND 58,254). An End of Phase 2 meeting was held on October 9, 2003 to discuss the phase 3 clinical program for the iron deficiency anemia indication. All clinical studies including phase 3 studies were conducted under the INDs. A Pre-NDA meeting was held between the sponsor and the Agency on July 20, 2007 to discuss the adequacy of the completed clinical, pre-clinical and chemistry, manufacturing and controls data for submitting an NDA and NDA format.

### **2.6 Other Relevant Background Information**

N/A

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

This NDA was submitted in eCTD format. There were 13 amendments to the original submission.

The following material in the NDA submission was reviewed:

- NDA 000, eCTD format, submitted December 18, 2007
- Amendment No. 0001, Response to 74-Day Letter Filing Communication and NDA Orientation Presentation, submitted on April 3, 2008
- Amendment No. 0002, Request for Review of Proprietary Name, submitted on April 10, 2008
- Amendment No. 0003, Response to Information Request, submitted on April 14, 2008
- Amendment No. 0004, 120-Day Safety Update, submitted on April 28, 2008

- Amendment No. 0005, Response to Information Request (Hypersensitivity reactions), submitted on May 20, 2008
- Amendment No. 0006, Response to Information Request (Treatment discontinuation), submitted on June 5, 2008
- Amendment No. 0007, Response to Information Request (Iron overload and Serum phosphate), submitted on June 23, 2008
- Amendment No. 0008, Response to Information Request (Risk management), submitted on July 14, 2008
- Amendment No. 0009, Physician sample labels, submitted on July 17, 2008
- Amendment No. 0010, Response to Information Request (Statistics-Data listing), submitted on July 24, 2008
- Amendment No. 0011, Pediatric Studies Description, submitted on August 4, 2008
- Amendment No. 0012, Draft Labeling, submitted on August 5, 2008
- Amendment No. 0013, Response to Information Request (CMC), submitted on August 7, 2008

The Division requested that three study sites with most patients enrolled in each of 3 pivotal studies be inspected by the Division of Scientific Investigations, Office of Compliance. The inspection result is pending.

### 3.2 Compliance with Good Clinical Practices

Informed consents were required from patients in all clinical trials. Independent ethics committees/institutional review boards at all participating centers were required to give permission for these studies.

### 3.3 Financial Disclosures

The sponsor certified that there was no financial arrangement with clinical investigators except 3 investigators as discussed below, who conducted the clinical studies (Form FDA 3454).

\_\_\_\_\_ between 2003 and 2005 and provided \_\_\_\_\_

As a component of the compensation mutually agreed to for his services, he was granted an option to purchase 10,000 company shares on March 17, 2003 and another 8,000 shares on May 3, 2005. \_\_\_\_\_, also participated in the ferumoxytol imaging clinical study \_\_\_\_\_ as the r \_\_\_\_\_ from \_\_\_\_\_, and then as a \_\_\_\_\_ through study completion in \_\_\_\_\_

b(6)

\_\_\_\_\_ and received \$10,000 for his participation in 2005 and 2006. As a \_\_\_\_\_, he was also granted an option to purchase 1,000 shares of the company common stock on August 2, 2005. \_\_\_\_\_ also participated as an \_\_\_\_\_ in ferumoxytol pivotal clinical studies ( \_\_\_\_\_)

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between August 2004 and August 2007. \_\_\_\_\_, enrolled \_\_\_\_\_ in study \_\_\_\_\_ and \_\_\_\_\_ in study \_\_\_\_\_.

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\_\_\_\_\_ received multiple separate payments for \_\_\_\_\_ that in aggregate totaled \$121,999.92 between 2004 and 2006. These payments were specifically made \_\_\_\_\_

\_\_\_\_\_. As a component of his compensation as a member of the \_\_\_\_\_, he was also granted an option to purchase 1,000 shares of company common stock on August 2, 2005. \_\_\_\_\_ participated as an \_\_\_\_\_ in all phase clinical studies \_\_\_\_\_ between July 2004 and August 2007; no subjects were enrolled in study \_\_\_\_\_ from his site. \_\_\_\_\_, enrolled \_\_\_\_\_ in study \_\_\_\_\_, in study \_\_\_\_\_, and \_\_\_\_\_ in study \_\_\_\_\_.

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#### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

##### 4.1 Chemistry Manufacturing and Controls

The CMC review (Dr. Xiao-Hong Chen, Ph.D. dated 8/29/2008) recommended approvable, provided that the CMC deficiencies identified for the proposed drug substance specifications are resolved, the Office of Compliance issues an overall "acceptable" recommendation for the application, and acceptable container/carton labeling is submitted. The sponsor has responded to the CMC deficiencies and the review is currently pending.

According to FDA CMC review, the drug substance is a non-stoichiometric magnetite, commonly called polyglucose sorbitol carboxymethylether (PSC)-covered superparamagnetic iron oxide. The chemical composition of ferumoxytol drug substance is as follows: approximately \_\_\_\_\_ carbohydrate and \_\_\_\_\_ iron oxide by weight. It is: \_\_\_\_\_

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The drug product of ferumoxytol is an aqueous colloid of superparamagnetic iron oxide covered with PSC, formulated with mannitol, USP, \_\_\_\_\_. It will be marketed in three strengths and is filled into three vial configurations: \_\_\_\_\_ vials \_\_\_\_\_. Each single-use vial (30 mg elemental iron/mL) contains 510 \_\_\_\_\_.

b(4)

mg, 255 mg, and 127.5 mg in 17 mL, 8.5 mL and 4.25 mL volumes, respectively. The drug product is manufactured \_\_\_\_\_

\_\_\_\_\_. The control and stability of the drug product is quite similar to that of the drug substance. The drug product has demonstrated good stability over 24 months at the recommended storage conditions: 20° to 25°C (68° to 77°F) with excursions allowed between 15° and 30°C (59° and 86°F). The proposed 24 month expiry is granted.

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#### 4.2 Clinical Microbiology

The Microbiology review recommended approval based on the sterility assurance of the product (Dr. Vinayak Pawar, Ph.D. dated in DFS 9/15/2008).

#### 4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review (Dr. David Bailey, Ph.D. dated 10/6/2008) recommended approval with labeling recommendations. The review concluded that Ferumoxytol is a relatively nontoxic product in a wide variety of nonclinical studies and species, and thus requires a very high dose to induce a toxic response. The initial pharmacological effects are those found in chronic iron overload which always precede any overt signs of toxicity. The findings are consistent with pharmacological effects of high doses of iron compounds administered intravenously.

The following is a summary of pre-clinical findings regarding hypersensitivity.

**Hypersensitivity:** A battery of studies was conducted to evaluate the potential of ferumoxytol to elicit tissue responses in rats, rabbits and guinea pigs. The rat paw edema study was negative when comparing the response of ferumoxytol to the severe edema observed with the IV administration of the positive control Dextran T70. The administration of ferumoxytol to rabbits by the subcutaneous, perivascular and intravenous routes resulted in no antigenicity, immunotoxicity or hypersensitivity type tissue reactions. Guinea pigs were given IV and SC injections of ferumoxytol over a 35 day induction period, followed by challenge IV doses of ferumoxytol. There were no hypersensitivity or anaphylactic responses observed from the administration of ferumoxytol in the Passive Cutaneous Assay, Passive Hemagglutination Assay or the Systemic Anaphylaxis Assay following induction and IV challenge with ferumoxytol. Although using a battery of animal studies as described here is generally predictive of risk of human anaphylactoid responses, animal studies are not always completely accurate in predicting human response.

#### 4.4 Clinical Pharmacology

##### 4.4.1 Mechanism of Action

See clinical pharmacology review. The review is currently pending.

#### 4.4.2 Pharmacodynamics

See clinical pharmacology review. The review is currently pending.

#### 4.4.3 Pharmacokinetics

See clinical pharmacology review. The review is currently pending.

### 5 Sources of Clinical Data

#### 5.1 Tables of Clinical Studies

Summary of completed clinical trials

Study Populations	Studies	Type of trials	Ferumoxytol group (N)	Control group (N)	Total patients enrolled
CKD Stage 1-5	62,745-6	Randomized, open-label, parallel group, superiority study	228	76 (oral iron)	304
	62,745-7	Randomized, open-label, parallel group, superiority study	227	77 (oral iron)	304
	62,745-4	Open-label, uncontrolled study	21	-	21
CKD Stage 5D (Hemodialysis) Hemodialysis	62,745-5	<b>Post-amendment</b> Randomized, open-label, parallel group, superiority study trial	114	116 (oral iron)	230
		<b>Pre-amendment</b> Randomized, open-label, parallel group, superiority study trial	126	22 (oral iron)	148
	62,745-3	Non-randomized, open-label, controlled study	26	10 (oral iron)	36
	62,745-2	Open-label, uncontrolled study	20	-	20
CKD all stages (safety study)	62,745-8	Single dose, cross-over safety study	750	750 (Placebo)	750
Healthy Volunteers	7228-01	Randomized, double-blind, placebo-controlled, PK and safety study	35	6 (placebo)	41
	62,745-9	Randomized, double-blind, thorough QTc and PK study	58	58 (placebo) 58 (Moxifloxacin)	174

Medical Imaging Subjects (patients and healthy volunteers)	58,254-2	Open-label, uncontrolled study	17	-	17
	58,254-4	Open-label, uncontrolled study	49	-	49

Reviewer's table

## 5.2 Review Strategy

Three randomized controlled phase 3 pivotal trials were reviewed for efficacy for the proposed indications. These three trials were reviewed separately in the same depth. These three trials and other trials were reviewed for safety.

## 5.3 Discussion of Individual Studies

Four phase 3 studies were submitted to support the efficacy and safety of Ferumoxytol. These included 3 pivotal studies (62,745-6, 62,745-7, and 62,745-5) for efficacy and safety and one study (62,745-8) for safety only. The following are summaries of study protocols and protocol changes for these 4 studies. The efficacy and safety results of these studies will be presented in Sections 6 and 7.

### Protocol 62,745-6 and 62,745-7

Two studies (62,745-6 and 62,745-7) were conducted in patients with CKD stage 1-5. These two studies had identical study protocols and protocol amendments. The following are the summary of the study protocol and protocol changes for these two studies.

#### Study Objectives

The objective of this study was to evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in subjects with CKD who were not on dialysis (stages 1-5).

#### Study Design

This was a randomized, open-label, oral iron-controlled, multicenter study of the safety and efficacy of ferumoxytol in subjects with CKD stages 1-5.

#### Study Population

For inclusion into the trial, subjects of all ethnic populations and races were considered for participation and were required to fulfill all of the following criteria:

#### Inclusion Criteria

1. Male or female chronic kidney disease patients  $\geq 18$  years of age.
2. Patient is able and willing to provide written informed consent and HIPAA Authorization to participate in the study.
3. Have chronic kidney disease per K/DOQI guidelines (Stage 1 or 2: eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup>; Stage 3: eGFR 30-59 ml/min/1.73 m<sup>2</sup>; Stage 4: eGFR 15-29 ml/min/1.73 m<sup>2</sup>; and Stage 5: eGFR  $< 15$  ml/min/1.73 m<sup>2</sup>).
4. Patients on EPO must have received stable supplemental EPO therapy for at least 10 ( $\pm 4$ ) days prior to dosing and be expected to remain on a stable dose for the duration of the study.
5. Have a hemoglobin of  $\leq 11.0$  g/dL at Day -10 ( $\pm 4$  days) and Day -5 ( $\pm 3$  days).
6. Have a transferrin saturation (TSAT)  $\leq 30\%$  within 5 days ( $\pm 3$  days) prior to dosing.
7. Have a serum ferritin of  $\leq 600$  ng/mL within 5 days ( $\pm 3$  days) prior to dosing.
8. Have a negative serum pregnancy test result prior to dosing, unless the patient is 2 years postmenopausal, or has a documented tubal ligation, or total hysterectomy, confirmed by the Principal Investigator.

#### Exclusion Criteria

1. Women who are pregnant, capable of becoming pregnant and not practicing an acceptable form of birth control, or who are breast feeding.
2. Patients currently participating in a clinical trial with another investigational drug or device or who have received an investigational drug or device within 30 days of enrollment in this study.
3. Patients who have been on parenteral or oral iron therapy between the Day -10 ( $\pm 4$  days) visit and until completion of the study.
4. Patients with active gastrointestinal (GI) bleeding or acute bleeding episodes within 4 weeks of enrollment.
5. Patients that have other causes of anemia other than iron deficiency (eg, systemic lupus erythematosus [SLE], myeloma, rheumatoid arthritis).
6. Major surgery within one month prior to enrollment in the study or planned surgery while the patient is on the study other than vascular access.
7. Patients who are refractory (not responding) or who are receiving in excess of 35,000 Units/week of EPO.
8. Patients receiving in excess of 120  $\mu$ g Aranesp<sup>®</sup> per 2 weeks.
9. Patients whose EPO status changes while on study.
10. Patients with active infections requiring ongoing treatment.
11. Patients with uncontrolled hyperparathyroidism (known parathyroid hormone [PTH]  $\geq 1,500$  pg/mL and on medication to treat the disease).
12. Patients who have had a malignancy (except for non-melanoma cancer of the skin) unless the patient has received curative treatment and has been disease free for  $\geq 2$  years.
13. Patients who the Investigator determines have a medical status that would preclude the patient's participation in this protocol.
14. Patients who receive blood transfusions within 2 weeks prior to enrollment and until completion of the study.
15. Patients on hemodialysis (HD).

16. Patients on peritoneal dialysis (PD).
17. Patients with any allergies to iron products or multiple (two or more) drug allergies.

### Study Treatment

Eligible subjects were randomized in a 3:1 ratio of ferumoxytol:oral iron. Subjects were assigned to one of two treatment groups:

- Ferumoxytol: Two separate doses of 510 mg ferumoxytol administered IV on Day 0 and Day 5 ( $\pm 3$  days). The cumulative dose was 1.02 g of iron.
- Oral iron: Ferro-Sequels® (containing 50 mg of elemental iron as ferrous fumarate), 2 tablets BID (morning and bedtime) starting at Day 0 until the Day 21 visit (Week 3) is completed. The daily dose was 200 mg of elemental iron. The cumulative dose over 21 days was 4.2 g of elemental iron.

Compliance with oral iron dosing was monitored at scheduled weekly visits, and a formal pill count was performed and recorded at Day 21.

Subjects in either the ferumoxytol or oral iron treatment group in the study who completed the study and who continued to meet the study entry criteria, including a Hgb measurement  $\leq 11$  g/dL (performed by the central laboratory) on Day 35, were eligible to be readmitted in the optional Readmission Phase. Subjects who readmitted in the Readmission Phase received another course of two 510 mg doses of ferumoxytol. These subjects represented a separate part of the study, were not randomized, and were not entered in the primary efficacy analysis.

### Study Plan

The following tables are the study procedure schedule.

**Time and Events Schedule**

Event	Oral Iron Dose Group									Ferumoxytol Dose Group							
	Pre-screen	D -10 $\pm 4$ d	D -5 $\pm 3$ d	D 0	Wk 1 D 7 $\pm 2$ d	Wk 2 D 14 $\pm 2$ d	Wk 3 D 21 $\pm 5$ d	D 35 $\pm 5$ d	Early Term a	Pre-screen	D -10 $\pm 4$ d	D -5 $\pm 3$ d	D 0	D 5 $\pm 3$ d	D 21 $\pm 5$ d	D 35 $\pm 5$ d	Early Term a
Hgb (site lab) $\leq 11$ g/dL within 8 weeks prior to Day 0	X									X							
Informed Consent/ HIPAA		X									X						
Hematology		X	X				X	X	X		X	X			X	X	X
Iron Panel		X	X				X	X	X		X	X			X	X	X
Clinical Chemistry			X <sup>b</sup>					X	X			X <sup>b</sup>				X	X
Physical Exam				X				X	X				X			X	X
Medical				X									X				

Clinical Review  
 Min Lu, M.D., M.P.H.  
 NDA 22-180/ N000  
 Ferumoxytol Injection

History c																		
Dosing d				X	X	X	X							Dose 1	Dose 2			
Vital Signs e		X	X	X	X	X	X	X	X		X	X	X f	X f	X	X	X	
Con Meds		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
AE monitoring g				X	X	X	X	X	X				X	X	X	X	X	

- a. Early Term=Early Termination visit. The Day 35 assessments were conducted for early termination of subjects.
  - b. Included a serum pregnancy laboratory draw for women of childbearing potential.
  - c. Medical history was completed after the Day -5 laboratory values confirmed subject eligibility and before the start of dosing. Review included current illnesses and symptoms as well as height and weight and Listing of medications.
  - d. Randomization occurred after Day -5 laboratory values confirmed subject eligibility and before the start of dosing.
  - e. Respiration, temperature, heart rate, and blood pressure.
  - f. Vital signs were taken within 30 minutes before each dose and 5, 10, 20, 30 (±5) and 60 (±5) minutes after each dose.
  - g. AEs were collected from the time of dosing until completion of Day 35 study visit events.
- Abbreviations: Con Meds=concomitant medications; D=Day, d=day(s), HIPAA=Health Insurance Portability and Accountability Act; Wk=Week  
 Sponsor's table

The laboratory parameters evaluated in this study are shown in the table below.

**Clinical Laboratory Evaluation**

Clinical Chemistry a	Hematology	Iron Panel b
Creatinine	Hemoglobin (Hgb) b	Serum iron
Blood Urea Nitrogen (BUN)	Hematocrit (Hct)	Serum Ferritin
Lactate Dehydrogenase (LDH)	Red Blood Cell (RBC) Count	Total Iron Binding Capacity (TIBC)
Calcium	Mean Corpuscular Volume (MCV)	Transferrin Saturation (TSAT)
Glucose	Platelet Count	Percent Hypochromic Red Cells
Chloride	White Blood Cell (WBC) Count	Reticulocyte Count
Total Protein	Differential:	Reticulocyte Hgb Content (CHR)
Phosphorus	Neutrophils	
Potassium	Lymphocytes	
Sodium	Monocytes	
Alkaline Phosphatase	Eosinophils	
Total Bilirubin	Basophils	
Aspartate Aminotransferase (AST)		
Alanine Aminotransferase (ALT)		
Gamma-glutamyltransferase (GGT)		

- a. A serum pregnancy test was collected for females of childbearing potential.
- b. Collected for both safety and efficacy assessments.

**Efficacy Endpoint**

The primary efficacy endpoint was the mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication.

Secondary efficacy endpoints and exploratory iron-related analyses include the following:

- Hemoglobin Responders defined as the proportion of subjects with an increase of at least 1.0 g/dL in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication

- Hemoglobin and Ferritin Responders defined as the proportion of subjects with an increase of at least 1.0 g/dL in Hgb at either post-initial dose timepoint (Day 21 or Day 35 visit) accompanied by an increase of at least 160 ng/mL in ferritin at either post-initial dose timepoint (Day 21 or Day 35 visit)
- The mean change from Baseline in ferritin at 3 weeks (Day 21 visit) post-initial dose of study medication
- Mean change from Baseline in Hgb at Day 21 post-initial dose of study medication
- Mean change from Baseline in serum ferritin at Day 35 post-initial dose of study medication
- Mean change from Baseline in serum iron at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in percent hypochromic red cells at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in TIBC at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in reticulocyte count at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in TSAT at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in CHr at Day 21 and Day 35 post-initial dose of study medication

### **Safety Assessments**

Safety assessments included AE monitoring, clinical laboratory evaluations, vital sign assessments, and physical examinations.

Vital signs (respiration rate, temperature, heart rate, blood pressure) were obtained using a standard procedure that maintained consistency in the position of each subject during all measurements.

For all subjects receiving ferumoxytol, vital signs were obtained before and after dose administration as follows:

- Pre-dose: within 30 minutes before dose administration
- Post-dose: 5, 10, 20, 30 ( $\pm 5$ ), and 60 ( $\pm 5$ ) minutes after dose administration

In addition, vital signs were obtained in subjects randomized to ferumoxytol at Day -10 ( $\pm 4$  days), Day -5 ( $\pm 3$  days), Day 21 ( $\pm 5$  days), and Day 35 ( $\pm 5$  days) or if the subject terminated early from the study.

### **Statistical and Analytical Plans**

#### **Determination of Sample Size**

Assuming a 0.6 g/dL difference between treatment groups in mean change from Baseline in Hgb

at the Day 35 visit and a common SD of 1.2 g/dL, the sample size would provide 90% power, with 57 subjects in the oral iron group and 171 subjects in the ferumoxytol group, to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (76 subjects) drop out rate due to potential exclusions from the ITT Population, a sufficient number of subjects were to be enrolled to result in 304 subjects randomized in a 3:1 ratio to ferumoxytol or oral iron.

### **Analyzed Populations**

The Intent-to-Treat (ITT) Population was defined as all subjects who were randomized. The ITT Population was used for the efficacy analyses.

The Safety Population was defined as all subjects who were randomized and had at least one dose of study medication. The Safety Population was used for the safety analyses.

### **Efficacy Analysis**

The primary efficacy analysis compared the mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication across treatment groups, ferumoxytol versus oral iron. The primary population for analysis was the ITT Population. The Efficacy Evaluable Population was used to confirm clinical efficacy.

The primary comparison used a two-sided, two-sample t-test with a 5% Type I error. The null hypothesis was that both ferumoxytol and oral iron provide an equivalent increase in Hgb from Baseline at the Day 35 visit; ie, the mean of subject-specific Hgb changes from Baseline among ferumoxytol treated subjects is equivalent to that of subjects treated with oral iron.

The secondary efficacy endpoints were separately evaluated using 5% Type I error. No adjustment for multiplicity was used.

### **Safety Analysis**

Safety analyses were carried out using the Safety Population. The number of events and number and percent of subjects experiencing AEs overall were tabulated using MedDRA Version 8.0 system organ class and preferred term classification.

### **Interim Analyses**

No interim efficacy analyses were planned. However, an independent DMC periodically reviewed safety analyses to ensure continued safety of the study participants. The DMC periodic review dates were 18 October 2005, 15 February 2006, 13 June 2006, 20 October 2006, and 02 March 2007.

### **Handling of Missing or Invalid Data**

If any component of a date was missing, it was presented as it was collected unless a reasonable determination could be made as to the time frame of the observation. For example, if the year component of the date was missing and all other observations were made in 2004, it was reasonable to assume 2004 as the correct year. If the day or month component of a given date

was missing, it was presented as collected.

Missing information for all safety measures (AEs, vital signs, clinical laboratory values, and physical examinations) were presented as collected. In cases where laboratory panels were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. For the primary and secondary efficacy variables, in the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.

### **Changes in the Conduct of the Study or Planned Analyses**

#### **Changes in the Conduct of the Study**

There were two amendments to the protocol that were implemented to:

- 1) clarify entry criteria;
- 2) clarify other text;
- 3) facilitate protocol compliance;
- 4) revise the primary efficacy endpoint; and
- 5) enhance safety monitoring (which included providing definitions for hypersensitivity and hypotension).

#### **Amendment 1 (26 October 2005)**

Protocol Amendment 1 (26 October 2005) implemented the following major modifications to the protocol:

- Study Population:
  - The intent to allow enrollment of subjects on an ESA was clarified, with the stipulation that the dose is stable. Erythropoietin use was previously allowed, but without requirement for dose stability.
  - The number of evaluable subjects was increased from 200 (150 on ferumoxytol and 50 on oral iron) to ‘up to 400’ (300 on ferumoxytol and 100 on oral iron), which was estimated to be sufficient to demonstrate a difference between the two treatment groups.
- Pre-screening and Hgb criteria for enrollment in the study:
  - The maximal pre-screening period and interval during which three Hgb measurements of  $\leq 11.0$  g/dL must be available was increased from 4 to 8 weeks.
  - Clarified that the three Hgb measurements of  $\leq 11.0$  g/dL at three different timepoints within 8 weeks prior to dosing included the pre-screening value and the values from “Day -10 ( $\pm 4$  days) and Day -5 ( $\pm 3$  days).”
  - Allowed the initial Hgb measurement prior to Day -10 but within 8 weeks (pre-screening value) to also be “obtained from ...HemoCue® values,” in addition to “record review of existing laboratory data”.
- Inclusion Criteria
  - The allowance of subjects on ESA was clarified by adding to inclusion criteria: “Patient on EPO must have received stable supplemental EPO therapy for at least

10 days ( $\pm 4$  days) prior to dosing and be expected to remain on a stable dose for the duration of the study.”

- Exclusion Criteria
  - Added exclusion of: “Patients with any allergies to iron products or multiple (two or more) drug allergies.”
- Vital Signs:
  - In the ferumoxytol group, the post-dosing time points for vital signs monitoring were expanded from 30 ( $\pm 5$ ) minutes post-dose to 5, 10, 20, 30 ( $\pm 5$ ), and 60 ( $\pm 5$ ) minutes post-dose. In addition, the days on which vital signs were monitored were increased from at dosing (Day 0) to Day -10, Day -5, Day 21, and Day 35.
- Dosing and administration of ferumoxytol:
  - Clarified that two doses of ferumoxytol were separate, and the window between administrations was increased to within 5 ( $\pm 3$ ) days from 5 ( $\pm 2$ ) days.

#### **Amendment 2 (08 June 2006)**

Protocol Amendment 2 (08 June 2006) implemented the following significant changes to the protocol:

- Study population: Subject enrollment was updated from ‘up to 400’ to 304 randomized subjects based upon sample size calculations using a treatment difference in Hgb of 0.6 g/dL (standard deviation 1.2 g/dL), with 90% power and 5% type I error. A 25% drop-out rate was assumed.
- Vital signs: the schedule for obtaining vital signs at Day -10, Day -5, and Day 35 in the oral iron group was expanded to include visit windows.
- Ferumoxytol administration:
  - For serious or life-threatening events, the protocol listed the emergency medical supplies that must be readily available.
  - The requirements for access to a 911 system, ability to perform CPR, and responsibility of the site physician to provide adequate emergency care were specified.

#### **Changes in the Planned Analysis of the Study**

##### **Changes Added by Protocol Amendment 1 (26 October 2005)**

Protocol Amendment 1 (26 October 2005) added the following major change in the planned analysis:

- An additional efficacy analysis was added to compare the number of subjects in the ferumoxytol group with a rise in Hgb of 1 g/dL or more (hemoglobin responders) versus the number of responders in the oral iron group.

##### **Changes Added by Protocol Amendment 2 (08 June 2006)**

Protocol Amendment 2 (08 June 2006) added the following changes in the planned analysis:

- Analysis of efficacy data:
  - The primary endpoint was clarified to “mean change from Baseline in Hgb at the Day 35 visit post-initial dose of study medication”, from “elevation in Hgb compared to Baseline with each subject acting as his/her own control.”
  - The secondary endpoints were clarified, including specification of Day 21 and Day 35 for assessing the difference between the treatment groups in the mean change from Baseline or proportion achieving endpoint.
  - Specified comparisons across treatment groups to be done using two-sided t-test for continuous variables and chi-square test for categorical variables.

### Changes to the Analysis

Changes to the Efficacy Evaluable Population prior to the original database lock date included:

- The window for the Hgb draw was extended from within 40 days post-dosing to **45 days post-dosing** since the protocol-allowed visit windows post-dosing were Day 21 ( $\pm 5$  days) and Day 35 ( $\pm 5$  days).
- The day after which receipt of any other iron product was prohibited, Day -6, was modified to be after the Day -10 lab draw, since any iron products taken after that time would impact the analysis of Hgb.
- The Efficacy Evaluable Population was redefined from subjects having taken at least 80% to subjects having taken at least 60% the prescribed amount, to enable a comparison of efficacy between subjects who received both doses of ferumoxytol and subjects who received a comparable dose of delivered oral iron. This corresponds to an administered dose of 2500 mg (50 pills of 50 mg each), which, factoring in the incomplete gastrointestinal absorption of oral iron (40%), represents a minimum delivered amount of 1000 mg iron.
- The day after which the initiation of ESA was prohibited, Day -10, was modified to be after the Day -10 lab draw, since any ESA initiation after that time would impact the analysis of Hgb.
- The day after which transfusion of packed red blood cells was prohibited, Day -10, was modified to be after the Day -10 lab draw, since any transfusion after that time would impact the analysis of Hgb.

### Protocol 62,745-5

#### Study Design

This was a randomized, open-label, oral iron-controlled, multicenter study of the safety and efficacy of ferumoxytol in subjects with CKD stage 5D on hemodialysis who were receiving supplemental ESA therapy.

The original protocol of 62,745-5 (25 March 2004, amended on 06 December 2004) was an open label, two dose regimens of ferumoxytol, 2 x 510 mg and 4 x 255 mg, oral iron-controlled study with a randomization ratio of 3:3:1 in 2 x 510 mg ferumoxytol:4 x 255 mg ferumoxytol: oral iron

control groups. The study was intended to enroll at least 50 evaluable subjects receiving oral iron, 150 subjects receiving two doses of 510 mg of ferumoxytol, and 150 subjects receiving four doses of 255 mg of ferumoxytol.

The protocol was amended on 26 October 2005 (Protocol Amendment 2) after 148 subjects had been randomized in the study to change the Hgb entry criteria from  $\leq 12.0$  to  $\leq 11.5$  g/dL, to remove the 4 x 255 mg ferumoxytol dose group, and to change the randomization to allocate treatment in a 1:1 ratio of 2 x 510 mg ferumoxytol: oral iron. A total of 230 subjects were to be randomized after this amendment; 115 subjects receiving oral iron, and 115 subjects receiving two doses of 510 mg of ferumoxytol.

Data collected for subjects randomized under the prior to Protocol Amendment 2 (referred to as Pre-amendment throughout the study report) are presented and evaluated separately from data collected after Protocol Amendment 2 (referred to as Post-amendment throughout the study report). Data from Post-amendment subjects were the primary analysis population and were used to evaluate efficacy and safety by the sponsor. Data from Pre-amendment subjects were used to evaluate safety only; efficacy analyses for these subjects are presented for descriptive purposes.

### Study Population

Study 62,745-5 was conducted in CKD patients with stage 5D on hemodialysis. The inclusion/exclusion criteria in this study were similar to those in Studies 62,745-6 and 62,745-7 except the following differences in inclusion/exclusion criteria.

#### Inclusion Criteria

- Have been undergoing hemodialysis for at least 90 days.
- Have received stable supplemental EPO therapy for at least 10 ( $\pm 4$ ) days prior to dosing and be expected to remain on a stable dose for the duration of the study.
- Have a Hgb  $\leq 11.5$  g/dL (post-amendment) at Day -10 ( $\pm 4$  days) and Day -5 ( $\pm 3$  days).

#### Exclusion criteria

- Major surgery within one month prior to enrollment in the study or planned surgery while the patient is on the study other than vascular access.
- Patients who are refractory (not responding) or who are receiving in excess of 35,000 Units/week of EPO.
- Patients whose EPO status changes while on study.

### Study Treatment

Prior to Protocol Amendment 2, subjects were randomly assigned to one of the three treatment groups in a 3:3:1 ratio of 2 x 510 mg ferumoxytol: 4 x 255 mg ferumoxytol: oral iron.

- 2 x 510 mg ferumoxytol: two intravenous doses of 510 mg ferumoxytol within 7 days
- 4 x 255 mg ferumoxytol: four intravenous doses of 255 mg ferumoxytol within 14 days

- Oral Iron: Ferro-Sequels® 2 tablets twice daily (200 mg oral iron/day) for 21 consecutive days

After Protocol Amendment 2, subjects were randomly assigned to one of the two treatment groups in a 1:1 ratio of 2 x 510 mg ferumoxytol: oral iron.

- Ferumoxytol: Two separate doses of 510 mg ferumoxytol within 5 days ( $\pm 3$  days) on sequential dialysis procedures
- Oral Iron: Ferro-Sequels® 2 tablets twice daily (200 mg oral iron/day) starting at Day 0 until the Day 21 visit (Week 3)

Compliance with oral iron dosing was monitored at scheduled weekly visits, and a formal pill count was performed and recorded at Day 21.

Subjects in either the ferumoxytol (2 x 510 mg and 4 x 255 mg) or oral iron treatment group who completed the study and who continued to meet the study entry criteria, including a Hgb measurement  $\leq 11.5$  g/dL (performed by the central laboratory) on Day 35 were eligible to enter the optional Readmission Phase and to receive two separate 510 mg doses of ferumoxytol within 5 ( $\pm 3$ ) days in sequential dialysis sessions. Subjects participating in the Readmission Phase represented a separate nonrandomized part of the study with a different (pre-treated) subject population. They were not randomized, and their data were not included in the primary efficacy analysis.

### **Study Plan**

The study procedure schedule and laboratory evaluation were similar to Studies 62,745-6 and 62,745-7 described above.

### **Efficacy Endpoint**

The primary efficacy endpoint was the mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication.

Secondary efficacy endpoints and exploratory iron-related analyses were same as for Studies 62,745-6 and 62,745-7 described above.

### **Safety Assessments**

Safety assessments included AE monitoring, clinical laboratory evaluations, vital sign assessments, and physical examinations.

Vital signs (respiration rate, temperature, heart rate, blood pressure) were obtained using a standard procedure that maintained consistency in the position of each subject during all measurements.

For all subjects receiving ferumoxytol, vital signs were obtained before and after dose administration as follows:

- Pre-dose: within 30 minutes before dose administration
- Post-dose: 5, 10, 20, 30 ( $\pm 5$ ), and 60 ( $\pm 5$ ) minutes after dose administration

In addition, vital signs were obtained in subjects randomized to ferumoxytol at Day -10 ( $\pm 4$  days), Day -5 ( $\pm 3$  days), Day 21 ( $\pm 5$  days), and Day 35 ( $\pm 5$  days) or if the subject terminated early from the study.

### **Statistical and Analytical Plans**

#### **Determination of Sample Size**

Assuming a 0.6 g/dL difference between treatment groups in mean change from Baseline in Hgb at the Day 35 visit and a common SD of 1.2 g/dL, the sample size would provide 90% power, with 86 subjects in the oral iron group and 86 subjects in the ferumoxytol group, to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (58 subjects) drop out rate, a sufficient number of subjects were to be enrolled to result in 230 subjects randomized in a 1:1 ratio to oral iron or ferumoxytol.

#### **Analyzed Populations**

Subjects randomized after Protocol Amendment 2 (26 October 2005) and Protocol Amendment 3 (08 June 2006), i.e., Post-amendment, which included only 2 x 510 mg ferumoxytol and oral iron dose groups in a 1:1 ratio, were used to evaluate both efficacy and safety.

The Intent-to-Treat (ITT) subject population was defined as all subjects who were randomized. The ITT Population was used for the efficacy analyses.

The Safety Population was defined as all subjects who were randomized and received at least any dose of study medication. The Safety Population was used for the safety analyses.

Subjects enrolled under the original protocol (Protocol 62,745-5 [25 March 2004]) and Protocol Amendment 1 (06 December 2004), i.e., Pre-amendment, which included 2 x 510 mg ferumoxytol, 4 x 255 mg ferumoxytol, and oral iron dose groups, were used to evaluate safety only; efficacy analyses for these subjects were presented for descriptive purposes. The Pre-amendment Safety Population was defined as all subjects who were randomized and received any dose of study medication. Efficacy analyses were performed on all randomized Pre-amendment subjects; no EE Population was defined for Pre-amendment subjects.

#### **Interim Analyses**

No interim efficacy analyses were planned. However, an independent Data Monitoring Committee (DMC) periodically reviewed safety analyses to ensure continued safety of the study participants. The DMC periodic review dates were 18 October 2005, 15 February 2006, 13 June 2006, 20 October 2006, and 02 March 2007.

#### **Handling of Missing or Invalid Data**

The study used the same method as Studies 62,745-6 and 62,745-7 described above.

#### **Efficacy analyses**

The primary efficacy analysis compared the mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication across treatment groups, ferumoxytol (2 x 510 mg) versus oral iron. The primary population for analysis was the Post-amendment ITT Population. The Post-amendment Efficacy Evaluable Population was used to confirm clinical efficacy.

The primary comparison used a two-sided, two-sample t-test with a 5% Type I error. The null hypothesis was that both ferumoxytol and oral iron provide an equivalent increase in Hgb from Baseline at the Day 35 visit; ie, the mean of subject-specific Hgb changes from Baseline among ferumoxytol treated subjects is equivalent to that of subjects treated with oral iron.

#### **Changes in the Conduct of the Study or Planned Analyses**

The original protocol (Protocol 62,745-5 [25 March 2004]) was amended three times (06 December 2004, 26 October 2005, 08 June 2006) to include administrative and editorial changes, and significant changes in study requirements or analyses. Only changes in study requirements or analyses are presented in this summary.

#### **Changes in the Conduct of the Study**

##### **Amendment 1 (06 December 2004)**

The following significant changes in the investigational plan for this study were added by Protocol Amendment 1 (06 December 2004):

- Specified that subjects re-entering the study during the Readmission Phase would receive the 2 x 510 mg ferumoxytol dose after meeting the inclusion criteria of  $\leq 12$  g/dL Hgb performed by the central laboratory at Day 35 if scheduling permits, or on Day -5R
- Updated the ESA dosing by indicating that it could be adjusted  $\pm 25\%$  at the discretion of the Investigator

##### **Amendment 2 (26 October 2005)**

The following significant changes in the investigational plan for this study were added by Protocol Amendment 2 (26 October 2005):

- The study population was amended to enroll up to 290 evaluable subjects: 145 subjects receiving oral iron, and 145 subjects receiving two doses of 510 mg of ferumoxytol; the 4 x 255 mg ferumoxytol group was removed
- Subjects were to be pre-screened for up to 8 weeks prior to the start of dosing; the pre-screening Hgb must be  $\leq 11.5$  mg/dL

##### **Changes added by Protocol Amendment 3 (08 June 2006)**

The following significant changes in the investigational plan for this study were added by

#### Protocol Amendment 3 (08 June 2006)

- The study population was amended to enroll up to 230 randomized subjects: 115 subjects to oral iron and 115 subjects to 2 x 510 mg of ferumoxytol in a 1:1 ratio
- The sample size was calculated assuming a 0.6 g/dL difference between treatment groups in Hgb mean change from Baseline and a common SD of 1.2 g/dL. With 86 patients in the oral iron group and 86 subjects in the ferumoxytol group, there was 90% power to detect a difference using a two-sample t-test with 5% Type I error. Assuming 25% (58 subjects) drop out rate, 230 subjects needed to be randomized
- Emergency medical supplies to be readily available at study sites were specified, including epinephrine, diphenhydramine, and corticosteroids

#### Changes in the Planned Analyses for the Study

##### Changes added by Protocol Amendment 2 (26 October 2005)

The following changes in the data analysis plan for this study were added by Protocol Amendment 2 (26 October 2005):

- Additional efficacy analyses to be performed included: a comparison of the number of subjects in the 510 mg ferumoxytol group with a Hgb increase of 1 g/dL or more (responders) versus the number of responders in the oral iron group; the ability of ferumoxytol compared to oral iron to elevate both Hgb and ferritin; and the ability of ferumoxytol compared to oral iron to increase iron stores, as measured by serum ferritin
- Because changes in the use of ESA may confound the efficacy analysis, ESA dosing must remain stable during the study. The ESA dose could only be increased if there was a drop in Hgb >0.5 g/dL or a Hgb <11.0g/dL on two consecutive measurements. The ESA dose could only be decreased if Hgb  $\geq$ 13 g/dL on any two consecutive measurements

##### Changes added by Protocol Amendment 3 (08 June 2006)

The following major changes in the data analysis plan for this study were added by Protocol Amendment 3 (08 June 2006):

- Based upon guidance given at the FDA meetings in June 2005 and January 2006, the primary efficacy endpoint was amended to be a comparison across treatment groups for the mean change in Hgb from Baseline at Day 35, as determined by a two-sided, two-sample t-test with a statistical significance of  $p \leq 0.05$
- The secondary efficacy analyses were amended by adding additional specificity, including the criteria for an increase in serum ferritin (at least 160 ng/mL), the timepoints for analysis, and the specific analytic methods used

#### Changes Added to the Analyses following Approval of the Statistical Analysis Plan

Changes to the Efficacy Evaluable Population prior to database lock included:

- The window for the Hgb draw was extended from within 40 days post-dosing to 45 days post-dosing since the protocol-allowed visit windows post-dosing were Day 21 ( $\pm 5$  days) and Day 35 ( $\pm 5$  days).

- The day after which receipt of any other iron product was prohibited, Day -6, was modified to be after the Day -10 lab draw, since any iron products taken after that time would impact the analysis of Hgb.
- The Efficacy Evaluable Population was redefined from subjects having taken at least 80% to subjects having taken at least 60% the prescribed amount, to enable a comparison of efficacy between subjects who received both doses of ferumoxytol and subjects who received a comparable dose of delivered oral iron. This corresponds to an administered dose of 2500 mg (50 pills of 50 mg each) which, factoring in the incomplete gastrointestinal absorption of oral iron (40%), represents a minimum delivered amount of 1000 mg iron.

### **Study 62,745-8**

#### **Study Objectives**

The objective of this study was to compare the safety of a single 510 mg dose of ferumoxytol administered IV versus a single dose of placebo (normal saline administered IV) in subjects with all stages of CKD (stages 1-5 and 5D).

#### **Study Design**

This was a randomized, double-blind, placebo-controlled, multicenter, crossover study to evaluate the safety of a single 510 mg dose of ferumoxytol in subjects with all stages of CKD (stages 1-5 and 5D).

#### **Study Population**

##### **Inclusion Criteria**

For inclusion into the trial, patients of all ethnic populations and races were required to fulfill all of the following criteria as taken from the protocol:

1. Male or female chronic kidney disease patients  $\geq 18$  years of age
2. Patient is able and willing to provide written informed consent and HIPAA Authorization to participate in the study
3. Have chronic kidney disease per K/DOQI guidelines
4. Have a Hgb of  $\geq 9.0$  and  $\leq 12.5$  g/dL at Day -5 ( $\pm 2$  days)
5. Have a transferrin saturation (TSAT)  $\leq 50\%$  at Day -5 ( $\pm 2$  days)
6. Have a serum ferritin of  $\leq 600$  ng/mL at Day -5 ( $\pm 2$  days)
7. Have been undergoing dialysis for at least 90 days if entering the study as a dialysis patient
8. Have a negative serum pregnancy test result prior to dosing, unless the patient is 2 years postmenopausal, or has had a documented tubal ligation or total hysterectomy, confirmed by the PI

##### **Exclusion Criteria**

Any of the following conditions were regarded as a criterion for exclusion from the trial:

1. Women who are pregnant, capable of becoming pregnant and not practicing an acceptable form of birth control, or are breast feeding.

2. Patients currently participating in a clinical trial with another investigational drug or device or who have received an investigational drug or device within 30 days of enrollment in this study.
3. Patients on parenteral or oral iron therapy between the Day -5 ( $\pm 2$  days) visit and until the completion of the study.
4. Patients that have other causes of anemia other than iron deficiency (eg, SLE, myeloma, rheumatoid arthritis).
5. Major surgery within one month prior to enrollment in this study or anticipated surgery while the patient is on the study.
6. Patients with active infections requiring ongoing treatment.
7. Patients who have had a malignancy (except for non-melanoma cancer of the skin) unless the patient has received curative treatment and has been disease free for  $\geq 2$  years.
8. Patients who receive blood transfusions within 2 weeks prior to enrollment and until completion of the study.
9. Patients who the Investigator determines have a medical status that would preclude the patient's participation in this protocol.
10. Patients with any allergies to iron products or multiple (two or more) drug allergies.

#### **Study Treatments**

After qualifying for entry into the study, subjects were randomly assigned to one of two treatment sequences and received double-blind study medication as follows.

- Sequence 1: A single 510 mg dose of ferumoxytol administered IV on Day 0 followed by a single dose of placebo (IV normal saline) administered on Day 7 ( $\pm 2$  days), or
- Sequence 2: A single dose of placebo (IV normal saline) administered on Day 0 followed by a single 510 mg dose of ferumoxytol administered IV on Day 7 ( $\pm 2$  days).

#### **Study Plan**

During the 14-day double-blind treatment period, safety was assessed at study visits scheduled on Day 0 and on Days 7 and 14. Follow-up safety monitoring was also conducted either by telephone or by study visit on the day after ferumoxytol or placebo was administered.

#### **Time and Events Schedule**

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Event	pre-Screen	Day -5 (±2 days)	Day 0	Day 1 <sup>a</sup>	Day 7 (±2 days)	Day 8 <sup>a</sup>	Day 14 (±2 days)	Early Termination
Hgb ≥9 and ≤12.5 g/dL and Serum Ferritin ≤600 ng/mL within 8 weeks prior to Day 0	X							
Informed Consent/HIPAA		X						
Hematology <sup>b</sup>		X			X <sup>c</sup>		X	X
Iron Panel <sup>b</sup>		X			X <sup>c</sup>		X	X
Clinical Chemistry <sup>b</sup>		X <sup>d</sup>			X <sup>c</sup>		X	X
Physical Examination <sup>e</sup>			X		X		X	X
Medical History <sup>f</sup>			X					
Administration of First Dose of Study Medication <sup>g</sup>			X					
Administration of Second Dose of Study Medication <sup>h</sup>					X			
Vital Signs <sup>i</sup>		X	X <sup>j</sup>		X <sup>j</sup>		X	X
Concomitant Medications		X	X	X	X	X	X	X
Adverse Event Monitoring <sup>k</sup>			X	X	X	X	X	X

- a. Follow-up safety monitoring was conducted after IV administration of each dose of study medication (ferumoxytol or placebo) on the calendar day after dosing either in person (office visit) or by telephone.
- b. A central laboratory /  was used for all clinical laboratory tests. For hemodialysis subjects, all laboratory measurements were taken prior to the initiation of hemodialysis.
- c. The Day 7 laboratory draw was done prior to administration of the second dose of study medication (ferumoxytol or placebo).
- d. Included a serum pregnancy laboratory draw for women of childbearing potential.
- e. A physical examination was conducted prior to dosing with each test article, on Day 14, and at Early Termination.
- f. Medical history was completed after the qualifying pre-dose laboratory results were obtained and prior to the start of dosing (ie, between Day -5 and Day 0). Current illnesses and symptoms as well as height and weight (including a dry weight for subjects on hemodialysis and peritoneal dialysis) were reviewed and recorded. All medications were listed.
- g. The order of dosing was determined by accessing ClinPhone (see Section 9.4.3): 17 ml of either a single, blinded dose of ferumoxytol (510 mg) or placebo (normal saline). Any person except for the Test Article Administrator(s) (TAA) was to remain blinded to the identity of study medication. Study medication was administered IV at a rate of 1 mL/second (17 seconds), but not >60 seconds. Subjects on hemodialysis were dosed after 60 minutes into the hemodialysis session and prior to the last 60 minutes of hemodialysis. Subjects on peritoneal dialysis were treated similarly to subjects with CKD stages 1-5.
- h. The second dose of study medication was the alternate from the first dose of study medication. Any person except for the TAA(s) was to remain blinded to the identity of study medication. Study medication was to be administered at a rate of 1 mL/second (17 seconds), but not >60 seconds. Subjects on hemodialysis were dosed after 60 minutes into the hemodialysis session and prior to the last 60 minutes of hemodialysis. Subjects on peritoneal dialysis were treated similarly to subjects with CKD stages 1-5.
- i. Blood pressure, temperature, heart rate and respiration rate.
- j. For subjects not on hemodialysis: within 30 (±5) minutes before dosing and then at 5, 10, 20, 30 (±5) minutes, and 60 (±5) minutes after dosing. For subjects on hemodialysis, vital signs were measured before and after each hemodialysis procedure and administration of study medication as follows: 15 (±5) minutes prior to the start of hemodialysis; when 60 minutes into hemodialysis, vital signs were measured 15 (±5) minutes prior to dosing, and then at 5, 10, 20, 30 (±5) minutes, and 60 (±5) minutes after dosing.
- k. Adverse events that occurred from the time of administration of study medication (ferumoxytol or placebo) on Day 0 until the administration of study medication on Day 7 (±2 days) (ferumoxytol or placebo) were assigned a relationship to the drug administered on Day 0. Adverse events that occurred from the time of administration of study medication on Day 7 (±2 days) until the final visit on Day 14 (±2 days) were assigned a relationship to the study medication administered on Day 7. Serious adverse events (SAEs) were reported from the time of consent until 30 days following the last study visit; SAEs that occurred after Day 14 were attributed to the second test article.

b(4)

### Safety Assessments

The safety of ferumoxytol was assessed on the basis of AEs, clinical laboratory tests (hematology, clinical chemistry, and iron panel), vital sign measurements (blood pressure, heart rate, respiration rate, and temperature), and physical examinations. Safety evaluations were performed for all subjects enrolled in the study.

### **Collection of Adverse Events Related to Vital Signs and Hypersensitivity**

Vital signs were monitored during the study. Adverse Events relating to vital signs were recorded on the CRF. Subjects were closely monitored during and after study medication (ferumoxytol or placebo) administration. Subjects were observed for any signs and symptoms of hypersensitivity reactions, hypotension, or acute effects for 60 ( $\pm 5$ ) minutes after each study medication administration. Adverse events potentially associated with hypersensitivity reactions and hypotension, as described below, were recorded and described on the AE CRF page.

Adverse events potentially associated with hypersensitivity reactions included one or more of the following:

- Urticaria and/or rash with or without pruritus
- Facial edema
- Laryngeal edema or pharyngeal edema
- Asthma or other allergic reactions

Hypotension was defined as:

- A decrease in systolic blood pressure (SBP) of  $>20$  mmHg that results in a value less than 90 mmHg
- A decrease in diastolic blood pressure (DBP) of  $>15$  mmHg that results in a value less than 50 mmHg

### **Vital Signs**

Vital signs (respiration rate, temperature, heart rate, blood pressure) were obtained using a standard procedure with consistency in the position of each subject during all measurements (ie, seated or supine).

### **Vital Sign Monitoring in Non-hemodialysis Subjects with CKD Stages 1-5 and 5D on Peritoneal Dialysis**

Vital signs were obtained from subjects with CKD stages 1-5 and subjects with stage 5D who were on peritoneal dialysis before and after dosing administration as follows:

- PRE-DOSE (all doses): Within 30 minutes before administration of study medication (ferumoxytol or placebo)
- POST-DOSE (all doses): 5, 10, 20, 30 ( $\pm 5$ ) minutes, and 60 ( $\pm 5$ ) minutes after administration of study medication (ferumoxytol or placebo)

### **Vital Sign Monitoring in Subjects with CKD Stage 5D on Hemodialysis**

Vital signs were obtained from subjects with CKD stage 5D on hemodialysis before and after each hemodialysis procedure and study medication administration as follows:

- PRE-HEMODIALYSIS: 15 ( $\pm 5$ ) minutes before initiation of hemodialysis
- PRE-DOSE: 60 minutes into the hemodialysis session, vital signs were obtained 15 ( $\pm 5$ ) minutes prior to study medication administration
- POST-DOSE: 5, 10, 20, 30 ( $\pm 5$ ) minutes, and 60 ( $\pm 5$ ) minutes after administration of study medication (ferumoxytol or placebo)

## **Statistical and Analytical Plans**

### **Analyzable Populations**

The Safety Population was defined as all subjects who were randomized and had at least one dose of study medication (either ferumoxytol or placebo). The Safety Population was used for all safety analyses.

### **Statistical Analysis of Safety**

Adverse events were summarized by treatment group (ferumoxytol or placebo) regardless of the treatment sequence. Adverse events that occurred from the time of the first injection of study medication (ferumoxytol or placebo) on Day 0 through the day of the second injection were attributed to the drug administered on Day 0. Adverse events that occurred following the second injection of study medication (ferumoxytol or placebo) on Day 7 ( $\pm 2$  days) until the end of the study (Day 14) were assigned a relationship to the drug administered on Day 7. Adverse events that occurred on the day of the second injection that could not be definitively assigned to a treatment based on the time of event relative to the time of injection were conservatively attributed to ferumoxytol, after the conclusion of the study. SAEs that occurred after Day 14 were attributed to the second test article.

### **Determination of Sample Size**

A sufficient number of subjects were enrolled to result in 750 randomized subjects who had the opportunity to receive both ferumoxytol and placebo.

## **Changes in the Conduct of the Study or Planned Analyses**

### **Protocol Changes**

The protocol was amended twice to include administrative and editorial changes and changes in study requirements or analyses.

### **Summary of Amendment 1 (26 October 2005)**

Protocol Amendment 1 (26 October 2005) implemented the following major changes to the protocol:

- Study Population:
  - The number of evaluable subjects receiving both ferumoxytol and placebo was updated from 500 to 1100 subjects.
- Inclusion Criteria:
  - “Have a hemoglobin of  $\geq 9.0$  and  $\leq 12.5$  g/dL at Day -5 ( $\pm 2$  days)” replaced the criterion “Patients with hemoglobin values  $\geq 9$  or  $\leq 13$  g/dL.”
  - “The following new inclusions were in effect with this amendment: “Have been undergoing dialysis for at least 90 days if entering the study as a dialysis patient.”
- Exclusion Criteria:
  - The following new exclusions were in effect with this amendment:

- Patients on parenteral or oral iron therapy within 5 days ( $\pm 2$  days) prior to dosing and until completion of the study.
- Patients with any allergies to iron products or multiple (two or more) drug allergies.
- New requirements were added for monitoring subjects during and up to 60 ( $\pm 5$ ) minutes after each administration of study medication for signs and symptoms of hypersensitivity reactions or hypotension.
- Dosing and Administration:
  - The timing of study drug administration for subjects with CKD stage 5D who were on hemodialysis was specified: “Hemodialysis patients are to be dosed while stable, any time after 60 minutes ( $\pm 15$  minutes) into the dialysis procedure. Both the time of the start of dialysis and the time of dosing must be recorded.”
- Adverse Event Monitoring and Recording:
  - New text was added to clarify the monitoring of patients for adverse reactions during and after administration of study medication, including “any signs and symptoms of hypersensitivity reactions and hypotension during and up to 60 ( $\pm 5$ ) minutes after test article administration.” Hypersensitivity events and hypotension were clearly defined.

#### **Summary of Amendment 2 (08 June 2006)**

- The number of randomized subjects receiving both ferumoxytol and placebo was updated from 1100 to 750 subjects.
- The observation period for evaluation of hypersensitivity events relative to study medication administration (ie, “for 60 minutes ( $\pm 5$  minutes) after each test article administration”) was clarified.

#### **Changes in the Planned Analysis of the Study**

There were no changes to the planned analysis of the study.

## **6 Review of Efficacy**

### **Efficacy Summary**

Three randomized controlled pivotal trials (62,745-6 and 62,745-7, and 62,745-5) were conducted to support the efficacy of ferumoxytol injection 510 mg for 2 doses for the proposed indication for the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD). Two studies were in patients with chronic kidney disease stage 1-5 (62,745-6 and 62,745-7) and one study was in patients with CKD stage 5D undergoing hemodialysis (62,745-5). All three clinical studies were designed as randomized, open-label, oral iron-controlled superiority trials. The mean change in hemoglobin level from baseline to Day 35 was used as the primary efficacy endpoint in all 3 trials. The results show that the difference in mean change in hemoglobin from baseline between ferumoxytol and oral iron groups was statistically significant based on ITT and evaluable populations in Studies 62,745-6, 62,745-7, and 62,745-5 post-amendment ( $p < 0.01$ ). The mean increase in hemoglobin on Day 35 ranged from 0.82 g/dL to

1.22 g/dL in ferumoxytol groups as compared to a range of 0.16 g/dl to 0.52 g/dL in oral iron groups in ITT populations, with a similar result in evaluable populations. The results from the secondary efficacy endpoints analyses including hemoglobin response rate and serum ferritin level were consistent with the primary efficacy analysis results. Subgroup analysis including age, gender, race, and geographic region were consistent with the primary efficacy analysis results.

## 6.1 Indication

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

### 6.1.1 Methods

Three randomized controlled pivotal trials were reviewed for efficacy for the proposed indications. These included two studies in patients with chronic kidney disease stage 1-5 and one study in patients with CKD stage 5D undergoing hemodialysis. These three trials are listed below.

**Summary of clinical studies for the proposed indications**

Study Populations	Clinical Studies	Number of patients enrolled
CKD Stage 1-5	62,745-6	304
	62,745-7	304
CKD Stage 5D Hemodialysis	62,745-5 Pre-amendment	148
	62,745-5 Post-amendment	230

Reviewer's table

All three clinical studies were randomized, controlled, open-label studies. Oral iron was used as active control treatment for all studies. All three studies were designed as superiority trials as comparing to oral iron. The following table shows the study design, treatment and major inclusion criteria in these 3 clinical trials.

#### Study design, treatment and major inclusion criteria in clinical trials

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Study Populations	Studies	Study design	Ferumoxytol group	Oral Iron	Major inclusion criteria
CKD Stage 1-5	62,745-6	Randomized, open-label, parallel group, superiority trial  Randomization: 3:1 ratio	228  510 mg for 2 doses within 5 days ( $\pm 3$ days)	76  Ferro-Sequels®: 2 tablets twice daily (200 mg oral iron/day) for 21 days	Hb $\leq 11.0$ g/dL at Day -10 ( $\pm 4$ days) and Day -5 ( $\pm 3$ days)  TSAT $\leq 30\%$ within 5 days ( $\pm 3$ days) prior to dosing.  Serum ferritin of $\leq 600$ ng/mL within 5 days ( $\pm 3$ days) prior to dosing.
	62,745-7		227  510 mg for 2 doses within 5 days ( $\pm 3$ days)	77  Ferro-Sequels®: (oral iron) 2 tablets twice daily for 21 days	
CKD Stage 5D Hemodialysis	62,745-5 Pre-amendment	Randomized, open-label, parallel group, 2 dosing regimens, superiority trial  Randomization: 3:3:1 ratio	126  510 mg for 2 doses within 7 days: n=64  255 mg for 4 doses within 14 days: n=62	22  Ferro-Sequels®: 2 tablets twice daily (200 mg oral iron/day) for 21 days	Hgb $\leq 12$ g/dL at three different time points within 4 weeks of dosing.  TSAT $\leq 30\%$ and a ferritin $\leq 600$ ng/mL within 5 $\pm 2$ days  Received stable supplemental erythropoietin therapy ( $\pm 25\%$ of current dose) for at least 2 weeks.
	62,745-5 Post-amendment		114  510 mg for 2 doses within 5 days ( $\pm 3$ days)	116  Ferro-Sequels®: 2 tablets twice daily (200 mg oral iron/day) for 21 days	

Reviewer's table

The definition of iron deficiency anemia was similar in the three clinical trials. Based on the inclusion criteria at study entry, hemoglobin was required to be  $\leq 11.5$  g/dL (except 62,745-5 pre-amendment where  $< 12$  g/dl was used); TSAT was required to be  $< 30\%$ ; and ferritin was required to be  $\leq 600$  ng/mL in all 3 studies. Stable supplemental EPO therapy for at least 10 ( $\pm 4$ ) days prior to dosing and expectation to remain on a stable dose for the duration of the study were

required for hemodialysis patients and for patients with CKD stage 1-5 who were on EPO prior to the studies.

## 6.1.2 Demographics and baseline characteristics

### Demographics

The following table shows the demographics of study patients in the three studies. There were similar demographics between ferumoxytol and oral iron groups in each study. Overall, the mean age for randomized subjects (n=944) was 63 years and was similar among treatment groups (2 x 510 mg ferumoxytol, 63.4 years; 4 x 255 mg ferumoxytol, 58.6 years; and oral iron, 63.2 years). Overall, 56.1% of the subjects were female, which was similar among treatment groups (2 x 510 mg ferumoxytol, 57.4%; 4 x 255 mg ferumoxytol, 56.7%; and oral iron, 53.4%). About half of study patients were Caucasian (52.0%) with a similar distribution in the 2 x 510 mg ferumoxytol (54.9%) and oral iron (49.5%) treatment groups; however, Caucasians represented 35.0% of the 4 x 255 mg ferumoxytol treatment group. Black or African-American subjects comprised 42.2% of subjects enrolled across the studies with 39.5 % in the 2 x 510 mg ferumoxytol group, 53.3% in the 4 x 255 mg ferumoxytol group and 45.9% in the oral iron group.

### Demographics, All Randomized Subjects (Modified ITT Population)

	N	Age (Years) Mean±SD	Gender (%) Male/Female	Race (%) C/B/O <sup>a</sup>
<b>Protocol 62,745-6</b>				
Ferumoxytol 2 x 510 mg	217	64.99±14.34	41.0/59.0	58.1/33.2/8.8
Oral Iron 200 mg/day	75	63.43±10.85	32.0/68.0	60.0/37.3/2.7
<b>Protocol 62,745-7</b>				
Ferumoxytol 2 x 510 mg	220	65.58±14.14	41.4/58.6	66.8/31.8/1.4
Oral Iron 200 mg/day	74	67.57±13.19	37.8/62.2	62.2/33.8/4.1
<b>Post-amendment Protocol 62,745-5</b>				
Ferumoxytol 2 x 510 mg	110	59.19±14.30	49.1/50.9	32.7/60.0/7.3
Oral Iron 200 mg/day	113	60.75±13.04	62.8/37.2	35.4/57.5/7.1
<b>Pre-amendment Protocol 62,745-5</b>				
Ferumoxytol 2 x 510 mg	58	57.10±14.15	41.4/58.6	39.7/51.7/8.6
Ferumoxytol 4 x 255 mg	60	58.55±14.86	43.3/56.7	35.0/53.3/11.7
Oral Iron 200 mg/day	17	60.18±11.51	41.2/58.8	41.2/58.8/0.0
<b>All Protocols</b>				
Ferumoxytol 2 x 510 mg	605	63.39±14.55	42.6/57.4	54.9/39.3/5.8

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Ferumoxytol 4 x 255 mg	60	58.55±14.86	43.3/56.7	35.0/53.3/11.7
Oral Iron 200 mg/day	279	63.24±12.70	46.6/53.4	49.5/45.9/4.7
<b>All Subjects</b>	944	63.04±14.08	43.9/56.1	52.0/42.2/5.8

a. Race: C=Caucasian; B=Black or African-American; O=Other (Asian, Pacific Islander, Native Hawaiian, American Indian, and Alaska Native).

Abbreviation: SD=Standard deviation.

Sponsor's table in summary of clinical efficacy

### CKD Stage

The following table summarizes the CKD stage in study patients in Studies 62,745-6 and 62,745-7. Most patients were in CKD stage 3 or 4 in both studies and the distributions in CKD stage were similar between Ferumoxytol and oral iron groups in these two studies.

#### CKD Stages in Studies 62,745-6 and 62,745-7

Sponsor's table in summary of clinical efficacy

### ESA therapy

The following table shows the ESA therapy in 3 efficacy trials. In Studies 62,745-6 and 62,745-7

	N	Stage 1 or 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)
<b>Study 62,745-6</b>					
Ferumoxytol 2 x 510 mg	217	4 (1.8)	78 (35.9)	101 (46.5)	30 (13.8)
Oral Iron 200 mg/day	75	2 (2.7)	29 (38.7)	36 (48.0)	8 (10.7)
<b>Study 62,745-7</b>					
Ferumoxytol 2 x 510 mg	220	3 (1.4)	84 (38.2)	103 (46.8)	25 (11.4)
Oral Iron 200 mg/day	74	1 (1.4)	29 (39.2)	39 (52.7)	4 (5.4)

in patients with CKD stage 1-5, 30-40% of patients received stable ESA therapy, 50-60% of patients were not receiving ESA, and <7% of patients started ESA or had ESA dose changed >25%. In Study 62,745-5 in patients undergoing hemodialysis, about 78% of patients who enrolled post-amendment received stable ESA therapy and 22% of patients started ESA or had dose changed >25%. A slightly lower percentage of patients who enrolled pre-amendment period were on stable ESA therapy. There was a similar distribution in ESA therapy between Ferumoxytol and oral iron groups.

#### ESA Therapy

	N	Not Receiving ESA Therapy n (%)	Received Stable ESA Therapy n (%)	Started ESA or Dose Change >25% n (%)
Study 62,745-6				
Ferumoxytol 2 x 510 mg	217	138 (63.6)	68 (31.3)	11 (5.1)
Oral Iron 200 mg/day	75	43 (57.3)	27 (36.0)	5 (6.7)
Study 62,745-7				
Ferumoxytol 2 x 510 mg	220	129 (58.6)	84 (38.2)	7 (3.2)
Oral Iron 200 mg/day	74	41 (55.4)	30 (40.5)	3 (4.1)
Study 62,745-5 Post-amendment				
Ferumoxytol 2 x 510 mg	110	0	86 (78.2)	24 (21.8)
Oral Iron 200 mg/day	113	0	88 (77.9)	25 (22.1)
Study 62,745-5 Pre-amendment				
Ferumoxytol 2 x 510 mg	58	0	29 (50.0)	29 (50.0)
Ferumoxytol 4 x 255 mg	60	0	34 (56.7)	26 (43.3)
Oral Iron 200 mg/day	17	0	12 (70.6)	5 (29.4)

Sponsor's table in summary of clinical efficacy

### 6.1.3 Patient Disposition

The following table shows the disposition of study patients in the three pivotal studies. More than 85% of study patients completed the study in all three studies (89% [271/304] in 62,745-6, 93% [282/304] in 62,745-7, 85% [125/148] in 62,745 pre-amendment, and 87% [201/230] in 62,745-5 post-amendment).

Overall, 879 (89.1%) subjects, who were randomized across the pivotal studies, completed the study including 579 (91.5%) subjects in the 2 x 510 mg ferumoxytol treatment group, 55 (88.7%) subjects in the 4 x 255 mg ferumoxytol treatment group, and 245 (84.2%) subjects in the oral iron treatment group.

The most common reason for withdrawal across all treatment groups was AE, which led to the withdrawal of 9 of 633 (1.4%) subjects in the 2 x 510 mg ferumoxytol treatment group, 3 of 62 (4.8%) subjects in the 4 x 255 mg ferumoxytol treatment group, and 25 of 291 (8.6%) subjects in the oral iron treatment group.

In all 3 pivotal studies, 986 subjects were randomized and 944 (95.7%) subjects received study medication and were included in the modified ITT population. This population included 605 (95.6%) subjects in the 2 x 510 mg ferumoxytol treatment group, 60 (96.8%) subjects in the 4 x 255 mg ferumoxytol treatment group, and 279 (95.9%) subjects in the oral iron treatment group.

**Subject Disposition in All Randomized Subjects in Three Studies**

	Randomized Subjects  N	Withdrawn Prior to Initial Dose n (%)	Modified ITT Population n (%)	Withdrawn Post-initial Dose by Reason n (% of Randomized Subjects)					Completed Study n (%)
				AEs	Lost to Follow- Up	Death	Withdrew Consent	Other <sup>a</sup>	
<b>Protocol 62,745-6</b>									
Ferumoxytol 2 x 510 mg	228	11 (4.8)	217 (95.2)	4 (1.8)	2 (0.9)	0	1 (0.4)	2 (0.9)	208 (91.2)
Oral Iron 200 mg/day	76	1 (1.3)	75 (98.7)	9 (11.8)	1 (1.3)	0	0	2 (2.6)	63 (82.9)
<b>Protocol 62,745-7</b>									
Ferumoxytol 2 x 510 mg	227 <sup>b</sup>	7 (3.1)	220 (96.9)	1 (0.4)	0	2 (0.9)	1 (0.4)	1 (0.4)	215 (94.7)
Oral Iron 200 mg/day	77	3 (3.9)	74 (96.1)	7 (9.1)	0	0	0	0	67 (87.0)
<b>Post-amendment Protocol 62,745-5</b>									
Ferumoxytol 2 x 510 mg	114	4 (3.5)	110 (96.5)	4 (3.5)	0	1 (0.9)	0	3 (2.6)	102 (89.5)
Oral Iron 200 mg/day	116	3 (2.6)	113 (97.4)	8 (6.9)	0	1 (0.9)	1 (0.9)	4 (3.4)	99 (85.3)
<b>Pre-amendment Protocol 62,745-5</b>									
Ferumoxytol 2 x 510 mg	64	6 (9.4)	58 (90.6)	0	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	54 (84.4)
Ferumoxytol 4 x 255 mg	62	2 (3.2)	60 (96.8)	3 (4.8)	0	0	0	2 (3.2)	55 (88.7)
Oral Iron 200 mg/day	22	5 (22.7)	17 (77.3)	1 (4.5)	0	0	0	0	16 (72.7)
<b>All Protocols</b>									
Ferumoxytol 2 x 510 mg	633	28 (4.4)	605 (95.6)	9 (1.4)	3 (0.5)	4 (0.6)	3 (0.5)	7 (1.1)	579 (91.5)
Ferumoxytol 4 x 255 mg	62	2 (3.2)	60 (96.8)	3 (4.8)	0	0	0	2 (3.2)	55 (88.7)
Oral Iron 200 mg/day	291	12 (4.1)	279 (95.9)	25 (8.6)	1 (0.3)	1 (0.3)	1 (0.3)	6 (2.1)	245 (84.2)
<b>All Subjects</b>	<b>986</b>	<b>42 (4.3)</b>	<b>944 (95.7)</b>	<b>37 (3.8)</b>	<b>4 (0.4)</b>	<b>5 (0.5)</b>	<b>4 (0.4)</b>	<b>15 (1.5)</b>	<b>879 (89.1)</b>

a. Other reasons for withdrawal include protocol violation, lack of compliance, and administrative reasons for withdrawal.

b. Includes one subject at Site 146 (Subject 105) that was randomized in error and was re-randomized to Subject 106 in the ferumoxytol treatment group.

Abbreviation: ITT=Intent-to-treat.

Sponsor's table in summary of clinical efficacy

**Treatment compliance**

The following table presents oral iron treatment compliance in three studies. Proportion of patients at least 80% compliant ranged from 77.9% to 89.2% among three studies with the lowest rate in hemodialysis patients in Study 62,745.

### Oral iron Compliance (200 mg/day) in 3 Phase 3 Studies

	62,745-6 N=75	62,745-7 N=74	62,745-5 Post-amendment N=113	62,745-5 Pre-amendment N=17
Oral iron administration	n (%)	n (%)	n (%)	n (%)
At least 80% compliant ( $\geq 3360$ mg iron)	65 (86.7)	66 (89.2)	88 (77.9)	14 (82.4)
At least 60% compliant ( $\geq 2500$ mg iron)	69 (92.0)	69 (93.2)	102 (90.3)	16 (94.1)

Reviewer's table

#### 6.1.4 Analysis of Primary Endpoint(s)

In all 3 pivotal trials for efficacy, the mean change in hemoglobin level from baseline to Day 35 was used as the primary efficacy endpoint. The following tables show the efficacy results based on the primary efficacy analysis in 3 trials. The difference in mean change in hemoglobin from baseline at Day 35 between Ferumoxytol and oral iron groups was statistically significant based on ITT and evaluable populations in Studies 62,745-6, 62,745-7, and 62,745-5 post-amendment ( $p < 0.01$ ). The mean increase in hemoglobin on Day 35 ranged from 0.82 g/dL to 1.22 g/dL in ferumoxytol groups as compared a range of 0.16 g/dL to 0.52 g/dL in oral iron groups in ITT populations, with similar results in evaluable populations. In Study 62,745 pre-amendment, the differences in mean changes in hemoglobin from baseline were not statistically significant among two ferumoxytol and oral iron groups. The mean increases in hemoglobin from baseline to Day 35 were 0.71 and 0.87 g/dL in two ferumoxytol groups as compared to 0.31 g/dL in the oral iron group.

#### Primary Efficacy Endpoint Analysis in Study 62,745-6 in ITT and Efficacy Evaluable Populations

Primary Efficacy Endpoint	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day	
	n	Mean $\pm$ SD	n	Mean $\pm$ SD
<b>Hgb (g/dL): ITT Population</b>	N=228		N=76	
Baseline	228	9.96 $\pm$ 0.69	76	9.95 $\pm$ 0.78
Day 35	206	10.88 $\pm$ 1.27	63	10.15 $\pm$ 1.07
Mean change from Baseline at Day 35	228	0.82 $\pm$ 1.24	76	0.16 $\pm$ 1.02
p-value for treatment difference	<0.001			
<b>Hgb (g/dL): EE Population</b>	N=181		N=55	

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Baseline	181	9.99±0.67	55	10.05±0.72
Day 35	181	10.84±1.27	55	10.11±1.07
Mean change from Baseline at Day 35	181	0.86±1.23	55	0.06±1.09
p-value for treatment difference	<0.001			

Sponsor's table in individual study report

**Primary Efficacy Endpoint Analysis in Study 62,745-7  
 in ITT and Efficacy Evaluable Populations**

Primary Efficacy Endpoint	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day	
	n	Mean±SD	n	Mean±SD
<b>Hgb (g/dL): ITT Population</b>	N=226		N=77	
Baseline	225	9.85±0.77	77	9.94±0.73
Day 35	214	11.15±1.33	68	10.55±1.14
Mean change from Baseline at Day 35	226	1.22±1.25	77	0.52±0.98
p-value for treatment difference	<0.001			
<b>Hgb (g/dL): EE Population</b>	N=183		N=54	
Baseline	183	9.90±0.71	54	9.94±0.79
Day 35	183	11.25±1.29	54	10.65±1.14
Mean change from Baseline at Day 35	183	1.35±1.25	54	0.71±1.01
p-value for treatment difference	<0.001			

Sponsor's table in individual study report

**Primary Efficacy Endpoint Analysis in Study 62,745-5 Post-amendment  
 in ITT and Efficacy Evaluable Populations**

Primary Efficacy Endpoint	n	Mean±SD	n	Mean±SD
<b>Hgb (g/dL): ITT Population</b>	N=114		N=116	
Baseline	114	10.59±0.67	115	10.69±0.57
Day 35	102	11.72±1.20	101	11.22±1.22
Mean change from Baseline at Day 35	114	1.02±1.13	116	0.46±1.06
p-value for treatment difference	<0.001			
<b>Hgb (g/dL): EE Population</b>	N=65		N=64	
Baseline	65	10.66±0.59	64	10.70±0.62
Day 35	65	11.79±1.07	64	11.16±1.02
Mean change from Baseline at Day 35	65	1.13±1.01	64	0.46±0.86

p-value for treatment difference	<0.001
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Sponsor's table in individual study report

**Primary Efficacy Endpoint Analysis in Study 62,745-5 Pre-amendment  
 in Randomized Population**

Hgb (g/dL)	Ferumoxytol 2x 510 mg N=64		Ferumoxytol 4 x 255 mg N=62		Oral Iron 200 mg/day N=22	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
Baseline a	64	11.08±0.72	62	11.11±0.58	22	11.19±0.63
Day 35	54	11.91±0.97	55	12.09±1.13	16	11.56±0.98
Mean change from Baseline at Day 35	64	0.71±1.00	62	0.87±1.14	22	0.31±0.82
p-value for treatment difference	0.10					

Sponsor's table in individual study report

**6.1.5 Analysis of Secondary Endpoints(s)**

Response rate based on the proportion of patients with hemoglobin increase  $\geq 1$ g/dL at Day 35, mean change in ferritin at Day 21, mean change in TSAT at Day 35, and others were used as the secondary efficacy endpoints. The following tables show the efficacy results based on the secondary efficacy endpoints. There were statistically significant differences in these secondary endpoints between Ferumoxytol and oral iron groups, which were consistent with the efficacy results based on the primary efficacy endpoint.

**Secondary Efficacy Endpoint Analysis in Study 62,745-6 in ITT Population**

Secondary Efficacy Endpoint (ITT Population)	Ferumoxytol N=228	Oral Iron N=76	p-value
Proportion of Hgb responders at Day 35 (increase $\geq 1.0$ g/dL from baseline), N (%)	89 (39.0%)	14 (18.4%)	0.001
Proportion of Hgb and ferritin responders (increase $\geq 160$ ng/mL from baseline), N (%)	98 (43.0%)	0 (0.0%)	<0.001
Mean change from Baseline in ferritin at Day 21, mean $\pm$ SD ng/mL	518.08±331.86	6.47±47.16	<0.001

Sponsor's table in individual study report

**Secondary Efficacy Endpoints Analysis in Study 62,745-7 in ITT Population**

Secondary Efficacy Endpoint (ITT Population)	Ferumoxytol N=226	Oral Iron N=77	p-value a
Proportion of Hgb responders at Day 35	117 (51.8%)	15 (19.5%)	<0.001

(increase $\geq$ 1.0 g/dL from baseline), N (%)			
Proportion of Hgb and ferritin responders (increase $\geq$ 160 ng/mL from baseline), N (%)	115 (50.9%)	0 (0.0%)	<0.001
Mean change from Baseline in ferritin at Day 21, mean $\pm$ SD ng/mL	412.58 $\pm$ 247.95	4.26 $\pm$ 48.22	<0.001

Sponsor's table in individual study report

### Secondary Efficacy Endpoints Analysis in Study 62,745-5 Post-amendment in ITT Population

Secondary Efficacy Endpoint (ITT Population)	Ferumoxytol N=114	Oral Iron N=116	P-value
Proportion of Hgb responders at Day 35 (increase $\geq$ 1.0 g/dL from baseline), N (%)	56 (49.1)	29 (25.0)	0.0002
Proportion of Hgb and ferritin responders (increase $\geq$ 160 ng/mL from baseline), N (%)	53 (46.5)	1 (0.9)	<0.0001
Mean change from Baseline in ferritin at Day 21, mean $\pm$ SD ng/mL	356.66 $\pm$ 247.12	-37.56 $\pm$ 106.98	<0.0001

Sponsor's table in individual study report

### Secondary Efficacy Endpoints Analysis in Study 62,745-5 Pre-amendment in Randomized Population

	Ferumoxytol 2 x 510 mg N=64	Ferumoxytol 4 x 255 mg N=62	Oral Iron 200 mg/day N=22	
Responders	n (%)	n (%)	n (%)	p-value a
Hgb Responders at Day 35 (increase $\geq$ 1.0 g/dL from baseline)	19 (29.7)	29 (46.8)	5 (22.7)	0.0517
Hgb and Ferritin Responders (increase $\geq$ 160 ng/mL from baseline)	23 (35.9)	32 (51.6)	0	0.0001

Sponsor's table in individual study report

#### 6.1.6 Other Endpoints

Other exploratory endpoints analyzed were mean change from baseline in hemoglobin at day 21, mean change from baseline in ferritin at day 35, iron-related analyses at day 21 and day 35 including serum iron, total iron binding capacity (TIBC) transferrin saturation (TSAT), percent hypochromic red cells, reticulocyte hemoglobin content (CHr), and reticulocyte count. These endpoints showed a statistically significant difference in the mean change from baseline between Ferumoxytol and oral iron except for no difference found in percent hypochromic red cells in all 3 studies, and reticulocyte count in 62,745-6 and 62,745, and serum iron in 62,745-5.

The following table shows the TSAT changes from baseline in 3 phase 3 studies.

**Mean Change from Baseline in Transferrin Saturation  
 in All Randomized Subjects (Modified ITT Population)**

	N	Baseline (%) Mean±SD	Week 3 Change from Baseline (%) Mean±SD	Week 5 Change from Baseline (%) Mean±SD
Protocol 62,745-6				
Ferumoxytol 2 x 510 mg	217	11.24±5.83	12.11±11.42	9.40±9.20
Oral Iron 200 mg/day	75	10.15±5.52	1.91±6.54	1.20±6.08
Protocol 62,745-7				
Ferumoxytol 2 x 510 mg	220	9.89±5.43	9.11±8.40	8.80±9.30
Oral Iron 200 mg/day	74	10.48±5.27	1.82±5.58	0.19±4.47
Post-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	110	15.71±7.20	5.65±11.69	6.35±12.49
Oral Iron 200 mg/day	113	15.96±6.31	1.27±8.48	0.53±8.15
Pre-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	58	17.28±6.49	8.50±13.56	5.92±10.78
Ferumoxytol 4 x 255 mg	60	16.95±5.41	7.43±11.67	4.71±7.98
Oral Iron 200 mg/day	17	16.24±5.54	5.32±16.84	0.18±9.20
All Protocols				
Ferumoxytol 2 x 510 mg	605	12.14±6.57	9.50±10.94	8.29±10.12
Ferumoxytol 4 x 255 mg	60	16.95±5.41	7.43±11.67	4.71±7.98
Oral Iron 200 mg/day	279	12.96±6.43	1.83±8.11	0.60±6.85

Abbreviations: ITT=Intent-to-treat; SD=standard deviation.  
 Sponsor's table in Summary of Clinical Efficacy

### 6.1.7 Subpopulations

The following table shows analysis of the mean change from baseline in Hgb at Week 5 across the demographic subgroups of age, gender, race, and geographic region. The treatment effects observed with ferumoxytol treatment were consistently greater than the effect observed with oral iron in these subgroups.

**Mean Change from Baseline in Hemoglobin by Treatment Group and Demographic Subgroups, Integrated Analyses for All Randomized Subjects (Modified ITT Population)**

	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
<b>Age</b>									
<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
<b>Gender</b>									
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
<b>Race</b>									
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
<b>Geographic Region</b>									
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

Sponsor's table in summary of clinical efficacy

**Age:**

The effect of a course of 2 x 510 mg ferumoxytol was similar across all age subgroups (ranged from 0.94 to 1.17 g/dL) with a recurring trend around 1.0 g/dL mean change from Baseline, including the ≥75 years subgroup. The positive changes observed with ferumoxytol treatment were consistently greater than the changes observed with oral iron treatment (ranged from 1.8 to 4.7 fold) that had a recurring trend around or less than 0.5 g/dL.

**Gender:**

The effect of a course of 2 x 510 mg ferumoxytol was similar across males and females and ranged from 0.93 to 1.17 g/dL, with a slightly larger treatment effect in males. The positive changes observed with ferumoxytol treatment were consistently greater (approximately 2.5 fold) than the changes observed with oral iron treatment (ranged from 0.38 to 0.47 g/dL).

**Race:**

The effect of a course of 2 x 510 mg ferumoxytol was similar across racial subgroups and ranged from 0.94 to 1.11 g/dL. The positive changes observed with ferumoxytol treatment were consistently greater (1.6 to 6.0 fold) than the changes observed with oral iron treatment (ranged from 0.16 to 0.59 g/dL). It appears that the difference of treatment effect between ferumoxytol and oral iron was smaller in African Americans as compared to Caucasians.

#### Geographic Region

The effect of a course of 2 x 510 mg ferumoxytol was similar across geographic region subgroups and ranged from 0.90 to 1.19 g/dL. The positive changes observed with ferumoxytol treatment were consistently greater (2.0 to 4.1 fold) than the changes observed with oral iron treatment (ranged from 0.22 to 0.49 g/dL).

#### Other Subgroups

The following table shows the analysis of the mean change from Baseline in Hgb at Week 5 across other subgroups including CKD stage, kidney transplant status, baseline Hgb, baseline ferritin, ESA therapy, use of ACE inhibitors/ARB and anticoagulants, and use of calcium-containing compounds for the integrated analyses across all randomized subjects in the mITT population. The positive treatment effects observed with ferumoxytol treatment were consistently greater than the effect observed with oral iron in these subgroups. It was noted that treatment effect of ferumoxytol was close to that of oral iron in patients who had Hgb between 11 and 12 g/dl at baseline.

**Mean change from baseline in hemoglobin by treatment group and other subgroup in MITT population**

	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
<b>CKD Stage</b>									
Stage 1 or 2	7	9.85±1.16	1.74±1.59	0	-	-	3	9.40±1.30	1.80±1.72
Stage 3	162	9.99±0.65	1.17±1.16	0	-	-	58	9.99±0.70	0.45±0.90
Stage 4	204	9.87±0.72	1.02±1.23	0	-	-	75	9.94±0.75	0.26±1.08
Stage 5	55	9.90±0.63	0.82±1.59	0	-	-	12	9.93±0.80	0.32±1.04
Stage 5D on HD	168	10.76±0.72	0.96±1.11	60	11.11±0.59	0.89±1.16	130	10.75±0.59	0.48±1.06
<b>Kidney Transplant Status</b>									
Native Kidney Function (Stages 1-5)	414	9.94±0.70	1.04±1.27	0	-	-	141	9.96±0.74	0.40±1.01
Functioning Kidney Transplant (Stages 1-5)	23	9.45±0.81	1.39±1.25	0	-	-	8	9.84±0.81	-0.16±1.33
Dialysis (Stage 5D)	168	10.76±0.72	0.96±1.11	60	11.11±0.59	0.89±1.16	130	10.75±0.59	0.48±1.06
<b>Baseline Hemoglobin</b>									

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<9.0 g/dL	50	8.45±0.47	1.69±1.30	0	-	-	18	8.33±0.39	0.97±1.04
9.0 to <10.0 g/dL	181	9.59±0.28	1.24±1.34	3	9.50±0.38	2.60±0.95	57	9.62±0.27	0.52±1.15
10.0 to <11.0 g/dL	289	10.44±0.27	0.90±1.14	18	10.59±0.21	1.02±1.02	148	10.49±0.27	0.31±0.95
11.0 to <12.0 g/dL	85	11.32±0.24	0.66±0.99	39	11.47±0.22	0.70±1.13	56	11.24±0.21	0.44±1.12
<b>Baseline Ferritin</b>									
<150 ng/mL	322	10.00±0.77	1.15±1.28	12	11.07±0.41	1.24±0.78	115	10.04±0.84	0.49±1.04
150 to <300 ng/mL	148	10.22±0.74	0.97±1.23	19	11.03±0.65	1.18±1.28	67	10.37±0.77	0.15±0.96
300 to <450 ng/mL	77	10.32±0.87	0.80±1.10	13	11.15±0.71	0.73±1.24	46	10.60±0.61	0.47±1.09
≥450 ng/mL	58	10.54±0.91	0.83±0.99	16	11.19±0.56	0.41±1.06	51	10.67±0.57	0.57±1.08
<b>ESA Therapy</b>									
Not Receiving ESA Therapy	267	9.94±0.70	0.79±1.05	0	-	-	84	10.04±0.70	0.20±0.77
Received Stable ESA Therapy	267	10.23±0.86	1.29±1.32	34	11.25±0.46	0.87±1.01	157	10.45±0.78	0.53±1.09
Started ESA Therapy or Dose Change >25% <sup>a</sup>	71	10.62±0.73	0.99±1.30	26	10.92±0.69	0.92±1.35	38	10.45±0.83	0.45±1.29
<b>ACE Inhibitors/ARB and Anticoagulants</b>									
ACE Inhibitors/ARB (AA only)	182	10.06±0.86	0.94±1.30	7	11.45±0.24	1.08±0.98	59	10.22±0.77	0.31±1.07
Anticoagulants (AC only)	111	10.24±0.80	1.14±1.17	23	11.26±0.52	0.98±1.12	69	10.35±0.87	0.68±0.91
ACE Inhibitors/ARB and Anticoagulants (both AA and AC)	220	10.13±0.70	1.02±1.20	18	10.97±0.45	0.36±1.15	101	10.28±0.70	0.40±1.02
Neither ACE Inhibitors/ARB Nor Anticoagulants (neither AA nor AC)	92	10.24±0.93	1.10±1.22	12	10.83±0.87	1.40±1.15	50	10.51±0.84	0.24±1.19
<b>Calcium-containing Compounds</b>									
No	436	10.08±0.79	1.07±1.27	29	11.01±0.67	0.87±1.24	162	10.22±0.81	0.43±1.01
Yes	169	10.33±0.82	0.94±1.11	31	11.20±0.49	0.91±1.09	117	10.47±0.73	0.41±1.10

a. The ESA therapy dose change could be an increase or decrease >25% at any time between Day -10 and Day 35.  
 Abbreviations: AC=anticoagulants; ACE= angiotensin converting enzyme, ARB= angiotensin receptor blocker, CKD=chronic kidney disease; ESA=Erythropoiesis stimulating agent(s); MITT=modified intent-to-treat; SD=standard deviation.  
 Sponsor's table in summary of clinical efficacy

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Ferumoxytol 510 mg for 2 doses was studied in all three pivotal trials and is the sponsor's proposed dosing regimen for labeling. No dose response phase 3 studies were conducted except for in 62,745-5 where ferumoxytol 255 mg x4 dosing group was discontinued in the early stage of trial.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In all three pivotal studies, Ferumoxytol was administered at Day 1 and Day 5 ( $\pm 3$ ) and oral iron was administered from Day 1 to Day 21. The primary efficacy endpoint of change in Hgb was assessed at Day 35. This may reflect the time needed for Hgb response. No efficacy assessment was beyond Day 35 in all 3 trials. There were only 69 patients who received the second cycle of Ferumoxytol in the non-randomized phase and efficacy and tolerance effects could not be assessed.

### 6.1.10 Additional Efficacy Issues/Analyses

The efficacy of Ferumoxytol was evaluated based on Hgb increase in three clinical trials. The relevant clinical improvement in anemia symptoms and signs was not evaluated in these trials.

Repeated cycles of Ferumoxytol treatment may be needed in clinical practice. There were only 69 patients who received the second cycles of Ferumoxytol treatment in the non-randomized phase in the whole database. The efficacy and safety of repeated cycle of Ferumoxytol should be further studied in clinical trials.

## 7 Review of Safety

### Safety Summary

A total of 1726 (1562 CKD and 164 non-CKD) subjects have exposed to ferumoxytol treatment in 11 clinical studies. Among the 1562 CKD patients, 938 had CKD stage 1-5, 581 had CKD stage 5D on hemodialysis, and 43 patients had CKD stage 5D on peritoneal dialysis. Among the CKD patients, 781 have exposed to 510 mg for 2 doses and additional 708 patients had exposed to 510 mg single dose.

The major risks of ferumoxytol treatment are hypersensitivity and hypotension reactions and possible iron overload. The incidence of hypersensitivity reactions was 3.7% with ferumoxytol treatment, 3.4% with oral iron, and 2.1% with placebo based on available clinical data. Hypotension was reported in 1.9% in the ferumoxytol-treated subjects as compared to 0.3% in the oral iron-treated patients, and 0.8% in the placebo-treated patients. For the proposed dosing regimen of ferumoxytol 510 mg for 2 doses, 4.9% of patients had serum ferritin  $\geq 800$  ng/mL and TSAT  $\geq 50\%$  during the post-treatment period, as compared 0% of patients in oral iron group.

A total of 19 deaths (1.1%) occurred in subjects treated with ferumoxytol and 8 deaths (2.8%) occurred in subjects treated with oral iron. The overall incidence of serious adverse events among subjects receiving a first course of ferumoxytol treatment (7.1%) was lower than in subjects receiving oral iron treatment (11.7%), but higher than in subjects receiving placebo (2.4%). The overall rate of treatment discontinuation in ferumoxytol-treated subjects was 2% as compared to 11% in oral iron-treated subjects.

The overall incidence of TEAEs, irrespective of relationship to study medication, was 32.8% with first course of ferumoxytol, 53.4% with oral iron, and 19% with placebo in CKD patients. The most commonly reported TEAEs among subjects in the ferumoxytol first course treatment group ( $\geq 1.0\%$  of subjects) were diarrhea (2.4%), hypotension (2.1%), nausea (2.0%), dizziness (1.9%), peripheral edema (1.5%), headache (1.4%), vomiting (1.4%), and constipation (1.1%). Adverse events that occurred more frequently with first course ferumoxytol treatment than with oral iron treatment included hypotension, dizziness, hypertension, fatigue, pruritus, upper respiratory tract infection, back pain, and gout.

The incidence of serum phosphate of 1.0 to  $<2.0$  mg/dL was 0.9% with ferumoxytol, 1.4% with oral iron and 0.3% with placebo. The incidence of serum phosphate of  $<1.0$  mg/dL was 0.1% with ferumoxytol, 0.3% with oral iron, and 0.1% with placebo.

There was a limited number of subjects (n=69) who had received the second cycle of ferumoxytol treatment. Clinical studies to evaluate the safety of repeated cycle of ferumoxytol treatment should be conducted.

## 7.1 Methods

### 7.1.1 Clinical Studies Used to Evaluate Safety

All 11 clinical studies listed under Section 5.1 Table of Clinical Studies were used to evaluate the safety of Ferumoxytol.

### 7.1.2 Adequacy of Data

The safety data are adequate for evaluating the first course of the Ferumoxytol treatment. There was limited safety data to evaluate the repeated course of Ferumoxytol treatment.

### 7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

Safety data were pooled across studies to estimate and compare mortality, incidence of all SAEs, cardiovascular events, hypersensitivity reactions, and hypotension events.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the sponsor's clinical development program, a total of 1726 subjects have exposed to Ferumoxytol treatment. These included 1562 CKD patients and 164 non-CKD subjects. Among the 1562 CKD patients, 938 had CKD stage 1-5, 581 had CKD stage 5D on hemodialysis, and 43 patients had CKD stage 5D on peritoneal dialysis. Among the CKD patients, 781 were exposed to 510 mg for 2 doses and additional 708 patients were exposed to 510 mg single dose.

The following table shows the treatment exposure in CKD patients by dosing regimen.

**Treatment Exposure by Dosing Regimen and Cumulative Dose in CKD Subjects (Safety Population)**

	N	Mean±SD (mg iron)	Median (range) (mg iron)
<b>Treatment Exposure a</b>			
Ferumoxytol First Course	1562	765.60±264.42	1020.00 (60.00-1050.00)
Ferumoxytol Second Course	69	2018.78±103.32	2040.00 (1380.00-2046.00)
Oral Iron	290	3980.69±1699.63	4100.00 (0.00-19500.00)
<b>Ferumoxytol Treatment Regimen a</b>			
1 x 125 mg	10	126.00±0.00	126.00 (126.00-126.00)
1 x 250 mg	10	252.00±0.00	252.00 (252.00-252.00)
1 x 510 mg	708	506.95±32.12	510.00 (60.00-570.00)
8 x 128 mg	15	816.00±284.28	1020.00 (382.50-1020.00)
4 x 255 mg	58	979.71±149.56	1020.00 (255.00-1026.00)
2 x 510 mg	692	1003.87±88.81	1020.00 (210.00-1050.00)
4 x 255 mg -> 2 x 510 mg	12	2040.50±1.73	2040.00 (2040.00-2046.00)
2 x 510 mg -> 2 x 510 mg	57	2014.21±113.31	2040.00 (1380.0-2040.00)
<b>Randomized, Open-label, Controlled Studies b</b>			
4 x 255 mg Ferumoxytol	60	980.85±147.13	1020.00 (255.00-1026.00)
2 x 510 mg Ferumoxytol	605	1002.10±94.31	1020.00 (210.00-1050.00)
Oral Iron	280	3781.79±963.83	4100.00 (0.00-5000.00)

a. Safety data included in the analyses by treatment exposure and ferumoxytol treatment regimen were derived from the following protocols: 62,745-2, 62,745-3, 62,745-4, 62,745-5, 62,745-6, 62,745-7, and 62,745-8.

b. Safety data in the analysis by randomized, open-label, controlled studies were derived from the following protocols:

62,745-5, 62,745-6, and 62,745-7.

Note: Cumulative iron exposure was calculated for ferumoxytol subjects using the volume of ferumoxytol received intravenously and for oral iron subjects using the difference between the number of pills administered and those returned multiplied by the amount of elemental iron contained in each pill.

Abbreviations: SD=standard deviation.

Sponsor's table in summary of clinical safety

The following table summarizes the interval duration between the two ferumoxytol doses by number of days for subjects in the three efficacy and safety studies (62,745-6, 62,745-7, and 62,745-5). In non-dialysis patients in studies 62745-6 and 62745-7, about 80% of patients received the second dose between 4 and 7 days following the first dose of ferumoxytol. In hemodialysis patients in Study 62,745-5, about 40% of patients received the second dose of ferumoxytol 2 days after the first dose, and 30% of patients received the second dose 7 days after the first dose, and remaining 30% received the second dose between 2 and 7 days after the first dose.

Across all subjects with CKD, about 80% of patients received their second dose between 4 and 8 days after the first dose of ferumoxytol.

**Number and Percent of Subjects by Interval (days) Between First and Second Dose of Ferumoxytol 510 mg in Studies 62,745-5, 62,745-6, and 62,745-7**

Interval in days	62745-5 Pre (N=56)	62745-5 Post (N=105)	62745-6 (N=213)	62745-7 (N=216)	CUMULATIVE TOTALS (N=590)
	Subjects N (%)	Subjects N (%)	Subjects N (%)	Subjects N (%)	Subjects N (%)
1	---	---	---	---	---
2	20 (35.7)	47 (44.8)	2 (0.9)	8 (3.7)	77 (13.1)
3	1 (1.8)	15 (14.3)	17 (8.0)	17 (7.9)	127 (21.5)
4	4 (7.1)	7 (6.7)	34 (16.0)	21 (9.7)	193 (32.7)
5	5 (8.9)	10 (9.5)	42 (19.7)	48 (22.2)	298 (50.5)
6	---	2 (1.9)	33 (15.5)	41 (19.0)	374 (63.4)
7	25 (44.6)	21 (20.0)	74 (34.7)	69 (31.9)	563 (95.4)
8	1 (1.8)	1 (1.0)	8 (3.8)	7 (3.2)	580 (98.3)
9	---	1 (1.0)	2 (0.9)	2 (0.9)	585 (99.2)
10	---	1 (1.0)	---	2 (0.9)	588 (99.7)
12	---	---	---	1 (0.5)	589 (99.8)
17	---	---	1 (0.5)	---	590 (100)

Sponsor's table submitted 9/23/2008

### 7.2.2 Explorations for Dose Response

No dose response phase 3 studies were conducted except for in 62,745-5 where ferumoxytol 255 mg x4 dosing group was discontinued in the early stage of the trial.

### 7.2.3 Special Animal and/or In Vitro Testing

See pharmacology/toxicology review. The review is currently pending.

### 7.2.4 Routine Clinical Testing

Hemoglobin, ferritin and TSAT should be monitored pre- and post-treatment period.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

See clinical pharmacology review. The review is currently pending.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hypersensitivity reactions are a known risk associated with the use of IV iron products for the treatment of iron deficiency anemia.

#### **Hypersensitivity reactions**

A total of 63 subjects (3.7%) in the ferumoxytol treatment groups had one or more AEs potentially associated with hypersensitivity including the two subjects reported to have a hypersensitivity event (discussed below). AEs potentially associated with hypersensitivity occurred in 3.4% (n=10) of subjects in the oral iron and 2.1% (n=16) of subjects in the placebo treatment groups. These included 6 (0.3%) SAEs in Ferumoxytol-treated subjects as compared to 2 (0.7%) SAEs in oral iron-treated subjects and 1 (0.1%) SAE in placebo patients.

Two reported hypersensitivity reactions:

- One subject had severe hypotension that was characterized as an anaphylactoid event (Study 62,745-8). This event was considered a serious adverse event and it occurred within minutes following a single 510 mg dose of ferumoxytol in a subject with known allergies to two medication classes; this subject responded promptly to treatment, was hospitalized overnight for observation, and discharged without sequelae.
- One subject reported a non-serious hypersensitivity AE (flushing and worsening of pre-existing rash) (Study 62,745-7; subject # 282-106); the event was of moderate intensity, occurred within minutes following a second 510 mg dose of ferumoxytol, and resolved in less than an hour without sequelae.

The following is the patient's narrative of the first subject who experienced anaphylactoid reactions.

**Patient ID 821.** \_\_\_\_\_

An 85-year-old male, enrolled in a cross-over, single dose, placebo-controlled safety study (62745-8), received Ferumoxytol injection over 44 seconds on \_\_\_\_\_ at 1508 hours. Two minutes later, he had "intense" hot flashes and his blood pressure was reported at 180/80 mm Hg. While lying down, it was reported he felt light-headed and his feet began to itch. The itching became intense. The investigator called Emergency Medical Services. At the time the patient's blood pressure was 140/80 mm Hg, but the patient reported he did not feel better and he was "pale and lethargic." Subsequently, his blood pressure dropped to 90 palpatory. The patient remained lethargic, answering questions with difficulty. His breathing was noted to be "okay." The investigator administered 1cc of epinephrine 1/10,000, via the subcutaneous route, and the patient slowly recovered. When the paramedics arrived, the patient's blood pressure was 110/60. He was subsequently transported to the emergency room. On \_\_\_\_\_ at 16:30 hours, the investigator visited the patient in the emergency room and reported that the patient was "looking much better." Vital signs were reported as stable, the patient was talking and reported "feeling better." The investigator decided to observe the patient for 24 hours in the emergency room.

b(6)

The patient was later admitted to the hospital for further observation. It was noted that overnight during his 23 hour observation on the telemetry floor that he had a run of non sustained ventricular tachycardia. The patient's cardiologist and primary care physician were called for evaluations. The cardiologist noted the patient had no significant reversible ischemia in \_\_\_\_\_ with a normal ejection fraction of 48%, which is slightly depressed. The patient underwent an adenosine stress test. The thallium scan showed no ischemia.

b(6)

On \_\_\_\_\_ the patient was cleared by cardiology for discharge and he was discharged home "in stable and improved condition."

b(6)

The investigator considered the anaphylaxis to be life-threatening, severe in intensity and 'related' to the study drug. The patient's treatment assignment was unblinded and it was determined that the patient had received ferumoxytol.

The investigator considered the non-sustained ventricular tachycardia prolonged hospitalization, moderate in intensity and 'not related' to the study treatment.

Medical history was significant for hypertension, coronary artery disease, hyperlipidemia, iron deficiency, anemia, constipation, metabolic acidosis, gout, chronic renal insufficiency, allergy to Levaquin, Cipro and Percocet, gastrointestinal bleed (2005), carotid artery disease, cerebrovascular accident, transient ischemic attack, gallbladder dyskinesia, transurethral resection of the prostate (1986) (1999), umbilical hernia repair (1989) (1990), carotid endarterectomy (1998), gastritis, duodenitis (2004), hyperkalemia, leg cramps, gastroesophageal junction ulcer (2004), and pancreatic rest. Concomitant medications included Zocor, quinine, vitamins, allopurinol, sodium bicarbonate, Aranesp, Plavix, folic acid, aspirin, felodipine, Travatan, fosinopril and Aciphex.

On 14 Nov 2006, follow up information was received from the investigator. A comprehensive review of the case was conducted by the principal investigator, sub-investigator and sponsor representatives on 30 Oct 2006. The conclusion of the review was that although some important features consistent with true anaphylaxis were not present in this patient, the investigator could not rule out an anaphylactoid-like reaction, which he had seen in association with other intravenous iron products. The investigator still considered the event serious, life-threatening and related to ferumoxytol. The SAE term was modified from anaphylaxis to anaphylactoid reaction/severe hypotension.

Other treatment-emergent serious adverse events (SAE) that may be potentially associated with hypersensitivity/allergic reactions are summarized in the following table. Two of the hypotension events occurred within a few minutes of dosing, other events occurred days or weeks after dosing.

Clinical Review  
 Min Lu, M.D., M.P.H.  
 NDA 22-180/ N000  
 Ferumoxytol Injection

**Treatment-emergent Serious Hypersensitivity/Allergic Reactions**

Protocol Number	Subject #/ ID	Age/ Sex	CKD Stage	Treatment Group	SAE Preferred Term	Time to Onset/ Duration	Severity	Outcome	Related -ness	Comments
62,745-8	239-821/	85/ M	5	1x510 mg ferumoxytol	Anaphylactoid Reaction	2 minutes/	Severe	Recovery, No sequelae	Related	The subject had preexisting allergies to two medication classes
					Hypotension	Several minutes/	Severe	Recovery, No sequelae	Related	

b(6)

Sponsor's table in Amendment 0005 submitted on May 20, 2008

**Treatment-emergent Serious Adverse Events Potentially Associated with Hypersensitivity/Allergic Reactions**

Protocol Number	Subject #/ ID	Age/ Sex	CKD Stage	Treatment Group	SAE Preferred Term	Time to Onset*/ Duration	Severity	Outcome	Related -ness	Other signs/symptoms
62,745-5	139-536/	74/ M	5D	2x510 mg ferumoxytol	Hypotension	3 mins/ 12 mins	Moderate	Recovery No sequelae	Related	No other signs/symptoms of hypersensitivity/allergic reactions. The sub-investigator regarded the hypotensive episode with transient chest pain during dialysis as hyperosmolarity reactions.
62,745-5	144-533/	82/ M	5D	2x510 mg ferumoxytol	Transient hypotension	5 mins/ 5 mins	Moderate	Recovery No sequelae	Related	No other signs/symptoms of hypersensitivity/allergic reactions.
62,745-5	251-515/	65/ F	5D	2x510 mg ferumoxytol	Hypotension, Gastroenteritis	11 day/	Moderate	Recovery No sequelae	Not related	No other signs and symptoms of hypersensitivity/allergic reactions. The hypotensive episodes during dialysis were attributed to the fluid loss from heavy vomiting and diarrhea due to gastroenteritis.

b(6)

62,745-7	127-140/	62/ F	4	2x510 mg ferumoxytol	Severe hypotension, Hypoglycemic shock, Grand mal seizure, Ventricular fibrillation, Pulmonary edema, Cardiac arrest	10 days/	Severe	Recovery, with sequelae	Not related	There were no other signs and symptoms of hypersensitivity/allergic reactions. The severe hypotension was likely related to hypoglycemic shock and concurrent cardiac conditions.
62,745-8	127-903/	57/ M	4	1x510 mg ferumoxytol	Dyspnea, Congestive heart failure, Elevated blood pressure	5 days/	Severe	Recovery, No sequelae	Not related	There were no other signs and symptoms of hypersensitivity/allergic reactions. The severe shortness of breath was likely related to congestive heart failure.
62,745-6	123-117/	80/ M	4	Oral iron	Worsening dyspnoea, Worsening anemia	3 days/ 3 days	Severe	Recovery, No sequelae	Not related	There were no other signs and symptoms of hypersensitivity/allergic reactions.
62,745-7	203-124/	76/ F	4	Oral iron	Hypotension, Bradycardia, Acute tubular necrosis	1 day/	Moderate	Recovery, with sequelae	Not related	There were no other signs and symptoms of hypersensitivity/allergic reactions.
62,745-8	139-808/	81/ F	3	Placebo	Petechiae	1 day/ 20 days	Mild	Recovery, No sequelae	Related	Diffuse petechiae on both lower extremities resembled leukocytoclastic vasculitis.

b(6)

Sponsor's table in Amendment 0005 submitted on May 20, 2008

The following are patients' narratives.

b(6)

**Patient ID 536/ — Hypotension**

A 74-year-old male, enrolled in study 62745-5, received his first dose of ferumoxytol 45 minutes into the dialysis run on 19 Apr 2006, at 8:25 AM. As of that time, the patient had 1385cc of fluid removed and his vital signs were as follows: blood pressure 125/64 mm Hg, respiratory rate of 16 breaths per minute, and heart rate of 80 beats per minute. The ferumoxytol was administered "over 55 seconds with a slow normal saline flush post administration." At 8:28AM, the patient stated "I am going out, my pressure must be dropping." An immediate (STAT) blood pressure revealed 83/43 mm Hg. The patient's heart rate was 90 beats per minute and respiratory rate was 14 breaths per minute. At 8:30 AM, the patient's blood pressure was 96/46 mm Hg, respiratory rate was 14 breaths per minute and heart rate was 78 beats per minute. The patient was noted to be diaphoretic, and complained of "hot" chest pain of "5" on a scale of 0 to 10. A 200 cc normal saline bolus was administered over 5 minutes and 10 cc of 23.4% hypertonic saline was given by the dialysis nurse. The patient was placed on 3 liters of nasal cannula oxygen. An immediate (STAT) electrocardiogram revealed no significant cardiac event. At 8:35AM the patient stated "I am back to normal." His blood pressure at that time was 106/52 mm Hg, his respiratory rate was 14 breaths per minute and his heart rate was 74 beats per minute. The chest pain resolved.

At 8:40 AM, the patient's blood pressure was recorded at 120/64 mm Hg. At 8:50 AM, the patient's blood pressure was recorded at 129/66 mm Hg, and at 9:00 AM, the patient's blood pressure was recorded at 131/66 mm Hg. The

patient experienced no further hypotension or chest pain throughout the treatment and he remained on 3 liters of nasal cannula oxygen throughout the treatment. He was discharged at 10:37 AM.

On 21 Apr 2006, the Sub-Investigator reported he saw no signs of hypersensitivity; the patient had no problem with prior doses of intravenous iron and had, in fact, had multiple doses of iron in the past. He noted that while the patient had 1385 cc of fluid removed, the patient was 3.8 kilograms above his dry weight and had 1+ edema at the time of the event. The Sub-Investigator regarded the SAE as a hypotensive episode with transient chest pain that clinically mimicked hyperosmolarity reactions he had seen in the past.

The investigator considered the hypotension as a significant medical event that required intervention to prevent a serious outcome, moderate in intensity and 'related' to ferumoxytol.

The patient's medical history was significant for hypertension (1990), non-insulin dependent diabetes (2002), fluid overload (2005), asthma (2000), junctional heart rhythm (2005) and enlarged heart (2005).

Concomitant medications included clonidine, sevelamar, NephroCaps, calcium acetate, lacosole, amlodipine besylate, simvastatin, doxercalciferol, 23.4% hypertonic saline, and normal saline.

**Patient ID 533/ — Hypotension/Back pain**

An 82-year-old male, enrolled in study 62745-5, received his first dose of ferumoxytol approximately 1 hour and 20 minutes into his dialysis session on 08 Aug 06. Within five minutes of injection the patient's blood pressure dropped from 124/62 mmHg to 79/49 mmHg, pulse 74 and shortly after was 78/52, pulse of 75. The patient complained of heat sensation and back pain. There was no chest pain, respiratory distress, shortness of breath or wheezing. There was no edema of the uvula, or buccal mucosa. The patient was placed in Trendelenberg position and no other treatment was administered. The patient's blood pressure returned to 126/69 five minutes after the event started and 1 17/71 promptly 10 minutes later. There was no diaphoresis and the patient's pulse remained in the 70/min range. The patient was otherwise comfortable. The patient's back pain began to resolve 15 minutes after onset, and had completely resolved at the end of the dialysis treatment.

After resolution of the patient's initial episode of hypotension, and just after discontinuation of dialysis, the patient experienced another episode of hypotension, approximately two hours later. The blood pressure readings have not yet been documented, but the patient was administered a bolus of approximately 600 cc of normal saline. The patient's blood pressure was reported to have returned to normal shortly after the bolus was complete. On 08 Aug 06, the patient recovered without sequelae.

This patient is known to the investigator and generally has stable blood pressure during dialysis treatments. During the patient's past several dialysis treatments, his blood pressure did not drop below 110 mmHg. The investigator considered the transient hypotension as life threatening, moderate in intensity and 'related' to ferumoxytol. He considered the event serious because of the rapidity of the drop in blood pressure. He considered the event medically significant because of the potential effect such a drop in blood pressure could have on an 80 year old patient. The investigator considered the event as unexpected because the hypotension was associated with severe back pain, and because it recurred two hours after initial resolution. The investigator said that he had observed back pain associated with hypotension in other intravenous iron products, but that this was the first time he had observed it in a ferumoxytol-treated patient.

The patient's medical history was significant for: hypertension, end stage renal disease on hemodialysis, diabetes mellitus, coronary artery disease, status post (s/p) coronary artery bypass graft (CABG), hypercholesteremia and iron deficiency anemia.

Concomitant medications included: Metoprolol, Norvasc, Zocor, Avandia, aspirin, Plavix, Tylenol #3, Prevacid, Epogen and normal saline.

**Patient ID 251-515 — Hypotension/Gastroenteritis**

b(6)

b(6)

A 65-year-old female, enrolled in study 62,745-5, received her first ferumoxytol 510 mg on 28 February 2007 and second dose of 510 mg on 5 March 2007.

On \_\_\_\_\_, the patient presented to her dialysis treatment stating that she had eaten soup and a tuna sandwich in the cafeteria and felt poorly afterwards complaining of an upset stomach. During the dialysis treatment, she was afebrile, had a blood pressure of 103/69 mm Hg, and a heart rate (HR) of 99 beats per minute (BPM). Two hours into her treatment she vomited a large amount of fluid which consisted mostly of food. A half an hour later, she vomited again fluid and mucus. The patient fainted and her blood pressure was noted to be 70/palpable and subsequently she was given a bolus of 200 ml's normal saline after which her blood pressure improved to 96/46 mm Hg. Thirty minutes later, her blood pressure again dropped to 70/palpable and she was given a second bolus of 200 mL normal saline. Her blood pressure recovered to 108/54 mm Hg and the hemodialysis was terminated 15 minutes prematurely. The patient was shaking and stated that she was feeling "terrible". She also experienced cramping and approximately five episodes of diarrhea in a 24 hour period, before and after the dialysis treatment. She was transferred and admitted to the hospital for observation. At the time of admission, the patient's temperature was noted as 97.7 F, blood pressure 109/40 mmHg, and heart rate 100 (BPM). Blood cultures were obtained and revealed "no growth after four days". A chest x-ray was performed and compared to a study done in February 2007 demonstrating that the lungs were clear with "no focal infiltrates". A diagnosis of gastroenteritis was made, and the patient was treated with Cipro.

b(6)

On \_\_\_\_\_ out of range laboratory findings were respectively as follows (reference ranges not provided): White blood cells (WBC's) 12.9 and 9.6, red blood cells (RBC's) 4.40 and 4.06, mean corpuscular hemoglobin concentration (MCHC) 33.0 and 31.5, lymphocytes percent 10.9 and 15.8.

b(6)

On \_\_\_\_\_ laboratory findings were as follows: glucose 161 mg/dl (reference range 70-110 mg/dl), blood urea nitrogen (BUN) 51 mg/dl (reference range 8-20 mg/dl), creatinine 10.2 mg/dl (reference range 0.6-1.1), BUN/creatinine ratio 5.0 (reference range 12.0-20.0), estimated glomerular filtration rate 4 (reference range <60 indicative of kidney disease), sodium (NA) 134 mEq/l (reference range 135-144), carbon dioxide 21 mmol/L (reference range 22-32), calcium 7.5 mg/dl (reference range 8.4-10.5), aspartate amino transferase (AST) 14 U/L (reference range 15-41), total creatinine kinase 277 u/L (reference range 26-140), magnesium 1.6 mg/dl (reference range 1.7-2.4), and phosphorus 5.1 mg/dl (reference range 2.5-4.5).

During the hospitalization, the patient was treated with the following medications: Esomeprazole Magnesium 20 mg p.o., Enalapril Maleate 20 mg p.o., Promethazine HCL 12.5 mg IM q 6-8 hrs pm, acetaminophen 650 mg q 4-6 p.o., and potassium chloride 40 mEq Nxl.

The Investigator considered the "hypotension" as requiring hospitalization, moderate in intensity, and "not related" to study drug, but rather to underlying/concomitant illness, gastroenteritis. On 16 March 2007, the Investigator assessed the patient as having recovery, no sequelae.

The investigator considered the "gastroenteritis" as requiring hospitalization, severe in intensity, and "not related" to study drug, but rather to underlying/concomitant illness.

On \_\_\_\_\_ the event had resolved and the patient was discharged from the hospital with recovery, no sequelae.

b(6)

A hospital progress note documented the following information: The patient seemed to have recovered from the "gastroenteritis". It was noted that the patient's blood pressure medications had been held pre-dialysis and her blood pressure had not dropped since admission to the hospital.

The patient's medical history is significant for gastroesophageal reflux disease, peripheral vascular disease, diabetes, hypertension, cerebrovascular accident, end stage renal disease, and secondary hyperparathyroidism.

The patient's concomitant medications included Nephrocaps 1 cap p.o., furosemide 40 mg p.o., warfarin 8 mg p.o., sevelamer HCl 7200 mg p.o., NPH insulin 25 units s.c., atorvastatin calcium 10 mg p.o., Nifedipine XL 60 mg p.o., Epogen 4000 units i.v., heparin 2000 units i.v., doxercalciferol 2 mcg i.v., and Cipro 400 mg i.v.

**Patient ID I40/ — , hypoglycemic shock**

**b(6)**

A 62-year-old female, enrolled in study 62745-7, received her first ferumoxytol dose of 510 mg on 17 March 2007 and second dose of 510 mg on 22 March 2007.

On ———, the patient was at the hairdresser where she suddenly developed acute diaphoresis and became unresponsive. The paramedics were called and she was found to be in "hypoglycemic shock." The glucometer reading was documented at 25 and one ampule of Dextrose 50 was given. The patient awoke in the ambulance hallucinating and confused. The family reported the patient experienced recent episodes of significant hypoglycemia which occurred in the early hours of the morning. She was recently diagnosed with renal insufficiency attributed to diabetic nephropathy. Upon arrival at the emergency room, the patient was "severely hypotensive and bradycardic." Her extremities were noted to have 2+ pretibial edema bilaterally. She experienced a grand mal seizure. She subsequently required advanced cardiac life support (ACLS) and intubation for asystole and ventricular fibrillation. A chest x-ray prior to intubation revealed transverse cardiomegaly, and bilateral infiltrates with vascular congestion consistent with pulmonary edema. She was stabilized following atropine, epinephrine, dopamine and Natrecor. Post intubation, films revealed decreased cardiomegaly and "somewhat improved" infiltrates.

Admitting laboratory results were as follows: hemoglobin 12.6, hematocrit 39, white blood count 10.6 with a normal differential. The comprehensive metabolic profile (CMP) revealed a serum glucose of 224, BUN 27, creatinine 2.2, brain natriuretic peptide (BNP) 480.2, lactic 5.8, creatine kinase (CK) 173, with a MB of 1.58, troponin is less than 0.04. Pre intubation arterial blood gases revealed: pH 6.972, PO2 285 and PCO2 206. Post intubation arterial blood gases revealed: pH 6.972, PO2 285 and PCO2 98. White blood count 8.9, hemoglobin 9.9, platelet count 223,000, CPK 373, Bun 27, creatinine 2.2, lactic acid 5.8, INR 1.1. An electrocardiogram revealed T-wave depression predominance in the anterior leads. The patient was admitted to the intensive care unit and her respiratory acidosis was corrected after the patient was adequately sedated and appropriate ventilation established.

On ———, serial cardiac enzymes revealed an elevation of the troponin levels consistent with an acute myocardial infarction. After metabolic stabilization, the pressor agents were no longer required and beta blocker therapy, angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) and nitrates were implemented per the hospital acute myocardial infarction protocol. An echocardiogram performed that same day revealed good left ventricular systolic performance, left ventricular diastolic dysfunction, small non-compromising pericardial effusion and no evidence of obstructive valvular disease present. The ejection fraction was 55-60%.

**b(6)**

On ———, the patient remained intubated and unresponsive. An electroencephalogram (EEG) was performed and showed "very slow delta rhythm with no reactivity." During this time hemodialysis was initiated, as the serum creatinine rose above 3. In an effort to stabilize the patient's metabolic status and optimize the central nervous system recovery. A follow up computed tomography scan revealed no evolution of stroke or hemorrhage.

On ———, a chest x-ray revealed lines and tubes were stable, improved aeration of the left lung base. Cardiomegaly persisted without an infiltrate, consolidation or effusion. There was no pneumothorax and the trachea was in the midline. Laboratory results for that same day were as follows: BUN 50, creatinine 3.5, CO2 31, estimated glomerular filtration rate (GFR, African American) 17, glucose 127, white blood count 13.0, hemoglobin 10.4 and hematocrit 30.

The patient's neurological status failed to improve despite several days of metabolic and hemodynamic stability. The issues were discussed with the family and in accordance with the previously stated wishes of the patient and with the concurrence of the family and medical personnel, the family declared the patient a do not resuscitate and requested discontinuation of artificial life support. The patient was subsequently extubated and managed with comfort measures. She progressed to asystole and was pronounced dead on 08 April at 3:25 AM.

The investigator considered the hypoglycemic shock as a significant medical event that required intervention to prevent a serious outcome, severe in intensity and 'not related' to study medication but rather associated with an underlying concomitant illness.

The investigator considered the severe hypotension as a significant medical event that required intervention to prevent a serious outcome, severe in intensity 'not related' to study medication but rather associated with an underlying concomitant illness.

The investigator considered the grand mal seizure as a significant medical event that required intervention to prevent a serious outcome, severe in intensity and 'not related' to study medication but rather associated with an underlying concomitant illness. The investigator considered the ventricular fibrillation as a significant medical event that required intervention to prevent a serious outcome, severe in intensity and 'not related' to study medication but rather associated with an underlying concomitant illness.

The investigator considered the pulmonary edema as a significant medical event that required intervention to prevent a serious outcome, severe in intensity resulting in death and 'not related' to study medication but rather associated with an underlying concomitant illness.

The investigator considered the cardiac arrest as severe in intensity resulting in death and 'not related' to study medication but rather associated with an underlying concomitant illness. The investigator stated he did not agree with capturing myocardial infarction and hypoxic encephalopathy as Serious Adverse Events. In his judgment, the hypoxic encephalopathy was the result of prolonged hypoglycemia. In addition, the elevated Troponin levels from \_\_\_\_\_ were not due to myocardial infarction but rather to the trauma of cardiopulmonary resuscitation.

b(6)

Medical history was significant for chronic kidney disease, diabetes mellitus for 20 years, insulin dependent for 5 years, hypertension, hyperparathyroidism, anemia, retinopathy, neuropathy, total abdominal hysterectomy and retinal hemorrhage.

Concomitant medications included Lantus insulin, Amaryl, InnoPran XL, minoxidil, Actos, Diovan, Klor-Con, metolazone, Demadex, Clonidine, Cosopt eye drops, Xalatan drops, K-Dur, Tylenol, Combivent, Norvasc, aspirin, atropine sulfate, Bumex, Capoten, Hibiclens, Dextrose 5 and normal saline, dopamine, epinephrine, Pepcid, Lasix, Heparin, labetalol, lidocaine, Visipaque, Ativan, magnesium sulfide, Mannitol, Desenex, mineral oil, morphine sulfate, Avelox in sodium chloride, Naprosyn, Nitro-Bid, Protonix, Potassium chloride, sodium bicarbonate, sodium chloride, Queiicin, Valsartan, vancornycin, calcium gluconate, sodium phosphate, propofol, Natrecor, Dextrose 5 and water, Dextrose and ½ normal saline, dopamine and Cardene.

**Patient ID 903/ \_\_\_\_\_ /Hypertension**

b(6)

A 57-year-old male with a past medical history of congestive heart failure and hypertension enrolled in study 62745-8, experienced congestive heart failure and elevated blood pressure five days following his second and final dose of test article. When the study was unblinded, it was revealed that the patient received the ferumoxytol dose second. Thus, the events occurred 5 days after the receipt of ferumoxytol.

On \_\_\_\_\_ at 13:30 hours, the patient called the investigator to report that he had awakened that morning with severe shortness of breath and "congestive heart failure." He reported his blood pressure was elevated at 210/140 mm Hg. He was taken to the emergency room where he was treated and released. The patient complained of a sudden severe shortness of breath from 6:30 AM until his arrival in the emergency room. He apparently got up to urinate early that morning and upon lying back down on the bed he became short of breath. He denied experiencing any chest pain.

b(6)

The patient was taken to the hospital by ambulance in the early morning of \_\_\_\_\_. During transport to the hospital, the patient's electrocardiogram (EKG) showed sinus tachycardia. He received oxygen by mask and intravenous normal saline. On exam, the patient had pedal edema and dyspnea at rest, however he was not using accessory muscles when breathing. Breath sounds demonstrated fine bibasilar crackles. The patient's heart rate was regular, and a cardiac exam revealed no murmurs, ectopy, gallops or rubs. A chest x-ray showed borderline cardiomegaly and congestive heart failure (CHF). An EKG showed a heart rate of 113 bpm, sinus tachycardia and non-specific ST-changes. Lab test results included the following: white blood cells (WBC)=12.7, hemoglobin

(Hgb)=13, Creatinine Kinase (CK)=240, CK-MB=2.54, Myoglobin and Troponin within normal limits, brain natriuretic peptide (BNP)=220, potassium (K)=3.5g,l ucose=202, blood urea nitrogen (BUN)=29, creatinine=3.1, and alkaline phosphatase=172.

The patient was treated with one inch of Nitropaste, 2 mg intravenous morphine and intravenous Lasix with complete resolution of his symptoms. His blood pressure and oxygen level were monitored.

The emergency room doctors explained to the patient the nature of his congestive heart failure (CHF) and the need for him to follow up with his personal physician or return to the emergency room if his condition returned or worsened.

The hospital discharge report from the ER concluded that he had mild congestive heart failure suspected to be caused by an elevated spike in systolic blood pressure (SBP) on arrival but which had returned to normal. There was no sign of myocardial infarction. Upon discharge that same day / \_\_\_\_\_ the patient was alert cooperative and in mild respiratory distress. He was discharged home accompanied by family.

b(6)

The investigator considered the congestive heart failure as a significant medical event that required intervention to prevent a serious outcome, moderate in intensity and "not related" to study medication but rather associated with a concomitant illness.

The investigator considered the elevated blood pressure as a significant medical event that required intervention to prevent a serious outcome, severe in intensity and "not related" to study medication but rather associated with a concomitant illness.

Medical history was significant for: congestive heart failure (1998), hypertension, chronic obstructive pulmonary disease, cellulitis of the lower extremities, proteinuria, hypocalcemia, metabolic acidosis, gout, diabetes mellitus, gastroesophageal reflux disease, neuropathy, chronic renal failure with a glomerular filtration rate of 26 (2005) and hyperlipidemia.

Concomitant medications included: Elavil, Lipitor, Lantus insulin, Lopressor, Glyburide, Advair, Norvasc, aspirin, Bumex, Plavix, Combivent, hydralazine, colchicine, Nexium, sodium bicarbonate, Lasix and Altace.

The following table summarizes the hypersensitivity and adverse events potentially associated with hypersensitivity at any time after any dose in all subjects (CKD and non-CKD).

**Adverse events potentially associated with hypersensitivity  
 by preferred term at any time after any dose in all subjects (CKD and non-CKD)**

Body System/Preferred Term	Ferumoxytol First Course (N=1726)		Ferumoxytol Second Course (N=69)		Oral Iron (N=290)		Placebo (N=775)	
	Events N	Subject N(%)	Events N	Subject N(%)	Events N	Subject N(%)	Events N	Subject N(%)
Anaphylactoid reaction	1	1 ( 0.1)	0	0	0	0	0	0
Hypersensitivity	1	1 ( 0.1)	0	0	0	0	0	0
Pruritus	20	18 ( 1.0)	1	1 ( 1.4)	1	1 ( 0.3)	7	7 ( 0.9)
Pruritus generalized	2	2 ( 0.1)	0	0	1	1 ( 0.3)	1	1 ( 0.1)
Rash	14	14 ( 0.8)	0	0	1	1 ( 0.3)	3	3 ( 0.4)
Rash generalized	2	2 ( 0.1)	0	0	0	0	0	0
Rash pruritic	4	3 ( 0.2)	0	0	0	0	0	0
Skin reaction	3	2 ( 0.1)	1	1 ( 1.4)	0	0	0	0
Petechia(e)	1	1 ( 0.1)	0	0	0	0	1	1 ( 0.1)
Urticaria	4	4 ( 0.2)	0	0	0	0	1	1 ( 0.1)
Swelling face	0	0	0	0	1	1 ( 0.3)	0	0
Orbital edema(ocdema)	1	1 ( 0.1)	0	0	0	0	0	0
Throat tightness	1	1 ( 0.1)	0	0	0	0	0	0
Wheezing	4	4 ( 0.2)	1	1 ( 1.4)	1	1 ( 0.3)	3	3 ( 0.4)
Bronchospasm	1	1 ( 0.1)	0	0	0	0	1	1 ( 0.1)
Dyspnea (dyspnoea)	15	14 ( 0.8)	2	2 ( 2.9)	3	3 ( 1.0)	1	1 ( 0.1)
Dyspnea (dyspnoea) exacerbated	2	2 ( 0.1)	0	0	2	1 ( 0.3)	2	2 ( 0.3)
Dyspnea (dyspnoea) exertional	0	0	1	1 ( 1.4)	0	0	0	0
Hypotension	37	33 ( 1.9)	0	0	1	1 ( 0.3)	7	6 ( 0.8)
Blood pressure decreased	1	1 ( 0.1)	0	0	0	0	0	0

Sponsor's table in Amendment 0005 submitted on May 20, 2008

The following table summarizes the hypersensitivity and adverse events potentially associated with hypersensitivity at  $\leq 24$  hours after any dose in all subjects (CKD and non-CKD).

**Adverse events potentially associated with hypersensitivity by preferred term at  $\leq 24$  hours after any dose in all subjects (CKD and non-CKD)**

Body System/Preferred Term	Ferumoxytol First Course (N=1726)		Ferumoxytol Second Course (N=69)		Oral Iron (N=290)		Placebo (N=775)	
	Events N	Subject N (%)	Events N	Subject N (%)	Events N	Subject N (%)	Events N	Subject N (%)
Anaphylactoid reaction	1	1 ( 0.1)	0	0	0	0	0	0
Hypersensitivity	1	1 ( 0.1)	0	0	0	0	0	0
Pruritus	11	10 ( 0.6)	0	0	0	0	2	2 ( 0.3)
Pruritus generalised	1	1 ( 0.1)	0	0	0	0	0	0
Rash	7	7 ( 0.4)	0	0	0	0	0	0
Rash generalised	1	1 ( 0.1)	0	0	0	0	0	0
Skin reaction	1	1 ( 0.1)	0	0	0	0	0	0
Urticaria	3	3 ( 0.2)	0	0	0	0	0	0
Throat tightness	1	1 ( 0.1)	0	0	0	0	0	0
Dyspnea (dyspnoea)	5	5 ( 0.3)	0	0	0	0	1	1 ( 0.1)
Hypotension	22	21 ( 1.2)	0	0	1	1 ( 0.3)	5	4 ( 0.5)
Blood pressure decreased	1	1 ( 0.1)	0	0	0	0	0	0

Data Version: Integrated Data - FINAL

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Sponsor's table in Amendment 0005 submitted on May 20, 2008

*Other Adverse Events Potentially Associated with Hypersensitivity*

Overall, 3.5% (n=61) of 1726 subjects treated with ferumoxytol (including first and second course, CKD and non-CKD subjects) had one or more AEs potentially associated with hypersensitivity; this is in addition to the two subjects mentioned above and subjects with hypotension alone. One percent (n=18) of subjects had these AEs occur within 24 hours of dosing, and the other AEs occurred days and sometimes weeks later. All of these AEs were mild or moderate in intensity. Similar to the ferumoxytol treated subjects, AEs potentially associated with hypersensitivity occurred in 3.4% (n=10) of subjects in the oral iron and 2.1% (n=16) of subjects in the placebo treatment groups.

In the double blind, randomized, placebo-controlled, crossover design phase III clinical trial (Study 62,745-8), one or more AEs potentially associated with hypersensitivity occurred in 1.5% (n=11) of subjects during the ferumoxytol treatment follow-up period and in 1.8% (n=13) of subjects during the placebo treatment follow-up period.

The greatest proportion of subjects with AEs potentially associated with hypersensitivity was among non-iron deficient healthy subjects who received a suprathreshold course of ferumoxytol (2 doses of 510 mg each within 24 hours) as part of the double-blind, placebo controlled ‘Thorough QTc Study’. Overall, 17% (10/58) of healthy volunteers treated with ferumoxytol had one or more AEs potentially associated with hypersensitivity; 12% (n=7) within 24 hours of ferumoxytol administration. All of these events were mild or moderate in intensity, and all AEs, with the exception of one AE of dyspnea, were dermatologic (eg, rash, pruritus, urticaria). Among the 58 healthy subjects in the ‘Thorough QTc Study’ who received placebo, 5% (n=3) subjects had one or more AEs potentially associated with hypersensitivity. The higher rate of these adverse events in this population of healthy volunteers may be due to the administration of a suprathreshold course of intravenous iron (1.02 g within 24 hours) to individuals who were not iron deficient.

*Pruritis, pruritus generalized or rash pruritic:*

Among the 1726 subjects treated with ferumoxytol, 1.4% (n=24) reported pruritus, pruritus generalized or rash pruritic. The majority of cases (n=21; 88%) were mild in intensity, 3 cases were moderate, and none were severe. In 0.6% (n=11) of subjects, these events occurred within 24 hours and 10 of these events were considered related by the investigator. Pruritus, pruritus generalized or rash pruritic was reported in 0.7% (n=2) of subjects in the oral iron group (one mild and one severe in intensity, and in 1.0% (n=8) of subjects following IV saline placebo (6 were mild, 2 moderate in intensity). Two (0.3% of subjects) of these eight events in the placebo group occurred within 24 hours.

*Rash, rash generalized, rash pruritic, petechiae or skin reaction:*

Among ferumoxytol treated subjects, 1.3% (n=23) reported rash, rash generalized, rash pruritic (counted both here and in pruritis section above), petechiae or skin reaction. The majority (n=19; 83%) were mild in intensity, 4 were moderate and none were severe. In 0.5% (n=9) of subjects, the events occurred within 24 hours; these acute AEs and 7 (0.4%) other rash AEs were considered related. Rash, rash generalized, rash pruritic, petechiae or skin reaction was reported

in 0.3 % (n=1) of subjects in the oral iron group (severe in intensity), and in 0.5% (n=4) of subjects following placebo (all mild).

*Urticaria*

Among ferumoxytol-treated subjects, 4 (0.2%) reported urticaria (3 were mild and 1 moderate in intensity). In 0.2% (n=3) of subjects, these events occurred within 24 hours and were considered related. Urticaria was not reported in the oral iron group, and was reported in 1 (0.1%) subject following placebo (mild in intensity).

*Wheezing/bronchospasm or dyspnea*

Among ferumoxytol-treated subjects, 1.4% (n=25) reported wheezing/bronchospasm or dyspnea (including exacerbated and exertional). The majority (n=18; 72%) were mild in intensity; 8 were moderate, and none was severe. In 0.3% (n=5) of subjects, these events occurred within 24 hours and most of these were considered related (n=4).

Wheezing/bronchospasm or dyspnea was reported in 1.7% (n=5) subjects in the oral iron group (4 were mild, 1 moderate/severe in intensity), and in 0.9% (n=7) subjects following placebo (4 mild, 3 moderate in intensity). One (0.1%) of these events in the placebo group occurred within 24 hours.

*Hypotension reactions*

Overall, 33 subjects (1.9%) in the ferumoxytol treatment groups had hypotension AEs, compared with 0.3% in the oral iron group, and 0.8% in the placebo group.

Among the 1726 subjects treated with ferumoxytol, 1.9% (n=33) reported hypotension (excluding 1 subject with blood pressure decreased), the majority of which were mild (n=19; 58%), 12 were moderate, and 3 severe in intensity; 0.3% (n=5) of these were reported as serious adverse events. The majority of hypotension AEs (n=18; 55% of hypotension cases) were regarded as unrelated to ferumoxytol treatment by the clinical investigators. Most hypotensive episodes were transient, managed by observation or volume expansion, and subjects recovered without sequelae. Nearly all of the 33 subjects with hypotension following ferumoxytol administration (n=29; 88% of hypotension cases) reported only isolated hypotension without other AEs potentially associated with a hypersensitivity reaction. Only 4 subjects reported hypotension in conjunction with one or more symptoms potentially associated with hypersensitivity reactions. Of the 4 subjects, two had preexisting dyspnea and pruritis, and both cases were judged by clinical investigators as unrelated events.

Among the remaining 2 subjects, one (Study 62,745-7; subject # 203-162) had non-serious adverse events of hypotension, pruritis, and urticaria within minutes after the first dose of ferumoxytol (510 mg); subsequently, the subject experienced accelerated hypertension, dizziness, and dyspnea. The other subject (Study 62,745-8; subject # 239-821) had severe hypotension that was considered an anaphylactoid reaction within minutes after the first dose of ferumoxytol (510 mg) and was discussed in the corresponding section above. In twenty-one

(1.2%) of the subjects with hypotension events, hypotension occurred within 24 hours after ferumoxytol administration.

In the double blind, randomized, placebo-controlled, crossover study (Study 62,745-8), hypotension was reported in 1.1% (8/713) of subjects in the ferumoxytol treatment follow-up period and 1.0% (7/711) in the placebo treatment follow-up period; two subjects experienced hypotension in both the ferumoxytol and placebo treatment periods.

### 7.3 Major Safety Results

#### 7.3.1 Deaths

There were 31 deaths in the clinical program. Thirty of the 31 deaths were in subjects with CKD (from Protocols 62,745-3, 62,745-4, 62,745-5, 62,745-6, 62,745-7, and 62,745-8) and one death was in an imaging subject (from Protocol 58,254-5); there were no deaths in healthy volunteers.

Four deaths occurred pre-dose in subjects who had signed an informed consent form but never received study treatment; only one of these four subjects died after randomization. Details for these subjects are provided below:

- Subject 121-503 (Not Randomized) in Study 62745-5 signed an informed consent, but was a screen failure for the study. The patient was not randomized to a treatment group and did not receive any study treatment.
- Subject 139-805 (Randomized to Sequence 1) in cross-over safety Study 62745-8 signed an informed consent, was randomized to treatment sequence 1 (ferumoxytol first followed by placebo administration), but did not receive any study treatment.
- Subject 239-801 (Not Randomized) in cross-over safety Study 62745-8 signed an informed consent, but was never randomized and never received any study treatment.
- Subject 259-118 (Not Randomized) in Study 62745-7 signed an informed consent, but died prior to randomization and prior to receipt of any study treatment.

Among the 27 post-dose deaths, 19 deaths (1.1%) occurred in subjects treated with ferumoxytol and 8 deaths (2.8%) occurred in subjects treated with oral iron. Deaths which occurred in Study 62,745-8 (cross-over study) following administration of both ferumoxytol and placebo were all conservatively attributed to ferumoxytol.

When deaths were examined by time to occurrence (pre-dose, and within 30 days, 30-60 days, and more than 60 days following the last dose of study treatment), there was a lower incidence of death with ferumoxytol in each time category relative to oral iron.

Deaths by treatment group and time to occurrence are summarized in the table below.

**All Deaths in the Clinical Development Program**

<b>Time relative to final dose of study drug</b>	<b>Ferumoxytol (N=1726)</b>	<b>Oral Iron (N=290)</b>	<b>Pre-dose</b>
Pre-dose	-	-	4
Within 30 days post final dose	12 (0.7%)	4 (1.4%)	-
30-60 days post final dose	4 (0.2%)	3 (1.0%)	-
More than 60 days post final dose	3 (0.2%)	1 (0.3%)	-
<b>TOTAL</b>	<b>19 (1.1%)</b>	<b>8 (2.8%)</b>	<b>4</b>

Sponsor's table in summary of clinical safety

The following table shows the deaths by treatment group in each study in CKD and non-CKD subjects.

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**Deaths in each study in CKD and Non-CKD subjects**

		Treatment group	N	Deaths N	Subjects with reported CV AE
All Subjects					
All 11 clinical studies		FER	1726	19	8
		Oral iron	290	8	3
		Placebo	775	04	0
		Moxifloxacin	58	0	0
		Pre-Dose		4	N/A
CKD Subjects					
62,745-2		FER -1x125 mg	10	0	0
		FER - 1x250 mg	10	0	0
62,745-3		FER- 8x128 mg	15	1	0
		FER - 2x510 mg	11	0	0
		Oral iron	10	0	0
62,745-4		FER - 4x255 mg	10	0	0
		FER - 2x510 mg	11	1	1
62,745-5	Randomized phase Readmission	FER - 4x255 mg	60	2	0
		FER - 2x510 mg	168	3	1
		Oral iron	131	3	1
		Pre-Dose		1	N/A
		FER 2x510 mg	751	0	0
62,745-6	Randomized phase Readmission	FER - 2x510 mg	217	2	1
		Oral iron	75	2	1
		Pre-Dose		1	N/A
		FER - 2x510 mg	602	1	1
62,745-7	Randomized phase Readmission.	FER - 2x510 mg	220	4	3
		Oral iron	74	3	1
		FER - 2x510 mg	513	0	0
62,745-8		FER -1x510 mg	713	4	1
		Placebo	711	0	0
		Pre-dose		2	N/A

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	Treatment group	N	Deaths N	Subjects with reported CV AE
TOTAL	FER	1562*	18	8
	Oral Iron	290	8	3
	Placebo	711	0	0
	Pre-Dose		45	N/A
NON-CKD Subjects				
7228-01	FER - $\leq 4$ mg/kg	35	0	0
	Placebo	6	0	0
62,745-9	FER - 2x510 mg	58	0	0
	Placebo	58	0	0
	Moxifloxacin	58	0	0
58,254-2	FER $\leq 4$ mg/kg	17	0	0
58,254-5	FER $\leq 4$ mg/kg	54	1	0
TOTAL	FER	164	1	0
	Placebo	64	0	0
	Moxifloxacin	58	0	0

Sponsor's table in Amendment 0001 submitted April 3, 2008

The death rate was examined by the type of trials including randomized, non-randomized and cross-over studies (see Table below). In randomized parallel controlled trials, Overall death rate was 1.45% in ferumoxytol-treated patients as compared to 1.99% in oral-iron-treated patients.

**Deaths in the All Clinical Studies**

	<b>Ferumoxytol</b>	<b>Control (oral iron, placebo, or moxifloxacin)</b>	<b>Pre-dose</b>
Randomized parallel group controlled studies	11/758 (1.45%)	8/402 (1.99%)	2
Uncontrolled studies	4/255 (1.57%)	0/10 (0.0%)	-
<b>TOTAL</b>	<b>15/1013 (1.5%)</b>	<b>8 /412 (1.9%)</b>	<b>2</b>
Cross-over study*	4/713 (0.56%)	0/711	2

\*Patients received ferumoxytol followed by placebo or placebo followed by ferumoxytol 7 days later  
 Reviewer's table

The following table shows the death rate by the type of trials in CKD patients. In randomized, parallel group controlled trials, the death rate was 1.65% with Ferumoxytol and 2.86% with oral iron.

**Deaths in CKD Patients**

	<b>Ferumoxytol</b>	<b>Oral Iron</b>	<b>Pre-dose</b>
Randomized parallel group controlled studies	11/665 (1.65%)	8/280 (2.86%)	2
Uncontrolled studies	3/184 (1.63%)	0/10 (0.0%)	-
<b>TOTAL</b>	<b>14/849 (1.65%)</b>	<b>8/290 (2.76%)</b>	<b>2</b>
Cross-over study*	4/713 (0.56%)	0/711 (placebo)	2

\*Patients received ferumoxytol followed by placebo or placebo followed by ferumoxytol 7 days later  
 Reviewer's table

The following table shows the death rate by CKD stage. The death rate was numerically lower in the ferumoxytol group (0.9%) as compared to the oral iron group (1.5%) in patients with CKD stage 1-5 as well as in patients undergoing hemodialysis (1.5% vs. 2.1%). They were only 43 patients undergoing peritoneal dialysis and no death occurred in these patients.

**Deaths by CKD Stage**

CKD Stage	Ferumoxytol	Oral Iron
CKD Stage 1-5	9/938 (0.9%)	5/149 (1.5%)
CKD Stage 5D-HD	9/581(1.5%)	3/141 (2.1%)
CKD Stage 5D-PD	0/43	-

Reviewer's table

The following table shows deaths that occurred in the 3 pivotal trials. Mortality rate in 2 trials in patients with CKD stage 1-5 was numerically lower than that in oral iron group (see Table below). Mortality rate was similar between the ferumoxytol group and the oral iron group in hemodialysis patients.

**Deaths in Three Phase 3 Studies**

Studies	Ferumoxytol	Oral Iron	Pre-dose
62,745-6 (CKD Stage 1-5)	3/255 (1.2%)	2/75 (2.7%)	1
62,745-7 (CKD Stage 1-5)	4/220 (1.8%)	3/74 (4.1%)	-
62,745-5 (HD)	5/228 (2.2%)	3/131 (2.3%)	1

Reviewer's table

The death rate was also examined by dosing regimens (see Table below). There was a lower incidence of death with the proposed regimen of 2 x 510 mg (1.3%) relative to oral iron (2.8%) overall, and in each of the time-to-occurrence categories. Two deaths occurred with the 4 x 255 mg ferumoxytol regimen (2.9%) and one death with the 8 x 128 mg regimen (6.7%). However, there was a limited number of subjects who had been exposed to these dosing regimens.

**Deaths in the Clinical Program, by Ferumoxytol Dosing Regimens that Provide the Proposed 1.02 g Therapeutic Course**

	Ferumoxytol	Oral Iron	Pre-dose
--	-------------	-----------	----------

Time relative to final dose of study drug	2 x 510 mg (N=749)	4 x 255 mg (N=70)	8 x 128 mg (N=15)	(N=290)	
Pre-dose	-	-	-	-	4
Within 30 days post final dose	6 (0.8%)	1 (1.4%)	1 (6.7%)	4 (1.4%)	-
30-60 days post final dose	3 (0.4%)	1 (1.4%)	-	3 (1.0%)	-
More than 60 days post final dose	1 (0.1%)	-	-	1 (0.3%)	-
<b>TOTAL</b>	<b>10 (1.3%)</b>	<b>2 (2.9%)</b>	<b>1 (6.7%)</b>	<b>8 (2.8%)</b>	<b>4</b>

Note: Only deaths associated with regimens providing the proposed 1.02 g therapeutic course are shown; four deaths following 1 x 510 mg ferumoxytol in a cross-over study, 1 death following 2 courses of 2 x 510 mg, and 1 death following 4 mg Fe/kg in imaging study are not shown.

Sponsor's table in summary of clinical safety

The causes of deaths are summarized in the following table. There was a similar incidence of cardiac deaths in ferumoxytol-treated patients (12, 0.7%) as compared to that in oral iron-treated patients (3, 1%). The deaths attributed to sepsis were also similar between the two treatments (0.1% vs. 0.3%). The other causes of deaths included suicide, colon cancer, cerebrovascular accident, and unknown cause in ferumoxytol patients and grand mal seizure, uremia, renal failure (2) in oral iron patients.

**Causes of Deaths in All Patients**

Causes of Deaths	Ferumoxytol (N=1726)	Oral Iron (N=290)	Pre-dose
Cardiac	12 (0.7%)	3 (1.0%)	3
Sepsis	3 (0.1%)	1 (0.3%)	1
Others	4 (0.2%)	4 (1.4%)	0

Reviewer's table

### 7.3.2 Nonfatal Serious Adverse Events

#### Nonfatal SAEs in CKD patients

The overall incidence of TESAEs among subjects receiving a first course of ferumoxytol treatment (7.1%) was lower than in subjects receiving oral iron treatment (11.7%), but higher than in subjects receiving placebo (2.4%). The incidence of TESAEs following a second course of ferumoxytol (8.7%) was slightly higher than following the first course.

The most commonly reported TESAEs, defined as those occurring in more than two subjects after treatment with a first course of ferumoxytol, had a similar or lower incidence relative to oral iron, and included cardiac failure congestive (0.7% vs. 1.0%), pneumonia (0.4% vs. 1.0%), hypotension (0.3% in each group), chest pain (0.3% vs. 0%), renal failure acute (0.3% in each group), renal failure chronic (0.2% vs. 0.3%), acute myocardial infarction (0.2% vs. 0%), coronary artery disease (0.2% vs. 0%), abdominal pain (0.2% vs. 0%), sepsis (0.2% vs. 0.7%), mental status changes (0.2% vs. 0%), and hypoglycemia (0.2% vs. 0.3%). The most commonly reported TESAEs for subjects treated with oral iron were anemia (1.4%), cardiac failure congestive (1.0%), and pneumonia (1.0%), which occurred with an incidence of 0%, 0.7%, and 0.4%, respectively, in subjects treated with a first course of ferumoxytol.

Only nine unique TESAEs were reported in six subjects treated with a second course of ferumoxytol while there were 24 unique TESAEs reported in 17 subjects treated with placebo.

The treatment emergent serious adverse events (TESAEs) that occurred in subjects with CKD are summarized in the following table.

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**Number (Percent) of Subjects with Treatment-emergent Serious Adverse Events by Treatment Exposure . CKD Subjects (Safety Population)**

<b>System Organ Class Preferred Term a</b>	<b>Ferumoxytol First Course N=1562 n (%)</b>	<b>Ferumoxytol Second Course N=69 n (%)</b>	<b>Oral Iron N=290 n (%)</b>	<b>Placebo N=711 n (%)</b>
<b>Overall</b>	111 (7.1)	6 (8.7)	34 (11.7)	17 (2.4)
<b>Blood and Lymphatic System Disorders</b>	0	0	4 (1.4)	0
Anemia	0	0	4 (1.4)	0
<b>Cardiac Disorders</b>	27 (1.7)	2 (2.9)	10 (3.4)	3 (0.4)
Acute coronary syndrome	1 (0.1)	0	0	0
Acute myocardial infarction	3 (0.2)	0	1 (0.3)	0
Angina pectoris	2 (0.1)	0	0	1 (0.1)
Angina unstable	2 (0.1)	0	1 (0.3)	0
Aortic valve disease	0	0	1 (0.3)	0
Aortic valve incompetence	1 (0.1)	0	0	0
Aortic valve stenosis	1 (0.1)	0	0	0
Arrhythmia	0	0	1 (0.3)	0
Atrial fibrillation	2 (0.1)	1 (1.4)	0	0
Atrial flutter	2 (0.1)	0	0	0
Atrioventricular block complete	1 (0.1)	0	0	0
Bradycardia	0	0	2 (0.7)	0
Cardiac arrest	2 (0.1)	0	1 (0.3)	0
Cardiac failure congestive	11 (0.7)	1 (1.4)	3 (1.0)	1 (0.1)
Cardiorespiratory arrest	1 (0.1)	0	0	0
Coronary artery disease	3 (0.2)	0	0	0
Electromechanical dissociation	0	0	0	1 (0.1)
Ischemic cardiomyopathy	1 (0.1)	0	0	0
Myocardial infarction	1 (0.1)	0	0	0
Pericardial effusion	1 (0.1)	0	0	0
Presyncope	0	0	1 (0.3)	0
Supraventricular tachycardia	1 (0.1)	0	0	0
Ventricular dysfunction	1 (0.1)	0	0	0
Ventricular fibrillation	1 (0.1)	0	0	0
Ventricular tachycardia	1 (0.1)	0	0	1 (0.1)

System Organ Class Preferred Term a	Ferumoxytol First Course N=1562 n (%)	Ferumoxytol Second Course N=69 n (%)	Oral Iron N=290 n (%)	Placebo N=711 n (%)
<b>Endocrine Disorders</b>	1 (0.1)	0	0	0
Adrenal insufficiency	1 (0.1)	0	0	0
<b>Gastrointestinal Disorders</b>	11 (0.7)	1 (1.4)	4 (1.4)	1 (0.1)
Abdominal pain	3 (0.2)	0	0	0
Collitis ulcerative	1 (0.1)	0	0	0
Diarrhea	2 (0.1)	0	0	0
Diverticulum	1 (0.1)	0	0	0
Esophagitis ulcerative	1 (0.1)	0	0	0
Gastric ulcer hemorrhage	0	1 (1.4)	0	0
Gastritis	0	0	1 (0.3)	0
Gastrointestinal hemorrhage	2 (0.1)	0	0	0
Hemorrhoidal hemorrhage	1 (0.1)	0	0	0
Hemorrhoids	1 (0.1)	0	0	0
Impaired gastric emptying	1 (0.1)	0	0	0
Nausea	0	0	1 (0.3)	0
Pancreatitis	0	0	1 (0.3)	1 (0.1)
Upper gastrointestinal hemorrhage	0	0	1 (0.3)	0
Vomiting	0	0	1 (0.3)	0
<b>General Disorders and Administrative Site Conditions</b>	6 (0.4)	0	3 (1.0)	1 (0.1)
Asthenia	1 (0.1)	0	0	0
Chest discomfort	1 (0.1)	0	0	0
Chest pain	4 (0.3)	0	0	1 (0.1)
Chills	0	0	1 (0.3)	0
Hypothermia	0	0	1 (0.3)	0
Multi-organ failure	0	0	1 (0.3)	0
Pyrexia	0	0	1 (0.3)	0
<b>Glucose Metabolism Disorders</b>	1 (0.1)	0	0	0
Diabetes mellitus	1 (0.1)	0	0	0
<b>Hepatobiliary Disorders</b>	2 (0.1)	0	0	0
Cholelithiasis	2 (0.1)	0	0	0

<b>System Organ Class Preferred Term a</b>	<b>Ferumoxytol First Course N=1562 n (%)</b>	<b>Ferumoxytol Second Course N=69 n (%)</b>	<b>Oral Iron N=290 n (%)</b>	<b>Placebo N=711 n (%)</b>
<b>Immune System Disorders</b>	1 (0.1)	0	0	1 (0.1)
Anaphylactoid reaction	1 (0.1)	0	0	0
Sarcoidosis	0	0	0	1 (0.1)
<b>Infections and Infestations</b>	26 (1.7)	2 (2.9)	8 (2.8)	8 (1.1)
Bacteremia	1 (0.1)	0	0	0
Catheter bacteremia	1 (0.1)	0	0	0
Cellulitis	2 (0.1)	1 (1.4)	2 (0.7)	3 (0.4)
Central line infection	0	1 (1.4)	0	0
Diverticulitis	1 (0.1)	0	0	0
Gangrene	2 (0.1)	0	1 (0.3)	1 (0.1)
Gastroenteritis	1 (0.1)	0	1 (0.3)	0
Listeriosis	1 (0.1)	0	0	0
Localized infection	2 (0.1)	0	0	0
Osteomyelitis	2 (0.1)	0	0	0
Peritonitis bacterial	2 (0.1)	0	0	0
Pneumonia	6 (0.4)	0	3 (1.0)	0
Postoperative infection	1 (0.1)	0	0	0
Sepsis	3 (0.2)	0	2 (0.7)	1 (0.1)
Septic shock	0	0	0	1 (0.1)
Serratia infection	1 (0.1)	0	0	0
Staphylococcal bacteremia	1 (0.1)	0	0	1 (0.1)
Urinary tract infection	0	0	0	1 (0.1)
<b>Injury, Poisoning, and Procedural Complications</b>	3 (0.2)	0	2 (0.7)	4 (0.6)
Compression fracture	0	0	1 (0.3)	0
Fall	1 (0.1)	0	0	0
Graft thrombosis	0	0	0	1 (0.1)
Hip fracture	1 (0.1)	0	1 (0.3)	0
Lower limb fracture	1 (0.1)	0	0	0
Patella fracture	0	0	0	1 (0.1)
Tendon rupture	0	0	0	1 (0.1)
Thermal burn	0	0	0	1 (0.1)

<b>System Organ Class Preferred Term a</b>	<b>Ferumoxytol First Course N=1562 n (%)</b>	<b>Ferumoxytol Second Course N=69 n (%)</b>	<b>Oral Iron N=290 n (%)</b>	<b>Placebo N=711 n (%)</b>
<b>Investigations</b>	4 (0.3)	0	2 (0.7)	0
Blood pressure increased	1 (0.1)	0	0	0
Catheterization cardiac	1 (0.1)	0	1 (0.3)	0
Hemoglobin decreased	2 (0.1)	0	0	0
Troponin increased	0	0	1 (0.3)	0
<b>Metabolism and Nutrition Disorders</b>	8 (0.5)	0	2 (0.7)	0
Fluid overload	0	0	1 (0.3)	0
Gout	1 (0.1)	0	0	0
Hypercalcemia	1 (0.1)	0	0	0
Hyperkalemia	1 (0.1)	0	0	0
Hypoglycemia	3 (0.2)	0	1 (0.3)	0
Hypovolemia	1 (0.1)	0	0	0
Shock hypoglycemic	1 (0.1)	0	0	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	2 (0.1)	0	0	0
Back pain	1 (0.1)	0	0	0
Neck pain	1 (0.1)	0	0	0
<b>Nervous System Disorders</b>	10 (0.6)	0	2 (0.7)	0
Cerebrovascular accident	1 (0.1)	0	0	0
Dementia Alzheimer.s type	1 (0.1)	0	0	0
Grand mal convulsion	1 (0.1)	0	1 (0.3)	0
Hypoxic encephalopathy	1 (0.1)	0	0	0
Lethargy	1 (0.1)	0	0	0
Loss of consciousness	0	0	1 (0.3)	0
Normal pressure hydrocephalus	1 (0.1)	0	0	0
Parkinsonism	1 (0.1)	0	0	0
Syncope	2 (0.1)	0	0	0
Transient ischemic attack	2 (0.1)	0	0	0
<b>Psychiatric Disorders</b>	5 (0.3)	0	0	0
Completed suicide	1 (0.1)	0	0	0
Confusional state	1 (0.1)	0	0	0
Mental status changes	3 (0.2)	0	0	0

<b>System Organ Class Preferred Term a</b>	<b>Ferumoxytol First Course N=1562 n (%)</b>	<b>Ferumoxytol Second Course N=69 n (%)</b>	<b>Oral Iron N=290 n (%)</b>	<b>Placebo N=711 n (%)</b>
<b>Renal and Urinary Disorders</b>	8 (0.5)	1 (1.4)	5 (1.7)	1 (0.1)
Azotemia	0	0	2 (0.7)	0
Micturition disorder	1 (0.1)	0	0	0
Renal failure acute	4 (0.3)	0	1 (0.3)	0
Renal failure chronic	3 (0.2)	1 (1.4)	1 (0.3)	0
Renal tubular necrosis	0	0	1 (0.3)	0
<b>Reproductive System and Breast Disorders</b>	1 (0.1)	0	0	0
Scrotal swelling	1 (0.1)	0	0	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	7 (0.4)	1 (1.4)	5 (1.7)	0
Acute pulmonary edema	0	0	1 (0.3)	0
Chronic obstructive airways disease exacerbated	2 (0.1)	0	2 (0.7)	0
Chronic obstructive pulmonary disease	1 (0.1)	0	0	0
Dyspnea	1 (0.1)	0	0	0
Dyspnea exacerbated	0	0	1 (0.3)	0
Hypoxia	1 (0.1)	0	0	0
Pulmonary edema	2 (0.1)	1 (1.4)	0	0
Pulmonary mass	0	0	1 (0.3)	0
Respiratory distress	1 (0.1)	0	0	0
<b>Skin and Subcutaneous Tissue Disorders</b>	2 (0.1)	0	0	1 (0.1)
Angioneurotic edema	1 (0.1)	0	0	0
Petechiae	0	0	0	1 (0.1)
Skin ulcer	1 (0.1)	0	0	0
<b>Vascular Disorders</b>	9 (0.6)	1 (1.4)	3 (1.0)	0
Aortic stenosis	1 (0.1)	0	0	0
Deep vein thrombosis	0	1 (1.4)	0	0
Hemorrhage	0	0	1 (0.3)	0
Hypertensive crisis	2 (0.1)	0	0	0
Hypertensive emergency	0	0	1 (0.3)	0

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Hypotension	5 (0.3)	0	1 (0.3)	0
Peripheral vascular disorder	1 (0.1)	0	0	0

a. Subjects may be counted under more than one preferred term.

Note: Safety data in this table were derived from the following protocols: 62,745-2, 62,745-3, 62,745-4, 62,745-5, 62,745 -6, 62,745-7, and 62,745-8.

Sponsor's table in summary of clinical safety

### **Treatment-emergent Serious Adverse Events in Randomized, Open-label, Controlled Studies**

In randomized phase 3 trials (62,745-5, 62,745-6, 62,745-7), the overall incidence of TESAEs in the first course ferumoxytol 2 x 510 mg treatment group was 13.3% as compared to 12.1% in the oral iron treatment group. The incidences of the most commonly reported TESAEs, defined as those occurring in more than two subjects ( $\geq 0.5\%$ ) in the 2 x 510 mg ferumoxytol group, comparing to oral iron, were cardiac failure congestive (0.5% vs. 1.1%), chest pain (0.5% vs. 0%), mental status changes (0.5% vs. 0%), and hypotension (0.5% vs. 0.4%). The most commonly reported TESAEs for subjects treated with oral iron were anemia (1.4%), cardiac failure congestive (1.1%), and pneumonia (1.1%), which occurred with an incidence of 0%, 0.5%, and 0.3%, respectively, in the 2 x 510 mg ferumoxytol treatment group. Few TESAEs were reported for subjects treated with four doses of 255 mg ferumoxytol.

The TESAEs that occurred in subjects with CKD are summarized for the three Phase 3 pivotal studies.

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**Number (Percent) of Subjects with Treatment-emergent Serious Adverse Events in Randomized, Open label, Active-Controlled Studies – CKD Subjects (Safety Population)**

<b>System Organ Class Preferred Term a</b>	<b>Ferumoxytol 4 x 255 mg N=60 n (%)</b>	<b>Ferumoxytol 2 x 510 mg N=605 n (%)</b>	<b>Oral Iron 200 mg N=280 n (%)</b>
<b>Overall</b>	8 (13.3)	59 (9.8)	34 (12.1)
<b>Blood and Lymphatic System Disorders</b>	0	0	4 (1.4)
Anemia	0	0	4 (1.4)
<b>Cardiac Disorders</b>	2 (3.3)	12 (2.0)	10 (3.6)
Acute coronary syndrome	0	1 (0.2)	0
Acute myocardial infarction	0	1 (0.2)	1 (0.4)
Angina unstable	0	2 (0.3)	0
Aortic valve disease	0	0	1 (0.4)
Aortic valve incompetence	0	1 (0.2)	0
Aortic valve stenosis	0	1 (0.2)	0
Arrhythmia	0	0	1 (0.4)
Atrial flutter	0	1 (0.2)	0
Bradycardia	0	0	2 (0.7)
Cardiac arrest	0	2 (0.3)	1 (0.4)
Cardiac failure congestive	1 (1.7)	3 (0.5)	3 (1.1)
Cardiorespiratory arrest	0	1 (0.2)	0
Coronary artery disease	0	2 (0.3)	0
Ischemic cardiomyopathy	0	1 (0.2)	0
Myocardial infarction	0	1 (0.2)	0
Pericardial effusion	1 (1.7)	0	0
Presyncope	0	0	1 (0.4)
Supraventricular tachycardia	0	1 (0.2)	0
Ventricular fibrillation	0	1 (0.2)	0
<b>Endocrine Disorders</b>	0	1 (0.2)	0
Adrenal insufficiency	0	1 (0.2)	0
<b>Gastrointestinal Disorders</b>	1 (1.7)	4 (0.7)	4 (1.4)
Abdominal pain	0	1 (0.2)	0
Colitis ulcerative	0	1 (0.2)	0
Esophagitis ulcerative	0	1 (0.2)	0

	Ferumoxytol 4 x 255 mg N=60 n (%)	Ferumoxytol 2 x 510 mg N=605 n (%)	Oral Iron 200 mg N=280 n (%)
<b>System Organ Class Preferred Term a</b>			
Gastritis	0	0	1 (0.4)
Gastrointestinal hemorrhage	1 (1.7)	0	0
Impaired gastric emptying	0	1 (0.2)	0
Nausea	0	0	1 (0.4)
Pancreatitis	0	0	1 (0.4)
Upper gastrointestinal hemorrhage	0	0	1 (0.4)
Vomiting	0	0	1 (0.4)
<b>General Disorders and Administrative Site Conditions</b>	0	3 (0.5)	3 (1.1)
Chest pain	0	3 (0.5)	0
Chills	0	0	1 (0.4)
Hypothermia	0	0	1 (0.4)
Multi-organ failure	0	0	1 (0.4)
Pyrexia	0	0	1 (0.4)
<b>Hepatobiliary Disorders</b>	0	2 (0.3)	0
Cholelithiasis	0	2 (0.3)	0
<b>Infections and Infestations</b>	3 (5.0)	14 (2.3)	8 (2.9)
Bacteremia	0	1 (0.2)	0
Catheter bacteremia	0	1 (0.2)	0
Cellulitis	0	1 (0.2)	2 (0.7)
Diverticulitis	0	1 (0.2)	0
Gangrene	0	1 (0.2)	1 (0.4)
Gastroenteritis	0	1 (0.2)	1 (0.4)
Localized infection	0	1 (0.2)	0
Osteomyelitis	0	1 (0.2)	0
Pneumonia	1 (1.7)	2 (0.3)	3 (1.1)
Postoperative infection	0	1 (0.2)	0
Sepsis	1 (1.7)	2 (0.3)	2 (0.7)
Serratia infection	1 (1.7)	0	0
Staphylococcal bacteremia	0	1 (0.2)	0

	Ferumoxytol 4 x 255 mg N=60 n (%)	Ferumoxytol 2 x 510 mg N=605 n (%)	Oral Iron 200 mg N=280 n (%)
<b>System Organ Class Preferred Term a</b>			
<b>Injury, Poisoning, and Procedural Complications</b>	0	1 (0.2)	2 (0.7)
Compression fracture	0	0	1 (0.4)
Fall	0	1 (0.2)	0
Hip fracture	0	0	1 (0.4)
<b>Investigations</b>	0	0	2 (0.7)
Catheterization cardiac	0	0	1 (0.4)
Troponin increased	0	0	1 (0.4)
<b>Metabolism and Nutrition Disorders</b>	0	5 (0.8)	2 (0.7)
Fluid overload	0	0	1 (0.4)
Hypercalcemia	0	1 (0.2)	0
Hyperkalemia	0	1 (0.2)	0
Hypoglycemia	0	1 (0.2)	1 (0.4)
Hypovolemia	0	1 (0.2)	0
Shock hypoglycemic	0	1 (0.2)	0
<b>Musculoskeletal and Connective Tissue Disorders</b>	0	1 (0.2)	0
Back pain	0	1 (0.2)	0
<b>Nervous System Disorders</b>	0	8 (1.3)	2 (0.7)
Cerebrovascular accident	0	1 (0.2)	0
Dementia Alzheimer.s type	0	1 (0.2)	0
Grand mal convulsion	0	1 (0.2)	1 (0.4)
Hypoxic encephalopathy	0	1 (0.2)	0
Lethargy	0	1 (0.2)	0
Loss of consciousness	0	0	1 (0.4)
Normal pressure hydrocephalus	0	1 (0.2)	0
Syncope	0	2 (0.3)	0
Transient ischemic attack	0	1 (0.2)	0
<b>Psychiatric Disorders</b>	0	5 (0.8)	0
Completed suicide	0	1 (0.2)	0
Confusional state	0	1 (0.2)	0
Mental status changes	0	3 (0.5)	0

	Ferumoxytol 4 x 255 mg N=60 n (%)	Ferumoxytol 2 x 510 mg N=605 n (%)	Oral Iron 200 mg N=280 n (%)
<b>System Organ Class Preferred Term a</b>			
<b>Renal and Urinary Disorders</b>	1 (1.7)	4 (0.7)	5 (1.8)
Azotemia	0	0	2 (0.7)
Renal failure acute	0	2 (0.3)	1 (0.4)
Renal failure chronic	1 (1.7)	2 (0.3)	1 (0.4)
Renal tubular necrosis	0	0	1 (0.4)
<b>Reproductive System and Breast Disorders</b>	0	1 (0.2)	0
Scrotal swelling	0	1 (0.2)	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	1 (1.7)	4 (0.7)	5 (1.8)
Acute pulmonary edema	0	0	1 (0.4)
Chronic obstructive airways disease exacerbated	0	1 (0.2)	2 (0.7)
Dyspnea exacerbated	0	0	1 (0.4)
Hypoxia	0	1 (0.2)	0
Pulmonary edema	1 (1.7)	1 (0.2)	0
Pulmonary mass	0	0	1 (0.4)
Respiratory distress	0	1 (0.2)	0
<b>Skin and Subcutaneous Tissue Disorders</b>	0	1 (0.2)	0
Angioneurotic edema	0	1 (0.2)	0
<b>Vascular Disorders</b>	1 (1.7)	5 (0.8)	3 (1.1)
Hemorrhage	0	0	1 (0.4)
Hypertensive crisis	1 (1.7)	1 (0.2)	0
Hypertensive emergency	0	0	1 (0.4)
Hypotension	0	3 (0.5)	1 (0.4)
Peripheral vascular disorder	0	1 (0.2)	0

a. Subjects may be counted in more than one AE category.

Note: Safety data in this table were derived from the following protocols: 62,745-5, 62,745-6, and 62,745-7.  
Sponsor's table in summary of clinical safety