CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-180

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science (OTS)
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-180	SE000
Drug Name:	Ferumoxytol (Intravenous Injection, Solution)	
Indication(s):	Treatment of iron deficiency anemia in patients with chronic kidney disease (CKD)	
Applicant:	AMAG Pharmaceuticals, Inc.	
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Keywords: Confidence Intervals, Open Label, Randomized, Sensitivity Analysis

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Ferumoxytol is a superparamagnetic iron oxide nanoparticle coated with polyglucose sorbitol carboxymethylether. It is an intravenous iron injection and is developed for treatment of iron deficiency anemia.

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

The efficacy and safety of Ferumoxytol for the treatment of iron deficiency anemia was studied in three randomized, active-controlled, multicenter, open-label, phase III clinical trials across the CKD continuum (Stages 1-5 and 5D as defined by the level of kidney function per K/DOQI guidelines) (Studies 62,745-5 (post –amendment), 62,745-6 and 62,745-7).

All these trials were designed as superiority trials. These studies assessed the efficacy and safety of two 510 mg doses of Ferumoxytol relative to oral iron in a total of 923 subjects with CKD stages 1-5 and 5D on hemodialysis (including 31 kidney transplant recipients). Primary and secondary endpoints were identical in these studies. The primary endpoint was the mean change in hemoglobin (Hgb) from baseline to Day 35. Secondary endpoints included the percentage of subjects who were hemoglobin responders at Day 35 (defined as a $\geq$1 g/dL increase in hemoglobin from baseline), the mean change from baseline in serum ferritin at Day 21 and the mean change from baseline in Transferrin Saturation (TSAT) (%) ferritin at Day 35.

The following table 1 summarizes the change in hemoglobin (Hgb) and iron parameters from baseline for each treatment group for three studies.

Table 1: Clinical Studies – Hemoglobin and Iron Parameters (ITT population)

Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)			
Endpoint	Ferumoxytol (n=114)	Oral Iron (n=116)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	1.02±1.13	0.46±1.06	0.0002
Secondary Endpoints			
% Hgb responders at Day 35[a]	49.1	25.0	0.0002
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	356.66±247.12	-37.56±106.98	<0.0001
TSAT change from baseline at Day 35 (%)	6.44±12.59	0.55±8.34	<0.0001
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)			
Endpoint	Ferumoxytol (n=228)	Oral Iron (n=76)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	0.82±1.24	0.16±1.02	<0.0001
Secondary Endpoints			
% Hgb responders at Day 35[a]	39.0	18.4	0.0010
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	518.08±331.86	6.47±47.16	<0.0001
TSAT change from baseline at Day 35 (%)	9.77±9.17	1.31±6.38	<0.0001
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)			
Endpoint	Ferumoxytol (n=226)	Oral Iron (n=77)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	1.22±1.25	0.52±0.98	<0.0001
Secondary Endpoints			
% Hgb responders at Day 35[a]	51.8	19.5	<0.0001
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	412.58±247.95	4.26±48.22	<0.0001
TSAT change from baseline at Day 35 (%)	9.20±9.37	0.28±4.65	<0.0001

[a] Hgb responders were defined as a ≥1 g/dL increase in hemoglobin from baseline.
* The nominal p-values on secondary endpoints are for information only.

As seen from the above table, protocol defined primary endpoints were met in each of the pivotal studies. The efficacy of Ferumoxytol in subjects treated with 2 x 510 mg, as assessed by the mean increase from baseline in hemoglobin, was statistically significantly greater than with oral iron. There was a (nominal) statistical significance on the protocol defined secondary endpoints. Subgroup and sensitivity analyses also revealed consistency in benefit. The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with 2 x 510 mg Ferumoxytol was similar to treatment with 200 mg/day oral iron. The evidence from the three key Phase 3 studies supports the efficacy of 1.02 g dose of Ferumoxytol for the proposed indication of the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

1.2 Brief Overview of Clinical Studies

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

Ferumoxytol for the treatment of iron deficiency anemia has been investigated in four randomized Phase III trials across the CKD continuum (Stages 1-5 and 5D as defined by the level of kidney function per K/DOQI guidelines).

In three randomized, active-controlled, multicenter, open-label clinical trials (Studies 62,745-5, 62,745-6 and 62,745-7), a total of 605 subjects were exposed to two doses of 510 mg of Ferumoxytol over 5 to 8 days for a mean cumulative iron dose of 1,002 mg and a total of 280 subjects were exposed to 200 mg/day of oral iron for 21 days for a mean cumulative oral elemental iron dose of 3,782 mg. These studies assessed the efficacy and safety of two 510 mg doses of Ferumoxytol relative to oral iron in a total of 923 subjects with CKD stages 1-5 and 5D on hemodialysis (including 31 kidney transplant recipients). Primary and secondary endpoints were identical in these studies. The primary endpoint was change from baseline in hemoglobin at Day 35 (week 5). Secondary endpoints included mean Serum Ferritin change from baseline at Day 21 (ng/mL), Transferrin saturation (TSAT) change from baseline at Day 35 (%) and Hgb Responders (increase in Hgb by $\geq$ 1) at Day 35.

All these trials were superiority trials. These trials are reviewed in detail in this report.

A fourth study was a phase 3, randomized, double-blind, placebo-controlled, cross-over study in CKD subjects. This study evaluated the safety of Ferumoxytol 510 mg single dose compared with placebo in 722 subjects with CKD stages 1-5 and 5D on hemodialysis or peritoneal dialysis. The sponsor provided protocol defined data on safety parameters (adverse reactions and serious adverse reactions). Efficacy data were not provided. The statistical evaluation of efficacy of this study was not protocol defined.

The focus of this review is three pivotal studies assessing the efficacy and safety of 1.02 g dose of Ferumoxytol relative to 200 mg/day of oral iron.

Efficacy was studied in 3 randomized, active-controlled, multicenter, open-label clinical trials (Studies 62,745-5, 62,745-6 and 62,745-7). The designs of these trials are summarized below:

Study 62,745-5 - Dialysis Dependent: CKD Stage 5D on Hemodialysis

Study 62,745-5 was a randomized, open label, active-controlled, multicenter study of the efficacy and safety of Ferumoxytol compared with oral iron for the treatment of iron deficiency anemia in subjects with CKD stage 5D on hemodialysis.

Under the initial protocol (pre-amendment) of this study, 148 subjects with CKD stage 5D on hemodialysis were randomized (3:3:1) to one of three treatment groups: Ferumoxytol two doses of 510 mg (N=64), Ferumoxytol four doses of 255 mg (N=62), or oral iron (N=22). Eligibility

criteria included subjects at least 18 years of age; on hemodialysis for at least 90 days; Hgb ≤12.0 g/dL; TSAT ≤30%.

Under the final protocol of this study, subjects were randomized 1:1, Ferumoxytol (N=114): oral iron (N=116). Eligibility criteria included subjects at least 18 years of age; on hemodialysis for at least 90 days; Hgb ≤11.5 g/dL; TSAT ≤30%; serum ferritin ≤600 ng/mL prior to dosing; and on stable therapy with ESAs.

Exclusion criteria included active gastrointestinal bleeding or acute bleeding episodes within 4 weeks of treatment; causes of anemia other than iron deficiency; active infections requiring ongoing treatment; treatment with greater than 25,000 units per week of Epogen or 120 µg Aranesp per 2 weeks; and any allergies to iron products or multiple (two or more) drug allergies. Ferumoxytol was given as a course of 1.02 g as 2 x 510 mg doses via rapid IV injections during separate hemodialysis sessions within 7 days. For oral iron, a total daily dose of 200 mg elemental iron (as ferrous fumarate [Ferro Sequels]) was given for 21 days.

Study 62,745-6 - Non-Dialysis Dependent: stages 1-5

Study 62,745-6 was a randomized, open label, active-controlled, multicenter study of the efficacy and safety of Ferumoxytol compared with oral iron for the treatment of iron deficiency anemia in subjects with CKD stages 1-5. Subjects were randomized 3:1, Ferumoxytol (N=228):oral iron (N=76). Eligibility criteria included subjects at least 18 years of age with CKD, Hgb ≤11.0 g/dL, TSAT ≤30%, and serum ferritin of ≤600 ng/mL prior to dosing. For subjects using ESAs, the ESA dose was to be stable for at least 10 days prior to dosing and throughout the study. Exclusion criteria included: active gastrointestinal bleeding or acute bleeding episodes within 4 weeks of treatment; causes of anemia other than iron deficiency; active infections requiring ongoing treatment; treatment with greater than 35,000 units per week of Epogen®(epoetin alfa) or 120 µg Aranesp® (darbepoetin alfa) per 2 weeks; and any allergies to iron products or multiple (two or more) drug allergies.

Ferumoxytol was given as a course of 1.02 g as 2 x 510 mg doses via rapid IV injections at a rate of up to 1 mL/sec for 5 to 8 days. For oral iron, a total daily dose of 200 mg elemental iron (as ferrous fumarate [Ferro Sequels]) was given for 21 days.

Study 62,745-7 - Non-Dialysis Dependent: stages 1-5

Study 62,745-7 was a randomized, open label, active-controlled, multicenter study of the efficacy and safety of Ferumoxytol compared with oral iron for the treatment of iron deficiency anemia in subjects with CKD stages 1-5. Subjects were randomized 3:1, Ferumoxytol (N=226): oral iron (N=77). Eligibility and exclusion criteria were identical to Study 62,745-6. Ferumoxytol was given as a course of 1.02 g as 2 x 510 mg doses via rapid IV injections at a rate of up to 1 mL/sec within 5±3 days. For patients in the oral iron arm, a total daily dose of 200 mg elemental iron (as ferrous fumarate (Ferro Sequels) was given for 21 days.

1.3 Statistical Issues and Findings

This reviewer evaluated the evidence in support of the efficacy of Ferumoxytol from the results of three key phase 3 studies. The selection of the efficacy evaluation for the primary endpoint, mean change in Hgb from baseline at Day 35 and statistical methodology used in evaluating the primary endpoint were pre-specified.

Hgb change from baseline at Day 35 (mean ± SD, g/dL) for the Study 62,745-5 (post – amendment) was 1.02±1.13 for Ferumoxytol (n = 114), and 0.46±1.06 for oral iron (n=116) (p=0.0002); for the Study 62,745-6 was 0.82±1.24 for Ferumoxytol (n = 228), and 0.16±1.02 for oral iron (n=76) (p<0.0001); for the Study 62,745-7 was 1.22±1.25 for Ferumoxytol (n = 226), and 0.52±0.98 for oral iron (n=77) (p<0.0001). The secondary endpoints also showed similar statistical significance.

Protocol defined endpoints were met on each of the pivotal studies. Results from the sensitivity analysis for the primary endpoint, the change in the mean Hgb from baseline, and various sub-group analyses including use of ESAs supported the efficacy of Ferumoxytol. The analyses of secondary endpoints and various subgroups in each of three pivotal studies show benefit favoring Ferumoxytol as compared to Oral iron. The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with 2 x 510 mg Ferumoxytol was similar to treatment with 200 mg/day oral iron. In the opinion of this reviewer, the evidence from the three key Phase 3 studies supports the efficacy of 1.02 g dose of Ferumoxytol for the proposed indication of the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

2. INTRODUCTION

2.1 Overview

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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. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives and the pH is 6 to 8.

Ferumoxytol is a new chemical entity and is intended for intravenous use. The drug product is provided in single use vials containing 510, 255, or 127.5 mg of elemental iron.

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

The ferumoxytol development program consisted of 11 clinical trials, of which seven trials were conducted in subjects with CKD. The efficacy was studied in three randomized, active-

controlled, multicenter, open-label clinical trials (Studies 62,745-5, 62,745-6 and 62,745-7). A total of 605 subjects were exposed to two doses of 510 mg of Ferumoxytol over 5 to 8 days for a mean cumulative iron dose of 1,002 mg and a total of 280 subjects were exposed to 200 mg/day of oral iron for 21 days for a mean cumulative oral elemental iron dose of 3,782 mg. These studies assessed the efficacy and safety of two 510 mg doses of Ferumoxytol relative to oral iron in a total of 923 subjects with CKD stages 1-5 and 5D on hemodialysis (including 31 kidney transplant recipients). Primary and secondary endpoints were identical in these studies. The primary endpoint was change from baseline in hemoglobin at Day 35 (week 5). Secondary endpoints included mean Serum Ferritin change from baseline at Day 21 (ng/mL), Transferrin saturation (TSAT) change from baseline at Day 35 (%) and Hgb Responders (increase in Hgb by ≥ 1) at Day 35. These trials were superiority trials.

These studies demonstrate the protocol defined efficacy endpoints were met for intravenous ferumoxytol given as a regimen of 2 x 510 mg for the treatment of iron deficiency anemia in the continuum of patients with CKD stages 1-5 and 5D. The safety profile of ferumoxytol was similar to 200 mg/day of oral iron.

2.2 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The clinical study reports and datasets are located at the following location:

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The data sets were well documented. The individual study reports and data were submitted for each study. The analysis dataset was not adequate and required data management and programming.

3. STATISTICAL EVALUATION

The efficacy was studied in three randomized, active-controlled, multicenter, open-label clinical trials (Studies 62,745-5, 62,745-6 and 62,745-7). These studies are the focus of this review. The study 62,745-5 also had an initial protocol referred as pre-amendment study (Pre) with three arms (Ferumoxytol two doses of 510 mg (N=64), Ferumoxytol four doses of 255 mg (N=62), or oral iron (N=22) randomized 3:3:1 and a final protocol referred as post-amendment study (Post) with two arms. The design of this study, inclusion/exclusion criteria, endpoints and safety evaluation were exactly the same as in the studies 62,745-6 and 62,745-7. The results of the initial protocol (pre-amendment) 62,745-5 are given for information only.

All the analyses were performed by this reviewer and the tables and graphs presented here are based on this reviewer's analyses. These results conform to the sponsor's results. The nominal p-values on secondary endpoints, sensitivity analyses and subgroup analyses related to the use of ESAs are exploratory and given for information only. There was no formal protocol defined α-allocation for these analyses.

3.1 Evaluation of Efficacy

3.1.1 Subject disposition

All three studies had a similar overall pattern of subjects competing the study and subject disposition. The percent of subjects not completing the study – post initial dose appear to be similar across various reasons for each treatment in the study. There was only 1 subject in the Ferumoxytol 2x510 mg treatment group and 1 subject in the Oral Iron 200 mg/day treatment group who were not treatment compliant. The subject withdrawals from the study due to adverse events was numerically higher in the Oral Iron 200 mg/day treatment group as compared to Ferumoxytol 2x510 mg treatment group. The details of these analyses are given in Appendix A.

3.1.2 Subject demographic and baseline characteristics

Certain subject demographic and baseline characteristics were relatively similar across studies and among treatment groups. There were more female than male in each study and treatment arm, ranging from 51% to 68%. The mean age in each treatment group by each study was similar across studies and among treatment groups. The number of subjects in each treatment arm by various age groups (< 50 years, 50 to < 65 years, 65 to < 75 years and ≥ 75) and studies was similar. Across the three randomized Phase III efficacy studies, 308 out of 605 subjects (51%) were ≥65 years of age and treated with 2 x 510 mg Ferumoxytol, 22/60 (37%) given 4 x 255 mg and 129/280 (46%) given 200 mg oral iron (n=129).

There were more Black/African Americans in study 62,745-5 (both pre and post amendment) as compared to Caucasians and more Caucasians in the other two studies 62,745-6 and 62,745-7 as compared to Black/African Americans. Regarding geographical location, more subjects came from South as compared to Northeast, Midwest and West. The trend was similar in each study and in each treatment arm with most subjects coming from South and least from West.

The distribution of Subject's CKD stage by treatment arm for each study was similar. A majority of subjects had a CKD stage of 4 or 5.

Subjects in the study 62,745-5 were all receiving ESA therapy. More than half of the subjects in the remaining two studies (62,745-6, and 62,745-7) were not receiving ESA therapy in each treatment arm.

Mean Hemoglobin levels (g/dL), Mean Ferritin (ng/mL), and Mean TSAT (%) at baseline were similar between oral iron group as compared to Ferumoxytol group for each study.

The details about subject's demographics and baseline characteristics by study are given in Appendix A.

3.1.3 Analysis population

All three studies used Intent-to-treat (ITT- subjects randomized to treatment) for the analysis population.

3.1.4 Efficacy variables

The primary efficacy variable in all three studies was the mean change in hemoglobin from baseline to Day 35. Secondary endpoints for all three studies included the percentage of subjects who were hemoglobin responders at Day 35 (defined as a $\geq$1 g/dL increase in hemoglobin from baseline), the mean change from baseline in serum ferritin at Day 21 and the mean change from baseline in Transferrin Saturation (TSAT) (%) ferritin at Day 35.

3.1.5 Statistical analysis methods for efficacy endpoints

The primary analysis was performed for the ITT population using analysis of means, student's t-test assuming unequal variances and Fisher's exact test for proportions. The sponsor used an algorithm for imputing missing values for the ITT analysis for the primary and secondary efficacy endpoints. The difference in hemoglobin values (or the secondary endpoints) was set to 0 if hemoglobin values had a missing evaluation on Day 35 or at baseline. When a visit was recorded as being "Day 35", but occurred less than 30 days post the first dose of study drug, then that result was set to missing value in the individual study datasets by the sponsor. Other supportive analyses were conducted for the modified ITT population (subjects exposed to treatment), and subjects who completed the study. Several subgroup and covariate analyses were also conducted. Several sensitivity analyses for missing values were also conducted.

3.1.6 Results of the statistical analysis of primary efficacy endpoint

The primary efficacy variable in all three studies was the mean change in hemoglobin from baseline to Day 35. Increase in mean Hgb (g/dL) from baseline to Day 35 was significantly more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies (Table 2 and Figure 1) (except in the study 62745-5-Pre-amendment – these results are given for information only). Hgb (g/dL) levels also increased in the oral iron treatment group, but the mean increase in the Ferumoxytol treatment group was statistically significantly more at Day 35 than the oral iron treatment group (except in the study 62745-5-Pre-amendment). The results for each study are given in Table 2 and Figure 1. Relative to oral iron, Ferumoxytol treated subjects had statistically significantly greater increases in hemoglobin at Day 35.

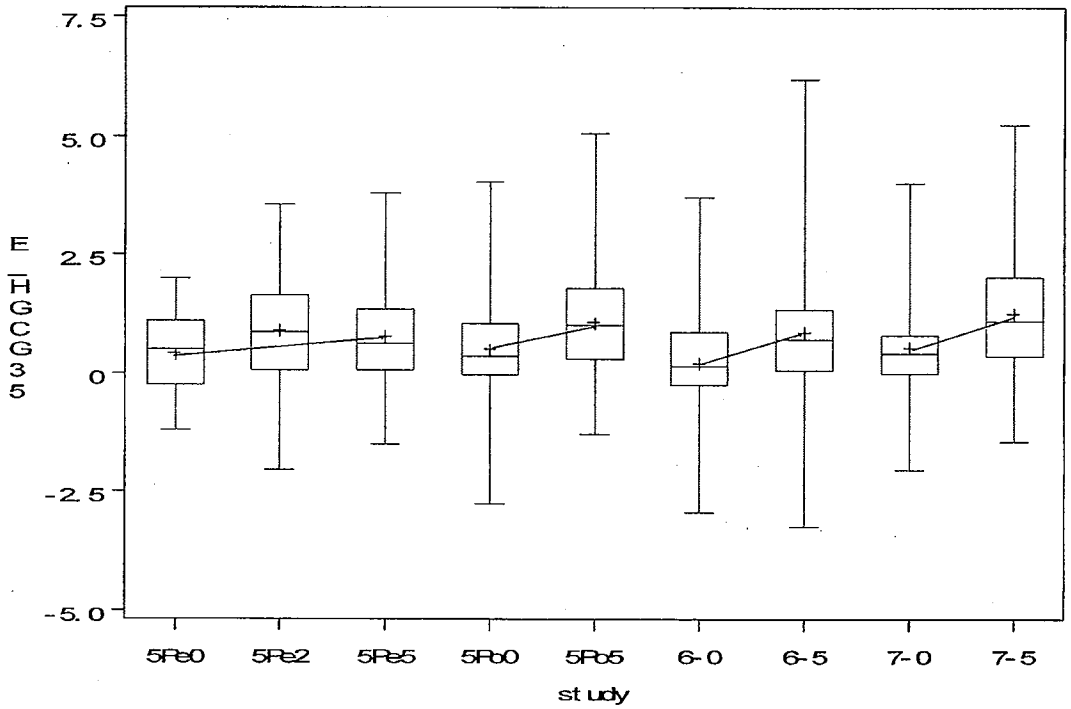
Table 2: Primary Endpoint – Mean Hgb change from baseline at Day 35 (g/dL) - Oral Iron versus Ferumoxytol treatment groups (ITT Population)

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.31 (0.82)	(-0.05, 0.67)	0. 0	(-0.14, 0.8)	(-1.2, 2.0)	
	Ferumoxytol 2x510 mg	64	0.71 (1.00)	(0.45, 0.95)	0.53	(0, 1.13)	(-1.5, 3.8)	0.0745
	Ferumoxytol 4x255 mg	62	0.87 (1.14)	(0.57, 1.15)	0.83	(0.0, 1.65)	(-2.1, 3.6)	0.0188
62745-5-Post	Oral (200 mg/day)	116	0.46 (1.06)	(0.28, 0.68)	0.35	(-0.04, 1.04)	(-2.8, 4.1)	0.0002
	Ferumoxytol 2x510 mg	114	1.02 (1.13)	(0.81, 1.24)	0.98	(0.15, 1.80)	(-1.3, 5.1)	
62745-6	Oral (200 mg/day)	76	0.16 (1.02)	(-0.03, 0.45)	0.15	(-0.25, 0.83)	(-2.9, 3,7)	<0.0001
	Ferumoxytol 2x510 mg	228	0.82 (1.24)	(0.66, 0.98)	0.7	(0, 1.3)	(-3.3, 6.2)	
62745-7	Oral (200 mg/day)	77	0.52 (0.98)	(0.29, 0.74)	0.35	(0, 0.8)	(-2.1, 4.0)	<0.0001
	Ferumoxytol 2x510 mg	226	1.22 (1.25)	(1.06, 1.38)	1.0	(0.25, 1.95)	(-1.5, 5.3)	

* t-test assuming unequal variance

Table 2 shows that increases in both mean and median change in hemoglobin from baseline to Day 35 were consistently more in Ferumoxytol treatment group as compared to Oral Iron. The 95% confidence intervals were non-overlapping in each of the three pivotal studies.

Figure 1: Primary Endpoint - Hgb change from baseline at Day 35 (g/dL) - Oral Iron versus Ferumoxytol treatment groups



Study codes:

5PeO = Study 62745-5 Pre-amendment Oral Iron
5Pe2 = Study 62745-5 Pre-amendment Ferumoxytol (4x255 mg)
5Pe5 = Study 62745-5 Pre-amendment Ferumoxytol (2x510 mg)
5PoO = Study 62745-5 Post-amendment Oral Iron
5Po5 = Study 62745-5 Post-amendment Ferumoxytol (2x510 mg)
6-O = Study 62745-6 Oral Iron
6-5 = Study 62745-6 Ferumoxytol (2x510 mg)
7-O = Study 62745-7 Oral Iron
7-5 = Study 62745-7 Ferumoxytol (2x510 mg)

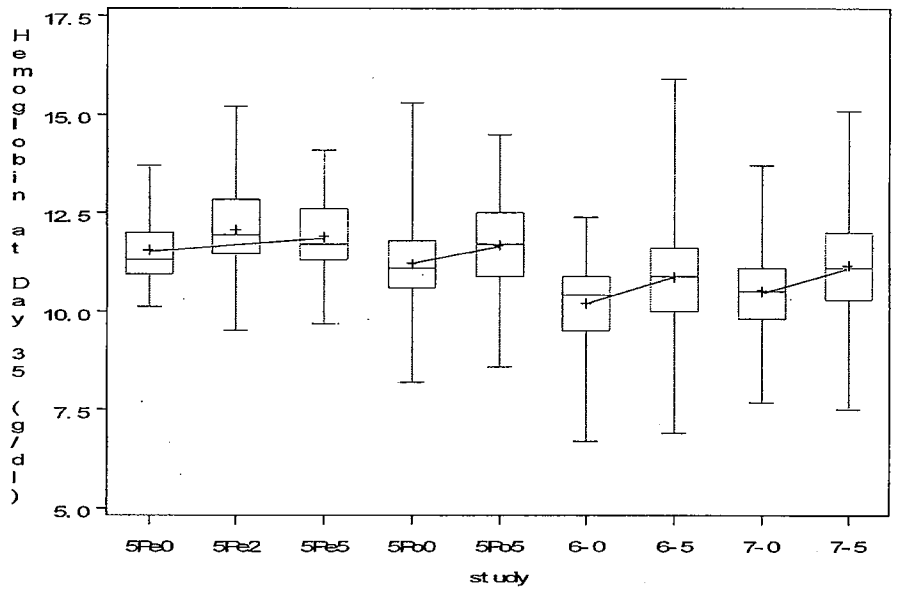
Figure 1 shows that the increases in mean change in hemoglobin from baseline to Day 35 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A great deal of variability in Hgb levels was observed in both Ferumoxytol and Oral Iron treatment groups.

Exploratory analysis was performed to evaluate hemoglobin levels at Day 35 for each study and treatment arm. The results are given in Table 3 and Figure 2. Table 3 shows that Ferumoxytol treated subjects had consistently more mean and median Hgb levels on Day 35 than Oral iron treated subjects. Also, a greater percent of subjects achieved Hgb levels >12g/dl in the Ferumoxytol treated group as compared to Oral iron treated group.

Table 3: Hgb levels at Day 35 (g/dL) - Oral Iron versus 2x510 mg Ferumoxytol treatment groups

Study	Group	N	Mean (sd)	95% CI	Median	Q1-Q3	Range	Hgb >12g/dl n (%)
62745-5-Post	Oral	109	11.2 (1.19)	(11.0, 11.4)	11.1	(10.6, 11.8)	(8.2, 15.3)	21 (19)
	Ferumoxytol	108	11.7 (1.23)	(11.4, 11.9)	11.7	(10.9, 12.5)	(8.6, 14,5)	39 (36)
62745-6	Oral	68	10.2 (1.07)	(9.9, 10.5)	10.4	(9.5, 10.9)	(6.9, 15.9)	1 (1)
	Ferumoxytol	208	10.9 (1.28)	(10.7, 11.0)	10.9	(10.0, 11.6)	(6.0, 15.9)	29 (14)
62745-7	Oral	71	10.5 (1.12)	(10.3, 10.8)	10.5	(9.8, 11.1)	(7.7, 13.7)	6 (8.5)
	Ferumoxytol	216	11.2 (1.33)	(11.0, 11.3)	11.1	(10.3, 12.0)	(7.5, 15.1)	50 (23)

Figure 2: Hemoglobin level at Day 35 (g/dl)



Study codes are as in Figure 1

Figure 2 shows that the increases in mean Hgb (g/dL) levels on Day 35 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A great deal of variability in Hgb levels on Day 35 was observed in both Ferumoxytol and Oral Iron treatment groups.

3.1.7 Results of the statistical analysis of secondary efficacy endpoints

The following were three major secondary endpoints of clinical importance for Oral Iron (200 mg/day) versus Ferumoxytol 2x510 mg.

- Mean Serum Ferritin change from baseline at Day21 (ng/mL)
- Transferrin Saturation (TSAT) change from baseline at Day 35 (%)
- Hgb Responders – increase in Hgb by $\geq$ 1 (ng/mL) from baseline at Day 35

The following were other secondary endpoints for Oral Iron (200 mg/day) versus Ferumoxytol 2x510 mg

- Mean Serum Ferritin change from baseline at Day 35 (ng/mL)
- Hgb change from baseline at Day 21 (g/dL)
- Hgb & Ferritin Responders –increase in Hgb by $\geq$ 1 (ng/mL) at Day 35 plus increase in ferritin by $\geq$ 160 ng/mL at Day 21 or 35

The evaluation of major secondary endpoints is given below. The analyses for other secondary endpoints are given in Appendix B. The nominal p-values in each of these tables are provided for information only. These p-values are not as interpretable because there was no protocol specified α-allocation.

- **Mean Serum Ferritin change from baseline at Day21 (ng/mL)**

The changes in mean serum ferritin from baseline at Day21 (ng/mL) observed in these groups for the ITT population are given in Table 4. Relative to oral iron, Ferumoxytol treated subjects had greater increases in mean serum ferritin from baseline at Day 21. Mean serum ferritin (ng/mL) in subjects in the oral iron treatment group went down or almost remained the same compared to the baseline (95% CI includes 0) at Day 21. (Table 4, Figures 3 & 4)

Table 4: Mean Serum Ferritin change from baseline at Day21 (ng/mL) - Oral Iron versus Ferumoxytol

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range (Q1-Q3)	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	-20.98 (43.86)	(-40.4, -1.5)	0	(-52.5, 2.38)	(-113, 57)	<0.001
	Ferumoxytol 2x510 mg	64	414.55 (296.47)	(340.5, 488.6)	380.5	(167.4, 595)	(0, 1251)	
	Ferumoxytol 4x255 mg	62	439.7 (270.2)	(371.1, 508.3)	448.28	(265.1,615.4)	(0, 1370)	<0.001
62745-5-Post	Oral (200 mg/day)	116	-37.56 (106.98)	(-57.2, -17.9)	-27.25	(-89.6, 5.7)	(-360, 431)	<0.001
	Ferumoxytol 2x510 mg	114	356.66 (247.12)	(310.8, 402.5)	340.0	(178.8, 519.4)	(0, 1221)	
62745-6	Oral (200 mg/day)	76	6.47 (47.16)	(-4.3, 17.2)	0	(-11.4, 18.2)	(-91, 167)	<0.001
	Ferumoxytol 2x510 mg	228	518.08 (331.86)	(474.8, 561.4)	498.2	(277.1, 685.5)	(0, 1494)	
62745-7	Oral (200 mg/day)	77	4.26 (48.22)	(-6.7, 15.2)	2.7	(-5.5, 19.7)	(-196, 127)	<0.001
	Ferumoxytol 2x510 mg	226	412.58 (247.95)	(384.0, 449.2)	397	(225.4, 565.4)	(0, 1490)	

* t-test assuming unequal variance – nominal p-values

Table 4 shows that increases in both mean and median change in mean serum ferritin from baseline at Day21 (ng/mL) observed in these groups were consistently more in Ferumoxytol treatment group as compared to Oral Iron. The 95% confidence intervals were non-overlapping in each of the three pivotal studies.

Figure 3: Day 21 serum Ferritin (ng/mL)

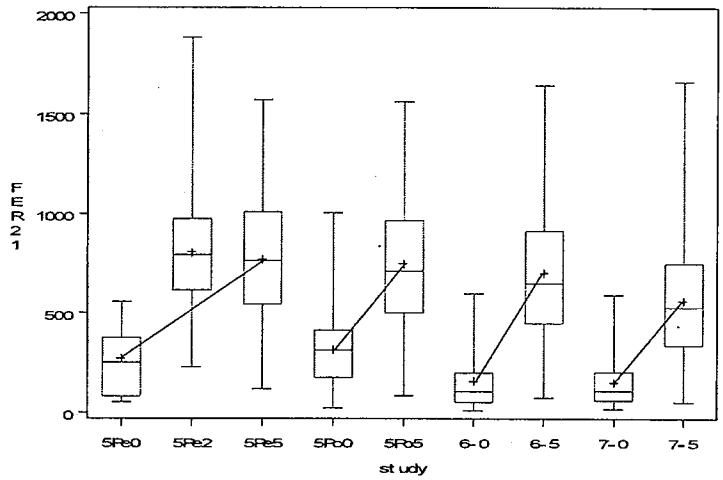
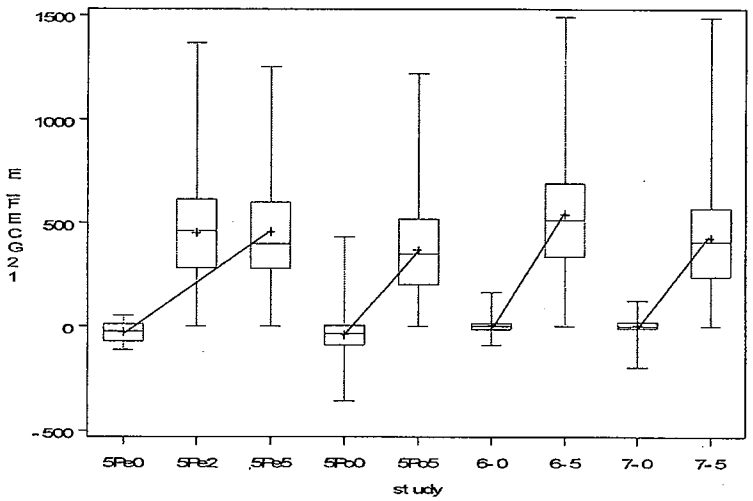


Figure 3 shows that the increases in mean serum Ferritin (ng/mL) at Day 21 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A greater variability in serum Ferritin (ng/mL) at Day 21 was observed in Ferumoxytol as compared to Oral Iron treatment group.

Figure 4: Day 21 change from baseline in serum Ferritin (ng/mL)



Study codes are as in Figure 1

Figure 4 shows that the increases in mean change in serum Ferritin (ng/mL) from baseline to Day 21 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A greater variability in serum Ferritin (ng/mL) change from baseline at Day 21 was observed in Ferumoxytol as compared to Oral Iron treatment group.

- **Transferrin Saturation (TSAT) change from baseline at Day 35 (%)**

The changes in mean Transferrin saturation (TSAT) from baseline at Day 35 (%) observed in these groups for the ITT population are given in Table 5. Relative to oral iron, Ferumoxytol treated subjects had greater increases in mean Transferrin saturation (TSAT) from baseline at Day 35. Transferrin saturation (TSAT) (%) in subjects in the oral iron treatment group went down or almost remained the same compared to the baseline (95% CI includes 0) at Day 35. (Table 5 and Figures 5 and 6).

Table 5: Transferrin Saturation (TSAT) change from baseline at Day 35 (%) Oral Iron versus Ferumoxytol

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.14 (8.03)	(-3.42, 3.7)	0	(-4.9, 1.5)	(-12.5, 18.5)	0.376
	Ferumoxytol 2x510 mg	64	5.37 (10.4)	(2.77, 7.96)	4.5	(0, 10.9)	(-14.5, 52.5)	
	Ferumoxytol 4x255 mg	62	4.56 (7.89)	(2.55, 6.56)	4	(0, 8.13)	(-14.5, 25.5)	
62745-5-Post	Oral (200 mg/day)	116	0.55 (8.34)	(-0.97, 1.99)	0	(-3.5, 4)	(-20.5, 54.5)	<0.001
	Ferumoxytol 2x510 mg	114	6.44 (12.59)	(3.84, 8.41)	3.75	(-0.63, 12.0)	(-20.5, 63.0)	
62745-6	Oral (200 mg/day)	76	1.31 (6.38)	(-0.21, 2.55)	0	(-1.4, 3.5)	(-15.5, 24.5)	<0.001
	Ferumoxytol 2x510 mg	228	9.77 (9.17)	(7.7, 10.1)	8.0	(2.0, 14.0)	(-23.5, 43.5)	
62745-7	Oral (200 mg/day)	77	0.28 (4.65)	(-0.8, 1.3)	0	(-1.8, 1.5)	(-11.5, 18.5)	<0.001
	Ferumoxytol 2x510 mg	226	9.20 (9.37)	(7.5, 9.9)	7.0	(2.5, 12.0)	(-9.0, 53.0)	

* t-test assuming unequal variance – nominal p-values

Table 5 shows that increases in both mean and median transferrin saturation (TSAT) from baseline at Day 35 (%) observed in these groups were consistently more in Ferumoxytol treatment group as compared to Oral Iron. The 95% confidence intervals were non-overlapping in each of the three pivotal studies.

Figure 5: Transferrin Saturation (TSAT) at Day 35 (%)

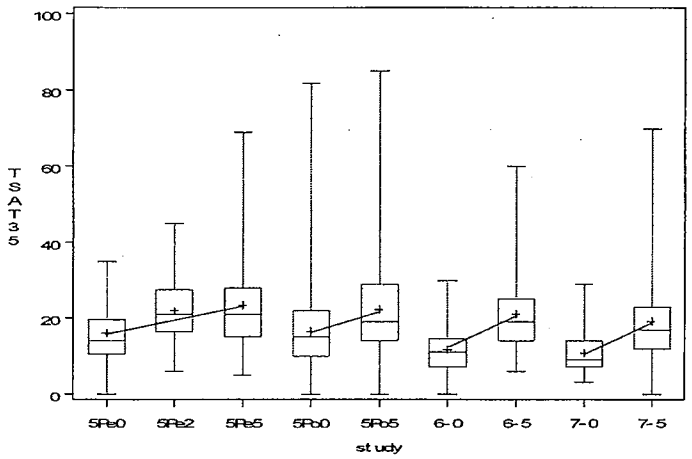
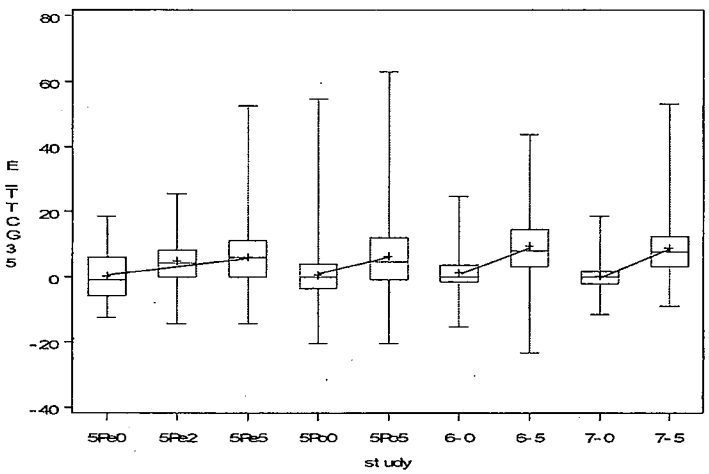


Figure 5 shows that the increases in mean TSAT (%) at Day 35 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A greater variability in TSAT (%) was observed in Ferumoxytol as compared to Oral Iron treatment group in two out of three pivotal studies.

Figure 6: Transferrin Saturation (TSAT) change from baseline at Day 35 (%)



Study codes are as in Figure 1

Figure 6 shows that the increases in mean change in TSAT (%) from baseline to Day 35 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A greater variability in TSAT (%) at Day 35 was observed in Ferumoxytol as compared to Oral Iron treatment group in two out of three pivotal studies.

- **Hgb Responders – increase in Hgb by ≥ 1 (ng/mL) from baseline at Day 35**

Hgb Responders - Increase in Hgb by ≥ 1 (ng/mL) from baseline at Day 35 - Oral Iron (200 mg/day) versus Ferumoxytol 2x510 mg observed in these groups for the ITT population are given in Table 6. Table 6 shows that relative to oral iron, ferumoxytol treated subjects had greater increases in Hgb Responders (%) from baseline at Day 35.

Table 6: Hgb Responders-Increase in Hgb by ≥ 1 (ng/mL) at Day 35 from baseline Oral Iron versus Ferumoxytol

Study	Group	N	Hgb Responder Day 35 n (%)	p-value Comparing Ferumoxytol to Oral Iron *
62745-5-Pre	Oral	22	5 (22.7)	
	Ferumoxytol 4x255 mg	62	29 (46.8)	0.0756
	Ferumoxytol 2x510 mg	64	19 (29.7)	0.5938
62745-5-Post	Oral	116	29 (25.0)	
	Ferumoxytol 2x510 mg	114	56 (49.1)	0.0002
62745-6	Oral	76	15 (19.7)	
	Ferumoxytol 2x510 mg	228	89 (39)	0.0010
62745-7	Oral	77	15 (19.5)	
	Ferumoxytol 2x510 mg	226	117 (51.8)	< 0.0001
	Ferumoxytol 2x510 mg	568	264 (48)	

* Fisher's Exact Test – nominal p-values

3.1.8 Sensitivity analyses

The analyses were performed on modified intent to treat population (subjects exposed to treatment) and completers population (subjects completing the study). The results were consistent with the ITT population. These results are not included here as there were very minor differences in the estimated values of evaluated study endpoints. The significance levels (nominal p-values) did not change.

Several analyses were performed for the missing values at study endpoint (Day 35) compared to baseline for the primary endpoint. These included:

- Last observation carried forward
- Average treatment group change assignment
- Worst case scenario – i.e., assigning the smallest observed group change.

Results were consistent with ITT analyses using above imputation methods for handling the missing data. The details are provided in Appendix C.

3.2 Evaluation of Safety

A total of 1,726 subjects were exposed to Ferumoxytol in the clinical program; 1,562 of these subjects had CKD (stages 1-5 and 5D) and 164 subjects were non-CKD subjects. The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with Ferumoxytol were 33% and 7%, respectively, with oral iron were 53% and 12%, respectively, and with placebo were 19% and 2.4% respectively. Adverse events leading to treatment discontinuation occurred in 2.1% of subjects with ferumoxytol, 11.0% with oral iron, and 0.8% with placebo. Adverse events leading to treatment discontinuation and occurring in ≥2 ferumoxytol-treated subjects included hypotension, infusion site swelling, increased serum ferritin level, chest pain, diarrhea, dizziness, ecchymosis, pruritis, chronic renal failure, and urticaria in clinical trials.)

The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with 2 x 510 mg Ferumoxytol similar to treatment with 200 mg/day oral iron. The incidence of adverse reactions was numerically lower in Ferumoxytol treated subjects compared to oral iron treated subjects; 44% (n=605) in 2 x 510 mg Ferumoxytol versus 54% (n=280) of subjects treated with 200 mg/day oral iron. The most commonly occurring adverse reactions, reported in ≥2% of subjects treated with 2 x 510 mg Ferumoxytol, included diarrhea, nausea, dizziness, hypotension, constipation and peripheral edema. A safety assessment of 3 clinical studies at patient level for oral iron versus Ferumoxytol is given in Table 7. The results of safety assessment exhibited similar trend between patients using ESA or not using ESA for each treatment group in each of the three pivotal studies. The details are given in the clinical report.

Table 7: Safety Assessment – 3 Clinical Studies – Patient Level -Oral Iron Ferumoxytol treatment groups

Study	Group	N	Death – AE related n (%)	Hospitalization due to AE n (%)	Serious AE (at least one) n (%)	Related Serious AE n (%)	Related AE (at least one) n (%)
62745-5-Pre	Oral	17	0	0	0	0	4 (23.5)
	Ferumoxytol 4x255 mg	60	2 (3.3)	7 (11.7)	8 (13.3)	0	1 (1.7)
	Ferumoxytol 2x510 mg	58	2 (3.4)	6 (10.3)	6 (10.3)	0	3 (5.2)
62745-5-Post	Oral	114	3 (2.6)	13 (11.4)	15 (13.2)	0	18 (15.8)
	Ferumoxytol 2x510 mg	110	1 (0.9)	17 (15.5)	19 (17.3)	1 (0.9)	9 (8.2)
62745-6	Oral	75	2 (2.7)	8 (10.7)	8 (10.7)	0	18 (24.0)
	Ferumoxytol 2x510 mg	217	2 (0.9)	12 (5.5)	13 (6.0)	0	23 (10.6)
62745-7	Oral	74	3 (4.1)	9 (12.2)	11 (14.9)	1 (1.4)	12 (16.2)
	Ferumoxytol 2x510 mg	220	4 (1.8)	19 (8.6)	21 (9.4)	0	47 (21.4)
All Pooled	Oral	280	8 (2.9)	30 (10.7)	34 (12.1)	1 (0.4)	52 (18.6)
	Ferumoxytol 4x255 mg	60	2 (3.3)	7 (11.7)	8 (13.3)	0	1 (1.7)
	Ferumoxytol 2x510 mg	605	9 (1.5)	54 (8.9)	59 (9.8)	1 (0.2)	82 (13.6)

Table 7 shows that the percentage of subjects experiencing any adverse event was numerically higher for oral iron treatment that ferumoxytol treatment in each of the three pivotal studies.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Data were analyzed by gender, race and age for the primary endpoint of Hgb change from baseline at Day 35 (g/dL) - Oral Iron (200 mg/day) versus Ferumoxytol treatment groups for 3 clinical studies.

Gender: Table 8 shows that the increase in mean Hgb (g/dL) from baseline to Day 35 was consistently more in Ferumoxytol treatment group as compared to Oral iron treatment group in all 3 pivotal studies in both gender groups (Female and Male).

Table 8: Hgb change from baseline at Day 35 (g/dL) by gender

	Female			Male		
	n	Mean ± sd	95% CI	n	Mean ± sd	95% CI
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	34	0.7 ± 1.0	(0.4, 1.1)	24	0.8 ± 1.0	(0.4, 1.3)
Ferumoxytol 4x255 mg	34	1.0 ± 1.3	(0.6, 1.4)	26	0.7 ± 1.0	(0.3, 1.2)
Oral Iron 200 mg/day	10	0.5 ± 0.9	(-0.2, 1.1)	7	0.3 ± 0.9	(-0.6, 1.2)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	56	1.0 ± 1.0	(0.7, 1.3)	54	1.1 ± 1.3	(0.8, 1.5)
Oral Iron 200 mg/day	42	0.3 ± 1.0	(0.0, 0.6)	72	0.6 ± 1.1	(0.3, 0.8)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	128	0.8 ± 1.3	(0.5, 1.0)	89	1.0 ± 1.2	(0.7, 1.3)
Oral Iron 200 mg/day	51	0.2 ± 1.0	(-0.1, 0.5)	24	0.2 ± 1.2	(-0.3, 0.7)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	129	1.1 ± 1.2	(0.9, 1.3)	91	1.5 ± 1.3	((1.2, 1.7)
Oral Iron 200 mg/day	46	0.6 ± 1.0	(0.3, 0.9)	28	0.4 ± 1.0	(0.0, 0.8)

Race: Table 9 shows that the increase in mean Hgb (g/dL) from baseline to Day 35 was consistently more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies in two race groups (Black/African American and Caucasian). Other race (Asians, Hispanics, etc.) constituted approximately 6% of the subjects . The trend in the other race was similar.

Table 9: Hgb change from baseline at Day 35 (g/dL) by race

	Black/African American			Caucasian		
	n	Mean ± sd	95% CI	n	Mean ± sd	95% CI
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	30	0.9 ± 1.0	(0.5, 1.3)	23	0.6 ± 1.1	(0.2, 1.1)
Ferumoxytol 4x255 mg	32	0.6 ± 1.1	(0.3. 1.0)	21	1.0 ± 1.0	(0.6, 1.5)
Oral Iron 200 mg/day	10	0.6 ± 0.9	(-0.1, 1.2)	7	0.1 ± 1.0	(-0.8, 1.0)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	66	1.1 ± 1.1	(0.8, 1.3)	36	1.1 ± 1.2	(0.7, 1.5)
Oral Iron 200 mg/day	66	0.6 ± 1.1	(0.4, 0.9)	40	0.2 ± 1.0	(-0.1, 0.6)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	72	0.8 ± 1.4	(0.5, 1.1)	126	0.9 ± 1.2	(0.7, 1.1)
Oral Iron 200 mg/day	28	0.4 ± 1.1	(-0.1, 0.8)	45	0.1 ± 1.0	(-0.2, 0.4)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	70	1.0 ± 1.2	(0.7, 1.3)	147	1.4 ± 1.2	(1.2, 1.6)
Oral Iron 200 mg/day	25	0.7 ± 1.1	((0.2, 1.1)	46	0.5 ± 1.0	(0.2, 0.8)

Age: Table 10 shows that the increase in mean Hgb (g/dL) from baseline to Day 35 was consistently more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies in both age groups (< 65 years or ≥ 65 years).

Table 10: Hgb change from baseline at Day 35 (g/dL) by age groups

	Age (< 65 Years)			Age (≥ 65 Years)		
	n	Mean ± sd	95% CI	n	Mean ± sd	95% CI
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	39	0.7 ± 1.1	(0.4, 1.1)	19	0.8 ± 1.0	(0.4, 1.3)
Ferumoxytol 4x255 mg	38	0.9 ± 1.2	(0.5, 1.3)	22	0.8 ± 1.1	(0.4, 1.3)
Oral Iron 200 mg/day	10	0.6 ± 0.9	(-0.02, 1.2)	7	0.1 ± 1.0	((-0.8, 1.0)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)						
Ferumoxytol 2x510 mg	68	1.1 ± 1.1	(0.8, 1.3)	42	1.1 ± 1.3	(0.7, 1.5)
Oral Iron 200 mg/day	69	0.5 ± 1.2	(0.3, 0.8)	45	0.4 ± 0.9	(0.1, 0.7)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	100	0.9 ± 1.3	(0.6, 1.1)	117	0.9 ± 1.2	(0.6, 1.1)
Oral Iron 200 mg/day	41	0.1 ± 1.2	(-0.3, 0.5)	34	0.4 ± 0.9	(0.1, 0.7)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)						
Ferumoxytol 2x510 mg	90	1.3 ± 1.3	(1.0, 1.5)	130	1.2 ± 1.3	(1.0, 1.5)
Oral Iron 200 mg/day	31	0.8 ± 1.1	(0.4, 1.2)	43	0.4 ± 0.9	(0.1, 0.6)

4.2 Other Special/Subgroup Populations

Two special groups (ESA use and CKD stage) of clinical relevance were identified by the clinical team. Data were analyzed for these two special groups (ESA use and CKD stage) for the primary endpoint of Hgb change from baseline at Day 35 (g/dL) - Oral Iron (200 mg/day) versus Ferumoxytol treatment groups for 3 clinical studies.

- **Efficacy by ESA Use**

For clinical Study 62745-5, all 359 subjects were receiving ESA. More than half of the subjects in the remaining two studies (62,745-6, and 62,745-7) were not receiving ESA therapy in each treatment arm. For clinical Study 62745-6, 181 subjects did not use ESA and 111 subjects used ESA. For clinical Study 62745-7, 170 subjects did not use ESA and 124 subjects used ESA. A greater mean change in Hgb was observed on Day 35 and also on Day 21 with ferumoxytol than with oral iron in both subjects receiving and not receiving ESAs.

Table 11 shows that a greater mean change in Hgb was observed on Day 35 with ferumoxytol than with oral iron in both subjects receiving and not receiving ESAs . The 95% confidence interval on the difference in means does not include 0 in each of the two pivotal studies for both the groups (subjects not receiving ESA and subjects receiving ESA) implying that a greater increase in Hgb levels at Day 35 in ferumoxytol group was observed as compared to oral iron group.

Table 11: Mean Hgb change from baseline at Day 35 by ESA Use

	Study 62,745-6 (CKD Stages 1-5)				Study 62,745-7 (CKD Stages 1-5)			
	Not Receiving ESA		Receiving ESA		Not Receiving ESA		Receiving ESA	
	Oral	FER	Oral	FER	Oral	FER	Oral	FER
n	43	138	32	79	41	129	33	91
Mean (sd)	0.15 (0.9)	0.65 (1.0)	0.30 (1.2)	1.22 (1.5)	0.27 (0.6)	0.94 (1.1)	0.9 (1.3)	1.7 (1.4)
Difference	0.50		0.92		0.67		0.83	
SE (Diff)	0.17		0.27		0.13		0.27	
95% CI	(0.17, 0.84)		(0.38, 1.46)		(0.42, 0.93)		(0.30, 1.37)	
p-value*	0.005		0.003		0.0001		0.003	

* Note that the nominal p-values are provided for information only.

These results are also depicted in the following Figure:

Figure 7: Change in Hemoglobin (g/dL) from baseline at Day 35 by ESA Use

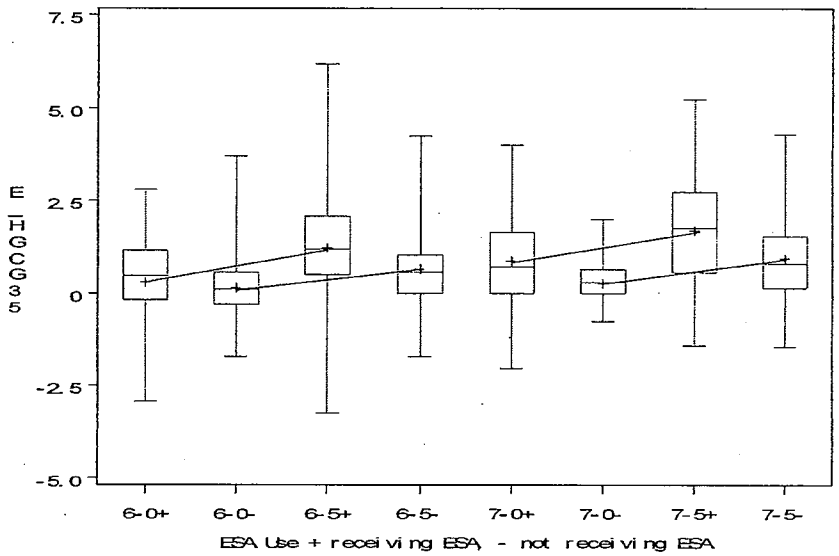


Figure 7 shows that subjects receiving ESA and subjects not receiving ESA had a greater increase in Hgb levels at Day 35 in ferumoxytol group as compared to oral iron group, and the gradient of the increase in both groups was similar across studies.

Table 12 shows that a greater mean change in Hgb was observed on Day 21 with ferumoxytol than with oral iron in both subjects receiving and not receiving ESAs. The 95% confidence interval on the difference in means does not include 0 in each of the two pivotal studies for both the groups (subjects not receiving ESA and subjects receiving ESA) implying that a greater increase in Hgb levels at Day 21 in ferumoxytol group was observed as compared to oral iron group.

Table 12: Mean Hgb change from baseline at Day 21 (g/dL) by ESA Use

	Study 62,745-6 (CKD Stages 1-5)				Study 62,745-7 (CKD Stages 1-5)			
	Not Receiving ESA		Receiving ESA		Not Receiving ESA		Receiving ESA	
	Oral	FER	Oral	FER	Oral	FER	Oral	FER
n	43	138	32	79	41	129	33	91
Mean (sd)	0.09 (0.7)	0.51 (0.8)	0.35 (0.8)	1.03 (1.1)	0.29 (0.7)	0.67 (0.9)	0.51 (0.9)	1.29 (1.1)
Difference	0.42		0.67		0.38		0.78	
SE (Diff)	0.12		0.19		0.13		0.20	
95% CI	(0.17, 0.66)		(0.29, 1.05)		(0.12, 0.64)		(0.38, 1.18)	
p-value*	0.0026		0.0027		0.0104		0.0005	

* Note that the nominal p-values are provided for information only.

These results are depicted in the following Figure 8:

Figure 8: Change in Hemoglobin (g/dL) from baseline at Day 21 by ESA Use

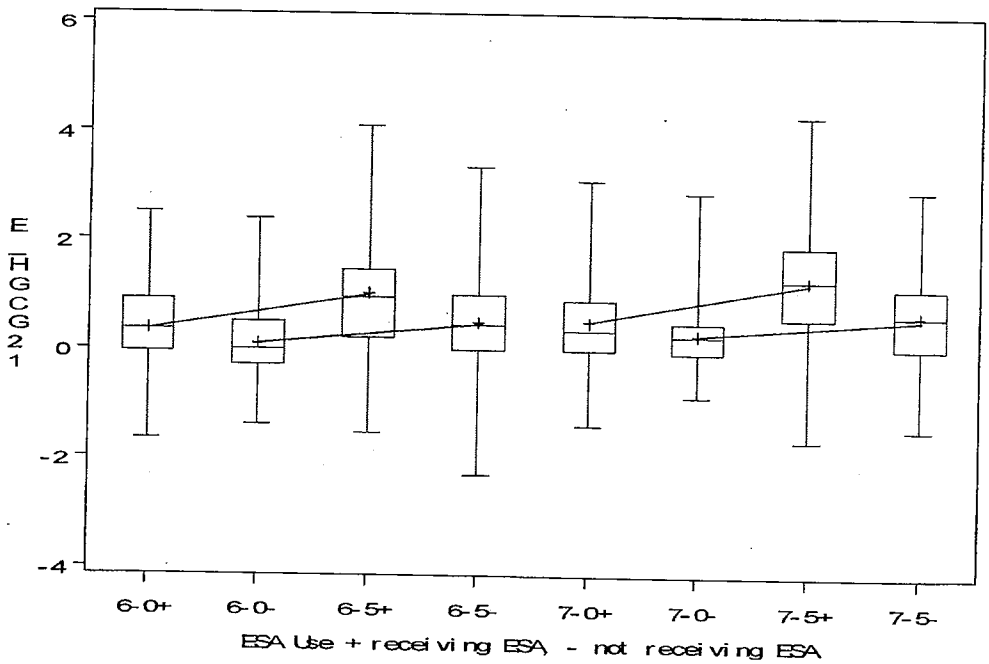


Figure 8 shows that subjects receiving ESA and subjects not receiving ESA had a greater increase in Hgb levels at Day 21 in ferumoxytol group as compared to oral iron group, and the gradient of the increase in both groups was similar across studies.

- **Efficacy by CKD stage**

Table 13 shows that the increase in mean Hgb (g/dL) from baseline to Day 35 was consistently more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies in most CKD stage groups.

Table 13: Mean Hgb change from baseline by CKD Stage

	n	Stage 1or 2 n (%) Mean ± sd	Stage 3 n (%) Mean ± sd	Stage 4 n (%) Mean ± sd	Stage 5 n (%) Mean ± sd
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg	217	4 (2) 1.4 ± 1.6	78 (37) 1.1 ± 1.2	101 (47) 0.8 ± 1.2	30 (14) 0.5 ± 1.5
Oral Iron 200 mg/day	75	2 (3) 2.0 ± 2.4	29 (39) 0.3 ± 0.8	36 (48) 0.1 ± 1.1	8 (10) 0.3 ± 1.1
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg	215 (5 missing)	3 (1) 2.2 ± 1.8	84 (39) 1.3 ± 1.1	103 (48) 1.2 ± 1.2	25 (12) 1.2 ± 1.6
Oral Iron 200 mg/day	73 (1 missing)	1 (1) 1.4	29 (40) 0.6 ± 1.0	39 (53) 0.5 ± 1.0	4 (6) 0.4 ± 1.1

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

This reviewer evaluated the evidence in support of the efficacy of Ferumoxytol from the results of three key phase 3 studies. The selection of the efficacy evaluation for the primary endpoint, mean change in Hgb from baseline at Day 35 and statistical methodology used in evaluating the primary endpoint were pre-specified. Results from the sensitivity analysis the Hgb endpoint, and various sub-group analyses including use of ESAs supported the efficacy of Ferumoxytol. The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with 2 x 510 mg Ferumoxytol was similar to treatment with 200 mg/day oral iron. In the opinion of this reviewer, the evidence from the three key Phase 3 studies supports the efficacy of 1.02 g dose of Ferumoxytol for the proposed indication of the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

5.2 Conclusions and Recommendations

Ferumoxytol is a superparamagnetic iron oxide nanoparticle coated with polyglucose sorbitol carboxymethylether. It is an intravenous iron injection and is developed for treatment of iron deficiency anemia.

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

The efficacy and safety of Ferumoxytol for the treatment of iron deficiency anemia was studied in three randomized, active-controlled, multicenter, open-label, phase III clinical trials across the CKD continuum (Stages 1-5 and 5D as defined by the level of kidney function per K/DOQI guidelines) (Studies 62,745-5 (post –amendment), 62,745-6 and 62,745-7).

All these trials were designed as superiority trials. These studies assessed the efficacy and safety of two 510 mg doses of Ferumoxytol relative to oral iron in a total of 923 subjects with CKD stages 1-5 and 5D on hemodialysis (including 31 kidney transplant recipients). Primary and secondary endpoints were identical in these studies. The primary endpoint was the mean change in hemoglobin (Hgb) from baseline to Day 35. Secondary endpoints included the percentage of subjects who were hemoglobin responders at Day 35 (defined as a $\geq$1 g/dL increase in hemoglobin from baseline), the mean change from baseline in serum ferritin at Day 21 and the mean change from baseline in Transferrin Saturation (TSAT) (%) ferritin at Day 35.

The following Table 14 summarizes the change in hemoglobin (Hgb) and iron parameters from baseline for each treatment group for three studies.

Table 14: Clinical Studies – Hemoglobin and Iron Parameters (ITT population)

Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)			
Endpoint	Ferumoxytol (n=114)	Oral Iron (n=116)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	1.02±1.13	0.46±1.06	0.0002
Secondary Endpoints			
% Hgb responders at Day 35[a]	49.1	25.0	0.0002
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	356.66±247.12	-37.56±106.98	<0.0001
TSAT change from baseline at Day 35 (%)	6.44±12.59	0.55±8.34	<0.0001
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)			
Endpoint	Ferumoxytol (n=228)	Oral Iron (n=76)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	0.82±1.24	0.16±1.02	<0.0001
Secondary Endpoints			
% Hgb responders at Day 35[a]	39.0	18.4	0.0010
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	518.08±331.86	6.47±47.16	<0.0001
TSAT change from baseline at Day 35 (%)	9.77±9.17	1.31±6.38	<0.0001
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)			
Endpoint	Ferumoxytol (n=226)	Oral Iron (n=77)	p-value*
Primary Endpoint			
Hgb change from baseline at Day 35 (mean±SD, g/dL)	1.22±1.25	0.52±0.98	<0.0001
Secondary Endpoints			
% Hgb responders at Day 35[a]	51.8	19.5	<0.0001
Ferritin change from baseline at Day 21 (mean±SD, ng/mL)	412.58±247.95	4.26±48.22	<0.0001
TSAT change from baseline at Day 35 (%)	9.20±9.37	0.28±4.65	<0.0001

[a] Hgb responders were defined as a ≥1 g/dL increase in hemoglobin from baseline.
* The nominal p-values on secondary endpoints are for information only.

As seen from the above table, protocol defined primary endpoints were met in each of the pivotal studies. The efficacy of Ferumoxytol in subjects treated with 2 x 510 mg, as assessed by the mean increase from baseline in hemoglobin, was statistically significantly greater than with oral iron. There was a (nominal) statistical significance on the protocol defined secondary endpoints. Subgroup and sensitivity analyses also revealed consistency in benefit. The overall incidence of adverse reactions and serious adverse reactions in CKD subjects following treatment with 2 x 510 mg Ferumoxytol was similar to treatment with 200 mg/day oral iron. The evidence from the three key Phase 3 studies supports the efficacy of 1.02 g dose of Ferumoxytol for the proposed indication of the treatment of iron deficiency anemia in patients with chronic kidney disease (CKD).

APPENDIX A: BASELINE CHACTERISTCS

Table 15 provides the number of subjects randomized in each of the three studies and number who completed the study.

Table 15: Number of Subjects in the randomized three studies

Treatment	Randomized (N)	Not Dosed (Withdrawn Prior to Initial Dose n (%)	Dosed n (%)	Completed Study [a] n (%)
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)				
Ferumoxytol 2x510 mg	64	6 (9.4)	58 (90.6)	54 (84.4)
Ferumoxytol 4x255 mg	62	2 (3.2)	60 (96.8)	55 (88.7)
Oral Iron 200 mg/day	22	5 (22.7)	17 (77.3)	16 (72.7)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)				
Ferumoxytol 2x510 mg	114	4 (3.5)	110 (96.5)	102 (89.5)
Oral Iron 200 mg/day	116	3 (2.6)	113 (97.4)	99 (85.3)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)				
Ferumoxytol 2x510 mg	228	11 (4.4)	217 (95.2)	208 (91.2)
Oral Iron 200 mg/day	76	1 (1.3)	75 (98.7)	63 (82.9)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)				
Ferumoxytol 2x510 mg	227 [b]	7 (3.1)	220 (96.9)	215 (94.7)
Oral Iron 200 mg/day	77	3 (3.9)	74 (96.1)	67 (87.0)

[a] Reasons for withdrawn post-initial dose include adverse events, lost to follow-up, death, withdrew consent, 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. Adjustment were made to count this subject once.

Table 16 provides the reasons for subjects not completing the study in each of the three studies by treatment group – post initial dose.

Table 16: Summary of reasons for not completing the study-post-initial dose

Treatment	N Randomized	Reasons for Not Completing Study n (%)								Completed
		Protocol Violation	Lack of Compliance	Adverse Event	Lost to Follow-up	Withdrew Consent	Death	Other	Total non-completers	
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)										
Ferumoxytol 2x510 mg	64	5 (7.8)	0	0	1 (1.6)	1 (1.6)	1 (1.6)	2 (3.1)	10 (15.6)	54 (84.4)
Ferumoxytol 4x255 mg	62	4 (6.4)	0	3 (4.8)	0	0	0	0	7 (11.3)	55 (88.7)
Oral Iron 200 mg/day	22	2 (9.1)	0	1 (4.5)	0	1 (4.5)	0	2 (9.1)	6 (27.3)	16 (72.7)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)										
Ferumoxytol 2x510 mg	114	4 (3.5)	0	5 (4.4)	0	0	1 (0.9)	2 (1.8)	12 (10.5)	102 (89.5)
Oral Iron 200 mg/day	116	4 (3.4)	0	9 (7.8)	0	1 (0.9)	1 (0.9)	1 (0.9)	16 (13.8)	100 (86.2)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)										
Ferumoxytol 2x510 mg	228	3 (1.3)	0	5 (2.2)	2 (0.9)	5 (2.2)	0	5 (2.2)	20 (8.8)	208 (91.2)
Oral Iron 200 mg/day	76	1 (1.3)	0	9 (11.8)	1 (1.3)	0	0	2 (2.6)	13 (17.1)	63 (82.9)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)										
Ferumoxytol 2x510 mg	227	4 (1.8)	1 (0.4)	2 (0.9)	1 (0.4)	1 (0.4)	2 (0.9)	1 (0.4)	12 (5.3)	215 (94.7)
Oral Iron 200 mg/day	77	1 (1.3)	1 (1.3)	8 (10.4)	0	0	0	0	10 (13.0)	67 (87.0)

Other = administrative reasons for withdrawal - 14 out of total 15 withdrew prior to dosing (determined ineligible, randomized in error, etc.) and remaining 1 waiver withdrawn.

Table 17 provides subject's age group and gender summaries by study and treatment groups.

Table 17: Subject's age group and gender in the randomized subjects (ITT)

		Age (Years)					Gender	
	n	Mean ± sd	< 50 n, (%)	50 - <65 n, (%)	65 - <75 n, (%)	≥ 75 n, (%)	Male n, (%)	Female n, (%)
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)								
Ferumoxytol 2x510 mg	58	57.1 ± 14.2	16 (28)	23 (40)	11 (19)	8 (14)	24 (41)	34 (59)
Ferumoxytol 4x255 mg	60	58.6 ± 14.9	18 (30)	20 (33)	12 (20)	10 (17)	26 (43)	34 (57)
Oral Iron 200 mg/day	17	60.1 ± 11.5	3 (18)	7 (41)	6 (35)	1 (6)	7 (41)	10 (59)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)								
Ferumoxytol 2x510 mg	110	59.2 ± 14.3	28 (25)	40 (36)	26 (24)	16 (15)	54 (49)	56 (51)
Oral Iron 200 mg/day	114	60.7 ± 13.0	20 (18)	49 (43)	25 (22)	20 (18)	42 (37)	72 (63)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)								
Ferumoxytol 2x510 mg	217	65.0 ± 14.3	34 (16)	66 (30)	60 (28)	57 (26)	89 (41)	128 (59)
Oral Iron 200 mg/day	75	63.4 ± 10.9	9 (12)	32 (43)	22 (29)	12 (16)	24 (32)	51 (68)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)								
Ferumoxytol 2x510 mg	220	65.6 ± 14.1	27 (12)	63 (29)	66 (30)	64 (29)	91 (41)	129 (59)
Oral Iron 200 mg/day	74	67.6 ± 13.2	6 (8)	25 (34)	17 (23)	26 (35)	28 (38)	46 (62)

Table 18 provides subject's race and geographic region summaries by study and treatment groups.

Table 18: Subject's race and geographic region in the randomized subjects (ITT)

		Race			Geographic Region			
	n	Caucasian n, %	Black/African American n, %	Other n, %	Northeast n, %	Midwest n, %	South n, %	West n, %
Study 62,745-5 Pre-amendment (Dialysis Dependent: stages 5D on HD)								
Ferumoxytol 2x510 mg	64	25 (39)	34 (53)	5 (8)	24 (38)	3 (5)	26 (41)	11 (17)
Ferumoxytol 4x255 mg	62	21 (34)	34 (55)	7 (11)	25 (40)	2 (3)	21 (34)	14 (23)
Oral Iron 200 mg/day	22	12 (55)	10 (45)	0	8 (36)	2 (9)	9 (41)	3 (14)
Study 62,745-5 Post-amendment (Dialysis Dependent: stages 5D on HD)								
Ferumoxytol 2x510 mg	114	37 (32)	69 (61)	8 (7)	40 (34)	24 (21)	30 (26)	22 (19)
Oral Iron 200 mg/day	116	40 (35)	67 (58)	8 (7)	39 (34)	24 (21)	29 (26)	22 (19)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)								
Ferumoxytol 2x510 mg	228	130 (57)	78 (34)	20 (9)	40 (18)	27 (12)	158 (69)	3 (1)
Oral Iron 200 mg/day	76	46 (61)	28 (37)	2 (2)	22 (29)	14 (18)	40 (53)	0
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)								
Ferumoxytol 2x510 mg	226	152 (67)	71 (31)	3 (1)	13 (6)	42 (19)	120 (53)	51 (23)
Oral Iron 200 mg/day	77	48 (62)	26 (34)	3 (4)	4 (5)	15 (21)	42 (55)	15 (19)

Table 19 provides subject's CKD stage summaries by study and treatment groups.

Table 19: Subject's CKD Stages in the randomized subjects in each of the two studies

	n	Stage 1or 2 n (%)	Stage 3 n (%)	Stage 4 n (%)	Stage 5 n (%)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg	228 (4 missing)	4 (2)	82 (36)	107 (47)	31 (14)
Oral Iron 200 mg/day	76	2 (3)	30 (39)	36 (47)	8 (11)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg (7 missing)	215 (7 missing)	3 (1)	85 (37)	107 (47)	25 (11)
Oral Iron 200 mg/day	73 (1 missing)	1 (1)	30 (39)	41 (53)	4 (5)

Table 20 provides subject's ESA use summaries by study and treatment groups.

Table 20: Subject's ESA Use in the randomized subjects

	n	Not receiving ESA Therapy (n, %)	Received Stable ESA Therapy (n, %)	Started ESA or Dose Change >25 (n, %)	Receiving ESA Therapy-Stable or Started (n, %))
Study 62,745-5 Pre-amandment (Dialysis Dependent: stages 5D on HD)					
Ferumoxytol 2x510 mg	64	0	34 (47)	30 (53)	64 (100)
Ferumoxytol 4x255 mg	62	0	36 (58)	26 (42)	62 (100)
Oral Iron 200 mg/day	22	0	17 (77)	5 (23)	22 (100)
Study 62,745-5 Post-amandment (Dialysis Dependent: stages 5D on HD)					
Ferumoxytol 2x510 mg	114	0	88 (77)	26 (23)	114 (100)
Oral Iron 200 mg/day	116	0	91 (78)	25 (22)	116 (100)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg	228	144 (63)	73 (32)	11 (5)	84 (37)
Oral Iron 200 mg/day	76	43 (56)	28 (37)	5 (7)	33 (43)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)					
Ferumoxytol 2x510 mg	226	132 (58)	90 (40)	7 (3)	97 (43)
Oral Iron 200 mg/day	77	43 (56)	31 (40)	3 (4)	34 (44)

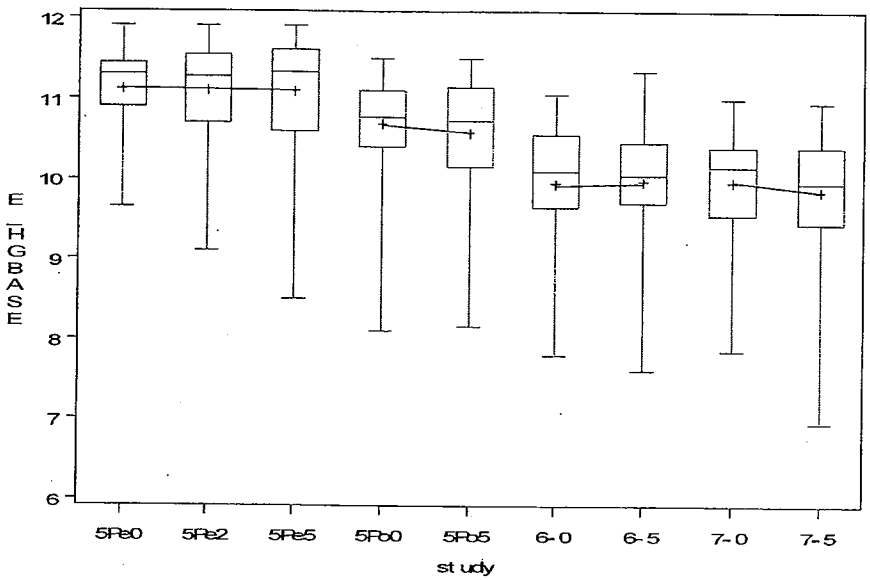
Table 21 provides mean hemoglobin levels (g/dL), mean ferritin (ng/mL), and mean TSAT (%) at the baseline for each study. This is also exhibited in Figures 1, 2 and 3.

Table 21: Subject's baseline characteristics in the randomized subjects in each of the three studies for Hgb (g/dL), Ferritin (ng/mL) and TSAT (%)

	n	Hgb (g/dL) Mean (sd)	Ferritin (ng/mL) Mean (sd)	TSAT (%) Mean (sd)
Study 62,745-5 Pre-amandment (Dialysis Dependent: stages 5D on HD)				
Ferumoxytol 2x510 mg	58	11.08 (0.72)	305.76 (164.07)	17.27 (0.49)
Ferumoxytol 4x255 mg	60	11.11 (0.58)	312.19 (167.02)	16.95 (5.41)
Oral Iron 200 mg/day	17	11.19 (0.63)	300.84 (170.06)	16.23 (5.54)
Study 62,745-5 Post-amandment (Dialysis Dependent: stages 5D on HD)				
Ferumoxytol 2x510 mg	110	10.59 (0.67)	340.52 (159.07)	15.71 (7.21)
Oral Iron 200 mg/day	114	10.69 (0.57)	357.56 (171.65)	15.91 (6.29)
Study 62,745-6 (Non-Dialysis Dependent CKD Stage 1-5)				
Ferumoxytol 2x510 mg	217	9.96 (0.69)	146.10 (173.55)	11.28 (6.10)
Oral Iron 200 mg/day	75	9.94 (0.78)	143.58 (144.87)	10.14 (5.47)
Study 62,745-7 (Non-Dialysis Dependent CKD Stage 1-5)				
Ferumoxytol 2x510 mg	220	9.85 (0.77)	123.74 (125.36)	9.79 (5.42)
Oral Iron 200 mg/day	74	9.94 (0.73)	148.18 (136.34)	10.37 (5.22)

Figure 9 shows that each study had similar baseline hemoglobin (g/dl) levels (means and variability) comparing oral iron to ferumoxytol.

Figure 9: Hemoglobin level at Base (g/dl)



Study Codes:

5PeO = Study 62745-5 Pre-amendment Oral Iron
5Pe2 = Study 62745-5 Pre-amendment Ferumoxytol (4x255 mg)
5Pe5 = Study 62745-5 Pre-amendment Ferumoxytol (2x510 mg)
5PoO = Study 62745-5 Post-amendment Oral Iron
5Po5 = Study 62745-5 Post-amendment Ferumoxytol (2x510 mg)
6-O = Study 62745-6 Oral Iron
6-5 = Study 62745-6 Ferumoxytol (2x510 mg)
7-O = Study 62745-7 Oral Iron
7-5 = Study 62745-7 Ferumoxytol (2x510 mg)

Figure 10 shows that each study had similar baseline serum Ferritin (ng/mL) levels (means and variability) comparing oral iron to ferumoxytol.

Figure 10: Baseline serum Ferritin (ng/mL)

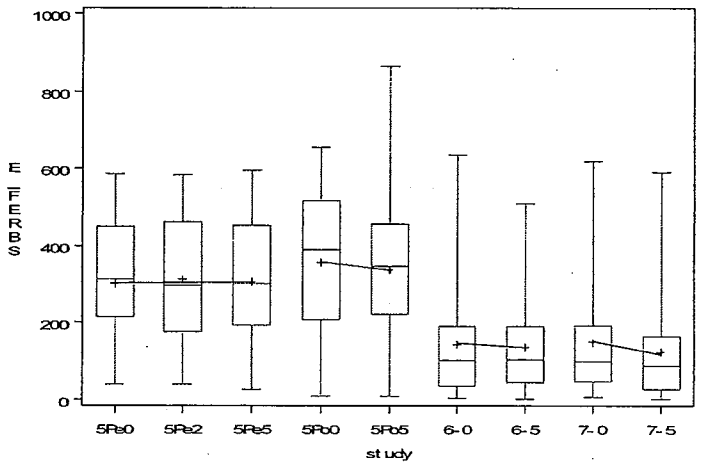
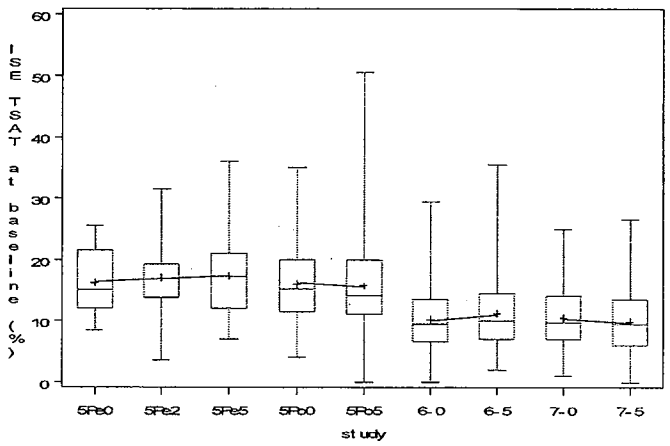


Figure 11 shows that each study had similar baseline Transferrin Saturation (TSAT) (%) levels (means and variability) comparing oral iron to ferumoxytol.

Figure 11: Transferrin Saturation (TSAT) at baseline (%)



Study codes are as in Figure 1

APPENDIX B: OTHER SECONDARY ENDPOINTS

Other Secondary endpoints:

- **Mean Serum Ferritin change from baseline at Day 35 (ng/mL)**

The changes in mean serum ferritin from baseline at Day 35 (ng/mL) observed in these groups for the ITT population are given in Table 22. Relative to oral iron, Ferumoxytol treated subjects had greater increases in mean serum ferritin from baseline at Day 35. Mean serum ferritin (ng/mL) in subjects in the oral iron treatment group went down or almost remained the same compared to the baseline (95% CI includes 0) at Day 35. (Table 22)

Table 22: Table: Secondary Endpoint - Mean Serum Ferritin change from baseline at Day 35 (ng/mL) - Oral Iron versus Ferumoxytol

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	-39.61 (47.03)	(-60.5, -18.8)	-25.97	(-83.1, 0)	(-157, 12)	<0.001
	Ferumoxytol 2x510 mg	64	288.42 (266.58)	(221.8, 355)	240.25	(60, 427.3)	(-66, 1092)	
	Ferumoxytol 4x255 mg	62	314.26 (224.43)	(257.3, 371.3)	255.67	(145.1, 451.9)	(0, 1024)	<0.001
62745-5-Post	Oral (200 mg/day)	116	-61.29 (109.22)	(-81.4,-41.2)	-45.75	(-117.8, 0)	(-358, 392)	<0.0001
	Ferumoxytol 2x510 mg	114	247.17 (201.62)	(209.8, 284.6)	239	(108.5, 321.5)	(-169, 1271)	
62745-6	Oral (200 mg/day)	76	9.45 (60.84)	(-4.5, 23.4)	2.05	(-18.8, 25.7)	(-120, 230)	<0.0001
	Ferumoxytol 2x510 mg	228	384.75 (278.2)	(348.4, 421.1)	347.8	(196.1, 503.5)	(-32, 1544)	
62745-7	Oral (200 mg/day)	77	2.80 (84.33)	(-16.3, 21.9)	0.55	(-18.5, 19.2)	(-276, 489)	<0.0001
	Ferumoxytol 2x510 mg	226	302.00 (142.55)	(273.8, 330.2)	266	(142.6, 440.5)	(-299, 1024)	

* t-test assuming unequal variance – nominal p-values

Table 22 shows that increases in both mean and median change in mean serum ferritin from baseline at Day 35 (ng/mL) observed in these groups were consistently more in Ferumoxytol treatment group as compared to Oral Iron. The 95% confidence intervals were non-overlapping in each of the three pivotal studies.

- **Hgb change from baseline at Day 21 (g/dL)**

Increase in mean Hgb (g/dL) from baseline to Day 21 was also significantly more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies (Table 23 and Figure 12) (except in the study 62745-5-Pre-amendment – these results are given for information only). Hgb (g/dL) levels also increased in the oral iron treatment group, but the mean increase in the Ferumoxytol treatment group was more at Day 21 than the oral iron treatment group. The results for each study are given in Table 23 and Figure 12. Relative to oral iron, Ferumoxytol treated subjects had greater increases in hemoglobin at Day 21.

Table 23: Mean Hgb change from baseline at Day 21 (g/dL) Oral Iron versus Ferumoxytol

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.17 (0.65)	(-0.12, 0.46)	0.03	(0, 0.53)	(-1.0, 1.5)	0.0060
	Ferumoxytol 2x510 mg	64	0.67 (0.83)	(0.47, 0.88)	0.55	(0, 1.1)	(-1.0, 3.2)	
	Ferumoxytol 4x255 mg	62	0.72 (0.95)	(0.48, 0.96)	0.6	(0.00, 1.56)	(-2.0, 3.0)	0.0046
62745-5-Post	Oral (200 mg/day)	116	0.35 (0.90)	(0.19, 0.52)	0.17	(-0.14, 0.80)	(-3.0, 3.0)	0.0068
	Ferumoxytol 2x510 mg	114	0.71 (1.07)	(0.51, 0.91)	0.53	(0, 1.2)	(-1.5, 6.6)	
62745-6	Oral (200 mg/day)	76	0.20 (0.73)	(0.03, 0.37)	0.00	(-0.25, 0.69)	(-1.7, 2.5)	<0.001
	Ferumoxytol 2x510 mg	228	0.66 (0.96)	(0.54, 0.79)	0.55	(-0.35, 1.2)	(-2.3, 4.1)	
62745-7	Oral (200 mg/day)	77	0.38 (0,80)	(0.19, 0.56)	0.25	(0, 0.7)	(-1.4, 3.1)	<0.001
	Ferumoxytol 2x510 mg	226	0.9 (1.01)	(0.77, 1.03)	0.8	(0.05, 1.55)	(-1.7, 4.3)	

* t-test assuming unequal variance – nominal p-values

Table 23 shows that increases in both mean and median change in hemoglobin from baseline to Day 35 were consistently more in Ferumoxytol treatment group as compared to Oral Iron.

Figure 12: Hemoglobin levels at Day 21 (g/dl)

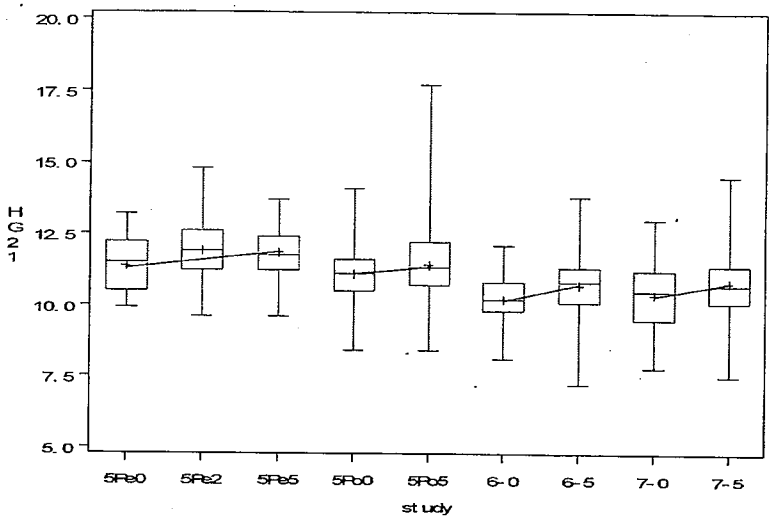
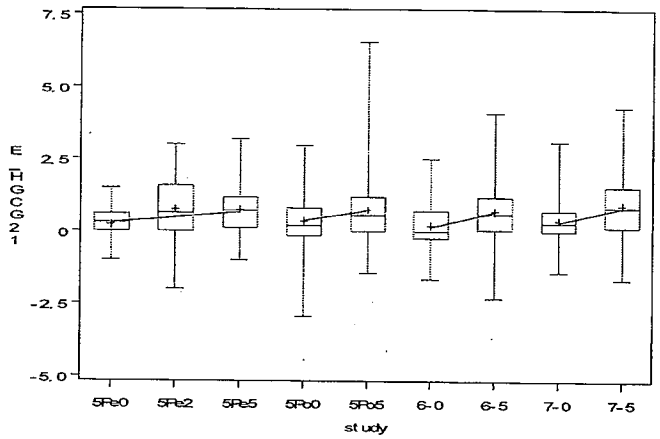


Figure 12 shows that the increases in mean Hgb (g/dL) levels on Day 21 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A great deal of variability in Hgb levels on Day 21 was observed in both Ferumoxytol and Oral Iron treatment groups.

Figure 13: Change in Hemoglobin Levels Change at Day 21 from Baseline (g/dl)



Study codes are as in Figure 1

Figure 13 shows that the increases in mean change in hemoglobin from baseline to Day 21 were consistent and had similar gradient when Ferumoxytol treatment group is compared to Oral Iron. A great deal of variability in Hgb levels was observed in both Ferumoxytol and Oral Iron treatment groups.

- **Hgb & Ferritin Responders –increase in Hgb by ≥ 1 (ng/mL) at Day 35 plus increase in ferritin by ≥ 160 ng/mL at Day 21 or 35**

Hgb & Ferritin Responders - Increase in Hgb by ≥ 1 (ng/mL) from baseline at Day 35 plus increase in ferritin by ≥ 160 ng/mL at Day 21 or 35 from baseline - Oral Iron (200 mg/day) versus Ferumoxytol 2x510 mg observed in these groups for the ITT population are given in Table 24. Relative to oral iron, Ferumoxytol treated subjects had greater increases in Hgb & Ferritin Responders (%) from baseline at Day 35.

Table 24: Hgb Responders - Increase in Hgb by ≥ 1 at Day 35 plus increase in ferritin by ≥ 160 ng/mL at Day 21 or 35 from baseline Oral Iron versus Ferumoxytol

Study	Group	N	Hgb & Ferritin Responder n (%)	p-value Comparing Ferumoxytol to Oral Iron *
62745-5-Pre	Oral	22	0	
	Ferumoxytol 4x255 mg	62	29 (47)	< 0.0001
	Ferumoxytol 2x510 mg	64	15 (23)	0.0093
62745-5-Post	Oral	116	1 (1)	
	Ferumoxytol 2x510 mg	114	49 (43)	< 0.0001
62745-6	Oral	76	0	
	Ferumoxytol 2x510 mg	228	81 (36)	< 0.0001
62745-7	Oral	77	0	
	Ferumoxytol 2x510 mg	226	104 (46)	< 0.0001
	Ferumoxytol 2x510 mg	568	234 (43)	

* Fisher's Exact Test – nominal p-values

APPENDIX C: SENSITIVITY ANALYSES

- **Last observation carried forward (LOCF) method for missing Day 35 hemoglobin values**

Minor changes (as compared to ITT analysis) in means and 95% CI for the primary endpoint of increase in mean Hgb (g/dL) from baseline to Day 35 were observed using LOCF method for missing values. Statistical significance was not affected. Increase in mean Hgb (g/dL) from baseline to Day 35 was significantly more in Ferumoxytol treatment group as compared to Oral iron treatment group in all studies (except in the study 62745-5-Pre-amendment which is included here for information). Hgb (g/dL) levels also increased in the oral iron treatment group, but increase in the Ferumoxytol treatment group was statistically significantly more at Day 35 than the oral iron treatment group. The details are given in Table 25.

Table 25: Hgb change from baseline at Day 35 (g/dL) - Last Observation Carried Forward (LOCF)

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.40 (0.91)	(-0.07, 0.87)	0.50	(-0.35, 1.15)	(-1.2, 2.0)	
	Ferumoxytol 2x510 mg	64	0.83 (1.03)	(0.56, 1.10)	0.70	(-0.16, 1.41)	(-1.5, 3.8)	0.1127
	Ferumoxytol 4x255 mg	62	0.91 (1.15)	(0.61, 1.2)	0.90	(0.11, 1.65)	(-2.1, 3.6)	0.0688
62745-5-Post	Oral (200 mg/day)	116	0.51 (1.08)	(0.31, 0.71)	0.38	(-0.06, 1.06)	(-2.8, 4.1)	0.0003
	Ferumoxytol 2x510 mg	114	1.06 (1.14)	(0.85, 1.28)	1.00	(0.29, 1.80)	(-1.3, 5.1)	
62745-6	Oral (200 mg/day)	76	0.23 (1.06)	(-0.01, 0.47)	0.20	(-0.25, 0.90)	(-3.0, 3.7)	<0.001
	Ferumoxytol 2x510 mg	228	0.87 (1.25)	(0.70, 1.04)	0.75	(0.10, 1.40)	(-3.3, 6.2)	
62745-7	Oral (200 mg/day)	77	0.53 (1.01)	(0.30, 0.76)	0.43	(-0.08, 0.83)	(-2.1, 4.0)	<0.001
	Ferumoxytol 2x510 mg	226	1.27 (1.25)	(1.10, 1.44)	1.10	(0.35, 2.05)	(-1.5, 5.3)	

* t-test assuming unequal variance – nominal p-values

- **Imputing average treatment group change for missing Day 35 hemoglobin result**

Missing hemoglobin values on Day 35 were assigned the mean of the mutually exclusive treatment groups to which they belong. Minor changes (as compared to ITT analysis) in means and 95% CI for the primary endpoint of increase in mean Hgb (g/dL) from baseline to Day 35 were observed using average treatment group change for missing values. Statistical significance was not affected. Increase in mean Hgb (g/dL) from baseline to Day 35 was significantly more in Ferumoxytol treatment group as compared to Oral Iron treatment group in all studies (except in the study 62745-5-Pre-amendment). Hgb (g/dL) levels also increased in the oral iron treatment group, but increase in the Ferumoxytol treatment group was statistically significantly more at Day 35 than the oral iron treatment group. The details are given in Table 26.

Table 26: Hgb change from baseline at Day 35 (g/dL) - average treatment group change assignment

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.43 (0.91)	(-0.04, 0.90)	0.50	(-0.35, 1.15)	(-1.2, 2.0)	
	Ferumoxytol 2x510 mg	64	0.83 (1.01)	(0.56, 1.09)	0.70	(0.14, 1.35)	(-1.5, 3.8)	0.1356
	Ferumoxytol 4x255 mg	62	0.95 (1.13)	(0.66, 1.25)	0.95	(0.26, 1.65)	(-2.1, 3.6)	0.0572
62745-5-Post	Oral (200 mg/day)	116	0.51 (1.07)	(0.31, 0.71)	0.40	(-0.06, 1.06)	(-2.8, 4.1)	<0.001
	Ferumoxytol 2x510 mg	114	1.09 (1.13)	(0.88, 1.30)	1.00	(0.35, 1.80)	(-1.3, 5.1)	
62745-6	Oral (200 mg/day)	76	0.24 (1.05)	(-0.01, 0.48)	0.24	(-0.25, 0.85)	(-3.0, 3.7)	<0.001
	Ferumoxytol 2x510 mg	228	0.90 (1.24)	(0.74, 1.07)	0.85	(0.25, 1.38)	(-3.3, 6.2)	
62745-7	Oral (200 mg/day)	77	0.56 (0.99)	(0.33, 0.79)	0.50	(-0.01, 0.83)	(-2.1, 4.0)	<0.001
	Ferumoxytol 2x510 mg	226	1.29 (1.24)	(1.12, 1.45)	1.13	(0.40, 2.04)	(-1.5, 5.3)	

* t-test assuming unequal variance – nominal p-values

- **Worst case scenario –assigning the smallest observed group change for Day 35 change in hemoglobin.**

Missing values for Ferumoxytol patients were assigned the smallest observed change from mutually exclusive membership group (respective treatment group and readmit arm). Oral iron patients were assigned the smallest observed change within their respective treatment group. Changes in means and 95% CI as for the primary endpoint of increase in mean Hgb (g/dL) from baseline to Day 35 were observed using worst case scenario for missing values. Increase in mean Hgb (g/dL) from baseline to Day 35 was significantly more in Ferumoxytol treatment group as compared to Oral Iron treatment group in 2 studies (62745-5-Post and 62745-7) and a trend was observed in the study 62745-6 The details are given in Table 27.

Table 27: Hgb change from baseline at Day 35 (g/dL) - assigning the smallest observed group change

Study	Group	N	Mean (sd)	95% CI	Median	Inter Quartile Range Q1-Q3	Range	p-value (FER compared to Oral) *
62745-5-Pre	Oral (200 mg/day)	22	0.64 (1.26)	(-0.01, 1.29)	0.50	(-0.35, 1.33)	(-1.2, 4.1)	
	Ferumoxytol 2x510 mg	64	0.83 (1.03)	(0.56, 1.10)	0.63	(0.05, 1.35)	(-1.5, 3.8)	0.8684
	Ferumoxytol 4x255 mg	62	0.75 (1.36)	(0.40, 1.10)	0.88	(-0.09, 1.65)	(-2.1, 3.6)	0.7515
62745-5-Post	Oral (200 mg/day)	116	0.67 (1.30)	(0.43, 0.91)	0.40	(-0.06, 1.31)	(-2.8, 4.1)	0.0351
	Ferumoxytol 2x510 mg	114	1.02 (1.21)	(0.80, 1.25)	1.00	(0.29, 1.80)	(-1.5, 5.1)	
62745-6	Oral (200 mg/day)	76	0.56 (1.46)	(0.22, 0.89)	0.35	(-0.25, 1.15)	(-3.0, 3.7)	0.4434
	Ferumoxytol 2x510 mg	228	0.71 (1.52)	(0.51, 0.91)	0.70	(0.03, 1.38)	(-3.3, 6.2)	
62745-7	Oral (200 mg/day)	77	0.70 (1.20)	(0.42, 0.98)	0.50	(-0.01, 0.98)	(-2.1, 4.0)	0.0019
	Ferumoxytol 2x510 mg	226	1.23 (1.30)	(1.05, 1.40)	1.10	(0.35, 2.04)	(-1.5, 5.3)	

* t-test assuming unequal variance – nominal p-values

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