

7.3.3 Dropouts and/or Discontinuations

The following table shows the summary of adverse events leading to treatment discontinuation (permanent and/or temporary) by treatment group in all study subjects (CKD and non-CKD). All subjects who experienced adverse events leading to treatment discontinuation in the ferumoxytol clinical program were CKD subjects except for one non-CKD subject. This subject was a healthy volunteer in study 62,745-9, who had treatment permanently discontinued due to mild headache, pruritus, and urticaria occurring on the day of the first dose of 510 mg of ferumoxytol.

The overall rate of treatment discontinuation in ferumoxytol-treated subjects was 2% as compared to 11% in oral iron-treated subjects.

**Summary of Adverse Events Leading to Treatment Discontinuation
 in All Subjects (CKD and non-CKD)**

Treatment Discontinuation	Ferumoxytol (N=1795*)		Oral Iron (N=290)		Placebo (N=775)	
	Events N	Subjects N (%)	Events N	Subjects N (%)	Events N	Subjects N (%)
Permanent and/or Temporary**	59	38 (2.12)	75	32 (11.03)	9	6 (0.77)
Temporary***	16	13 (0.72)	13	10 (3.45)	0	0 (0.00)
Permanent without discontinuation from study***	27	14 (0.78)	13	7 (2.41)	4	3 (0.39)
Permanent with discontinuation from study***	16	12 (0.67)	49	21 (7.24)	5	5 (0.65)

* Includes both first course (N=1726) and second course (N=69) ferumoxytol-treated subjects

** A subject is only counted once regardless of the type of treatment discontinuation

*** A subject is only counted once regardless of the number of adverse events the subject experienced
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Adverse events leading to treatment discontinuation and occurring in ≥ 2 ferumoxytol-treated subjects included: hypotension (0.28%), infusion site swelling (0.17%), serum ferritin increased (0.17%), and chest pain, diarrhea, dizziness, ecchymosis, pruritis, renal failure chronic, and urticaria (all occurring in 0.11%). Among these adverse events, infusion site swelling, serum ferritin increased, dizziness, ecchymosis, pruritis, and urticaria all occurred at a higher incidence in ferumoxytol-treated subjects than in oral iron-treated subjects.

Adverse events leading to treatment discontinuation and occurring in ≥ 2 oral iron-treated subjects included: diarrhea (2.8%), vomiting (1.38%), anemia (1.03%), nausea (1.03%), and headache, renal failure chronic, abdominal pain, pneumonia, constipation, and hemoglobin decreased (all occurring in 0.69%). All of these 10 adverse events occurred at a higher incidence in oral iron-treated subjects compared to ferumoxytol-treated subjects.

There was one subject who had vomiting events leading to treatment discontinuation in placebo-treated subjects.

The following table shows all individual adverse events leading to treatment discontinuation (permanent and temporary) in ≥ 2 subjects in any treatment group in all study subjects (CKD and non-CKD).

**Adverse Events Leading to Treatment Discontinuation (Permanent and Temporary) in ≥ 2 Subjects in Any Treatment Group
 All Subjects (CKD and non-CKD)**

Preferred Term	Ferumoxytol (N=1795*)	Oral Iron (N=290)	Placebo (N=775)
	Subjects (N %)	Subjects (N %)	Subjects (N %)
Hypotension	5 (0.28)	1 (0.34)	0 (0.00)
Infusion Site Swelling	3 (0.17)	0 (0.00)	0 (0.00)
Serum Ferritin Increased	3 (0.17)	0 (0.00)	0 (0.00)
Chest Pain	2 (0.11)	1 (0.34)	0 (0.00)
Diarrhoea	2 (0.11)	8 (2.76)	0 (0.00)
Dizziness	2 (0.11)	0 (0.00)	0 (0.00)
Ecchymosis	2 (0.11)	0 (0.00)	0 (0.00)
Pruritus	2 (0.11)	0 (0.00)	0 (0.00)
Renal Failure Chronic	2 (0.11)	2 (0.69)	0 (0.00)
Urticaria	2 (0.11)	0 (0.00)	0 (0.00)
Headache	1 (0.06)	2 (0.69)	0 (0.00)
Nausea	1 (0.06)	3 (1.03)	0 (0.00)
Pneumonia	1 (0.06)	2 (0.69)	0 (0.00)
Vomiting	1 (0.06)	4 (1.38)	1 (0.13)
Anemia	0 (0.00)	3 (1.03)	0 (0.00)
Abdominal Pain	0 (0.00)	2 (0.69)	0 (0.00)
Constipation	0 (0.00)	2 (0.69)	0 (0.00)
Haemoglobin Decreased	0 (0.00)	2 (0.69)	0 (0.00)

Note: A subject is counted in all preferred terms that led to discontinuation.

*Includes both first course (N=1726) and second course (N=69) ferumoxytol treated subjects

Sponsor's table in Amendment 0006 submitted June 5, 2008

7.3.4 Significant Adverse Events

See hypersensitivity reactions in Section 7.2.6.

7.3.5 Submission Specific Primary Safety Concerns

See hypersensitivity reactions in Section 7.2.6.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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%).

The following table shows the TEAEs that occurred in $\geq 0.5\%$ of subjects in the Ferumoxytol first course treatment group in CKD subjects. 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. All listed adverse events except pruritus occurred more frequently with ferumoxytol treatment than with placebo treatment.

Number (Percent) of Subjects with Treatment-emergent Adverse Events Occurring in $\geq 0.5\%$ of Subjects in the Ferumoxytol First Course Treatment Group by Treatment Exposure - CKD Subjects (Safety Population)

TEAE ^a Preferred Term	Ferumoxytol First Course N=1562 n (%)	Ferumoxytol Second Course N=69 n (%)	Oral Iron N=290 n (%)	Placebo N=711 n (%)
Diarrhea	37 (2.4)	4 (5.8)	23 (7.9)	9 (1.3)
Hypotension	33 (2.1)	0	1 (0.3)	6 (0.8)
Nausea	31 (2.0)	3 (4.3)	21 (7.2)	10 (1.4)
Dizziness	29 (1.9)	1 (1.4)	5 (1.7)	6 (0.8)
Edema Peripheral	23 (1.5)	1 (1.4)	9 (3.1)	8 (1.1)
Headache	22 (1.4)	1 (1.4)	6 (2.1)	9 (1.3)
Vomiting	22 (1.4)	2 (2.9)	14 (4.8)	8 (1.1)
Constipation	17 (1.1)	0	16 (5.5)	2 (0.3)

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Dyspnea	13 (0.8)	2 (2.9)	3 (1.0)	1 (0.1)
Edema	13 (0.8)	2 (2.9)	4 (1.4)	3 (0.4)
Hypertension	13 (0.8)	0	2 (0.7)	4 (0.6)
Chest Pain	12 (0.8)	0	3 (1.0)	3 (0.4)
Fatigue	12 (0.8)	0	1 (0.3)	4 (0.6)
Pain in Extremity	12 (0.8)	0	3 (1.0)	1 (0.1)
Cardiac Failure Congestive	12 (0.8)	1 (1.4)	5 (1.7)	1 (0.1)
Cough	11 (0.7)	0	4 (1.4)	0
Pruritus	11 (0.7)	1 (1.4)	1 (0.3)	5 (0.7)
Abdominal Pain	11 (0.7)	0	4 (1.4)	2 (0.3)
Urinary Tract Infection	10 (0.6)	1 (1.4)	7 (2.4)	2 (0.3)
Upper Respiratory Tract Infection	9 (0.6)	2 (2.9)	1 (0.3)	1 (0.1)
Back Pain	9 (0.6)	0	0	2 (0.3)
Muscle Spasms	9 (0.6)	1 (1.4)	4 (1.4)	2 (0.3)
Pneumonia	9 (0.6)	0	4 (1.4)	0
Cardiac Murmur	8 (0.5)	2 (2.9)	3 (1.0)	1 (0.1)
Pyrexia	8 (0.5)	1 (1.4)	2 (0.7)	3 (0.4)
Gout	8 (0.5)	0	1 (0.3)	1 (0.1)

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.

Abbreviations: TEAE=treatment-emergent adverse event.

Sponsor's table in summary of clinical safety

The most commonly reported TEAEs among subjects in the oral iron group ($\geq 2.0\%$ of subjects) were diarrhea (7.9%), nausea (7.2%), edema peripheral (3.1%), constipation (5.5%), vomiting (4.8%), urinary tract infection (2.4%), and headache (2.1%).

The TEAEs that occurred with a frequency of $\geq 2.0\%$ in subjects treated with a second course of ferumoxytol included diarrhea, nausea, vomiting, dyspnea, edema, upper respiratory tract infection, and cardiac murmur.

The TEAEs occurring in $\geq 1.0\%$ of CKD subjects in the ferumoxytol 2 x 510 mg treatment group, irrespective of relationship to study medication, are summarized for the three Phase 3 pivotal safety and efficacy studies (Protocols 62,745-5, 62,745-6, and 62,745-7) and presented in the following table.

Overall, 19 TEAEs occurred at an incidence of $\geq 1.0\%$ in the ferumoxytol 2 x 510 mg treatment group. Six TEAEs occurred with a frequency of $\geq 2\%$ in the 2 x 510 mg ferumoxytol group including diarrhea, nausea, dizziness, hypotension, constipation, and edema peripheral. Adverse

events that occurred with a higher frequency with ferumoxytol treatment than oral iron included dizziness, hypertension, edema, chest pain, pruritus, back pain, rash, hypertension, and pyrexia.

Number (Percent) of Subjects with the Most Common Treatment-emergent Adverse Events (Based on $\geq 1.0\%$ of Subjects in the Ferumoxytol 2 x 510 mg Treatment Group) in Randomized, Open-label, Controlled Studies by Treatment Group - CKD Subjects (Safety Population)

TEAE^a Preferred Term	Ferumoxytol 4 x 255 mg N=60 n (%)	Ferumoxytol 2 x 510 mg N=605 n (%)	Oral Iron N=280 n (%)
Diarrhea	0	24 (4.0)	23 (8.2)
Nausea	1 (1.7)	19 (3.1)	21 (7.5)
Dizziness	0	16 (2.6)	5 (1.8)
Hypotension	1 (1.7)	15 (2.5)	1 (0.4)
Constipation	0	13 (2.1)	16 (5.7)
Edema Peripheral	1 (1.7)	12 (2.0)	9 (3.2)
Headache	0	11 (1.8)	6 (2.1)
Edema	1 (1.7)	9 (1.5)	4 (1.4)
Vomiting	2 (3.3)	9 (1.5)	14 (5.0)
Chest Pain	1 (1.7)	8 (1.3)	2 (0.7)
Cough	1 (1.7)	8 (1.3)	4 (1.4)
Abdominal Pain	0	8 (1.3)	4 (1.4)
Pruritus	1 (1.7)	7 (1.2)	1 (0.4)
Back pain	0	1.0%	0
Muscle Spasms	0	1.0%	1.4%
Dyspnea	0	1.0%	1.1%
Rash	0	1.0%	0.4%
Hypertension	0	1.0%	0.7%
Pyrexia	1 (1.7%)	1.0%	0.7%

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

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

Abbreviations: TEAE=treatment-emergent adverse event.

Sponsor's table in summary of clinical safety

In cross-over study (62,745-8), the overall incidence of TEAEs, irrespective of relationship to study medication, was 21.3% with ferumoxytol 510 mg single dose, 16.7% with placebo in CKD patients.

Treatment-emergent AEs that occurred in $\geq 0.5\%$ of subjects following either treatment are summarized in the table below.

Number of Treatment-emergent Adverse Events and Number (percent) of Subjects with Treatment-emergent Adverse Events Occurring in $\geq 0.5\%$ of Subjects in Either Treatment Group (Safety Population, Study 62,745-8)

AE ^{a, b} Preferred Term	Ferumoxytol N=713		Placebo N=711	
	Events n	Subjects n (%)	Events n	Subjects n (%)
Any AE	242	152 (21.3)	178	119 (16.7)
Edema Peripheral	13	11 (1.5)	5	5 (0.7)
Nausea	10	10 (1.4)	8	8 (1.1)
Vomiting	10	10 (1.4)	7	6 (0.8)
Diarrhea	9	9 (1.3)	8	8 (1.1)
Hypotension	9	8 (1.1)	8	7 (1.0)
Headache	8	8 (1.1)	7	7 (1.0)
Dizziness	8	7 (1.0)	6	6 (0.8)
Fatigue	6	6 (0.8)	3	3 (0.4)
Pruritus	5	5 (0.7)	2	2 (0.3)
Dyspnea	5	4 (0.6)	1	1 (0.1)
Pain in Extremity	4	4 (0.6)	1	1 (0.1)
Wheezing	4	4 (0.6)	1	1 (0.1)
Cardiac Failure Congestive	4	4 (0.6)	0	0
Hypoglycemia	4	4 (0.6)	0	0
Hypertension	3	3 (0.4)	4	4 (0.6)
Asthenia	1	1 (0.1)	4	4 (0.6)

a. Subjects may be counted in more than one AE category and in both the ferumoxytol and placebo groups depending on the timing of the AE relative to the treatment sequence. Adverse events were only assigned to one treatment.

b. Treatment-emergent AEs were defined as AEs that occurred after receipt of study medication.

Sponsor's table in 62,745-8 study report

7.4.2 Laboratory Findings

Laboratory parameters for hematology, clinical chemistry, and iron panel tests were evaluated for the seven studies conducted in subjects with CKD and four studies conducted in non-CKD subjects.

Hematology

Summary of Laboratory Values Over Time

Hematology values at Baseline, Day 21 and Day 35 are summarized for CKD subjects and presented by treatment exposure in the following table.

Mean WBC counts were within the normal range at Baseline for all treatment exposure groups and remained within normal limits over the course of the study with small variability.

Mean platelet counts were within the normal range at Baseline for all treatment exposure groups. Mean changes from Baseline for ferumoxytol first course were -14.20 and -18.79 x 10³/μL, at Day 21 and 35, respectively. For ferumoxytol second course, mean changes from Baseline were -11.03 and 0.50 x 10³/μL on Day 21 and 35, respectively. In subjects receiving oral iron, mean change from Baseline was -5.02 and -9.30 x 10³/μL at Day 21 and Day 35, respectively.

Summary of Hematology Laboratory Values by Treatment Exposure at Baseline, Day 21, and Day 35 - CKD Subjects (Safety Population)

Hematology Parameter (unit)	Ferumoxytol First Course N=1562		Ferumoxytol Second Course N=69		Oral Iron 200 mg/day N=290	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
Hgb (g/dL)						
Day -10	663	10.25±0.88		-*	280	10.34±0.83
Day -5	1399	10.79±1.08	44*	10.35±1.10	280	10.31±0.82
Day 21	777	11.07±1.19	64	10.87±1.03	255	10.71±1.09
Day 35	787	11.31±1.29	65	11.03±1.08	273	10.81±1.22
Hct (%)						
Day -10	655	33.19±2.95		-*	276	33.07±2.72
Day -5	1376	34.85±3.48	44*	33.16±3.47	274	33.14±2.65
Day 21	765	35.48±4.03	63	34.37±3.17	253	34.15±3.61
Day 35	777	36.15±4.36	62	34.71±3.15	271	34.51±4.01
WBC (K/μL)						
Day -10	652	6.76±2.30		-*	275	6.51±2.03

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Day -5	1372	6.77±2.13	44*	6.32±1.92	273	6.58±2.09
Day 21	764	6.64±2.09	63	6.30±1.99	253	6.51±2.14
Day 35	774	6.73±2.19	61	6.82±2.10	271	6.53±2.33
Platelet Count (K/μL)						
Day -10	642	249.18±97.39		.*	271	241.21±86.44
Day -5	1336	238.46±83.38	42*	235.00±137.23	270	244.90±87.72
Day 21	749	229.33±80.15	62	218.31±95.18	250	235.72±81.14
Day 35	761	224.96±76.07	62	223.95±104.54	265	232.42±77.52

*Subjects readmitted for the second course within 8 days of Day 35 first course used their Day 35 laboratory values for their Readmission Baseline. Subjects readmitted more than 8 days after Day 35 had laboratory values at Day -5R, which was used as their Readmission Baseline.

Note: Baseline was defined as the last non-missing value prior to dosing; not all protocols required subjects to have data at each timepoint.

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

Abbreviations: Hct=hematocrit; Hgb=hemoglobin; K=thousand; WBC=white blood cells.

Sponsor's table in summary of clinical safety

Clinically Significant Abnormal Laboratory Results

The determination of clinical significance was subjective, as deemed by the Investigator at each site. For protocols 62745-5, 62745-6, 62745-7, and 62745-8, investigators classified lab results outside of the normal range as clinically significant or not. For protocols 62745-2, 62745-3, and 62745-4, investigators classified changes from Baseline as clinically significant or not.

Percentage of Clinically Significant Laboratory Values

For WBC and platelet count, fewer than 2% of values for any treatment group or timepoint were considered clinically significant.

Percentage of Grade 2 or Higher CTCAE Laboratory Values

For WBC and platelet counts fewer than 2% of subjects in any treatment group had CTCAE Grade 2 or higher at Days 21 or 35.

Clinical Chemistry

Summary of Laboratory Values Over Time

Clinical chemistry values at Baseline, Day 21 and Day 35 are summarized for CKD subjects and presented by treatment exposure in the following table.

Mean BUN and creatinine values were elevated in a manner consistent with CKD at Baseline. Mean changes from Baseline were variable and similar for all treatment exposure groups. Mean changes in serum sodium, potassium, chloride, calcium, and phosphorus were likewise variable and not clinically meaningful.

Mean AST and ALT were within the normal range at Baseline for all treatment exposure groups. At Day 35, mean AST increased by 1.21 U/L with the ferumoxytol first course, decreased by

1.29 U/L with the second course (to a value similar to the first course Baseline), and decreased by 0.43 U/L with oral iron. At Day 7, mean AST change from Baseline in placebo subjects was a decrease of 0.82 U/L. At Day 35, mean ALT increased 2.31 U/L with the ferumoxytol first course, 1.08 U/L with the second course, and decreased 0.07 U/L with oral iron. At Day 7, mean ALT change from Baseline in placebo subjects was a decrease of 0.14 U/L. Mean serum alkaline phosphatase, bilirubin, GGT and total protein were within the normal range at Baseline in all treatment exposure groups and mean changes from Baseline were small and variable and not clinically meaningful.

**Summary of Clinical Chemistry Laboratory Values by Treatment Exposure
at Baseline and Day 35 - CKD Subjects (Safety Population)**

Clinical Chemistry Parameter (unit)	Ferumoxytol First Course N=1562		Ferumoxytol Second Course N=69		Oral Iron 200 mg/day N=290	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
BUN (mg/dL)						
Day -10	36	47.19±21.60		-*	16	50.94±18.67
Day -5	1385	50.56±20.96	43	53.33±30.90	280	49.71±20.16
Day 35	756	51.31±22.49	65	49.97±22.41	263	49.48±20.86
Creatinine (mg/dL)						
Day -10	36	4.99±4.02		-*	16	7.02±4.27
Day -5	1385	4.75±3.48	43	4.44±3.03	280	5.26±3.70
Day 35	756	4.62±3.40	65	4.66±3.33	263	5.19±3.58
Sodium (mmol/L)						
Day -10	35	139.71±2.98		-*	15	140.13±3.42
Day -5	1385	139.37±3.39	43	140.07±3.10	280	139.72±3.08
Day 35	756	139.76±3.18	65	139.51±3.45	263	139.85±3.24
Potassium (mmol/L)						
Day -10	35	4.61±0.67		-*	16	4.60±0.80
Day -5	1383	4.55±0.65	43	4.48±0.67	278	4.51±0.62
Day 35	756	4.56±0.72	64	4.50±0.73	263	4.50±0.71
Chloride (mmol/L)						
Day -10	35	104.51±3.53		-*	16	102.44±5.46
Day -5	1385	103.95±5.70	43	103.74±5.30	280	103.92±5.31
Day 35	756	104.39±5.55	65	103.98±5.96	263	103.57±5.42
Calcium (mg/dL)						
Day -10	35	8.97±0.64		-*	16	8.71±0.52
Day -5	1385	8.90±0.69	43	8.79±0.77	280	8.86±0.64

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Day 35	756	8.94±0.71	65	8.75±0.70	263	8.85±0.74
Phosphorus (mg/dL)						
Day -10	36	4.58±1.31		-*	15	4.61±1.31
Day -5	1385	4.60±1.39	42	4.36±1.19	279	4.66±1.32
Day 35	756	4.53±1.31	65	4.54±1.49	261	4.68±1.51
AST (U/L)						
Day -10	35	18.63±8.54		-*	15	16.67±6.39
Day -5	1377	17.97±8.46	43	19.47±8.72	277	17.16±7.35
Day 35	747	18.94±12.13	65	17.14±7.64	260	16.80±6.86
ALT (U/L)						
Day -10	35	16.94±12.22		-*	14	12.57±3.96
Day -5	1346	15.55±11.47	41	17.17±13.61	272	14.63±8.42
Day 35	738	17.66±15.25	62	17.76±16.99	251	14.61±7.99
Alkaline Phosphatase (U/L)						
Day -10	35	109.03±50.58		-*	15	126.87±76.08
Day -5	1385	108.22±60.61	43	115.21±55.73	280	111.35±58.25
Day 35	756	113.33±63.94	65	123.63±67.27	263	110.76±57.27
Total Bilirubin (mg/dL)						
Day -10	34	0.29±0.11		-*	15	0.31±0.14
Day -5	1350	0.33±0.19	43	0.35±0.21	274	0.32±0.18
Day 35	734	0.34±0.19	64	0.34±0.19	260	0.32±0.17
GGT (U/L)						
Day -10	35	50.09±71.57		-*	16	42.50±59.29
Day -5	1383	46.50±71.71	43	73.86±148.27	280	45.96±73.95
Day 35	756	55.84±87.81	65	72.42±124.52	263	44.40±67.57
LDH (U/L)						
Day -10	35	195.14±39.76		-*	15	214.87±45.49
Day -5	1385	206.12±55.69	43	211.95±68.10	280	205.50±53.46
Day 35	756	207.01±58.59	65	205.42±57.92	263	206.56±53.01
Total Protein (g/dL)						
Day -10	35	6.98±0.63		-*	15	7.03±0.46
Day -5	1385	6.86±0.66	43	6.86±0.63	280	6.83±0.62
Day 35	756	6.91±0.63	65	6.69±0.97	263	6.87±0.78

*Subjects readmitted for the second course within 8 days of Day 35 first course used their Day 35 laboratory values for their Readmission Baseline. Subjects who readmitted more than 8 days after Day 35 had laboratory values at Day -5R, which was used as their Readmission Baseline.

Note: Baseline was Day 00 for the First Course and Oral Iron and Day -5R for the Second Course; not all protocols required

subjects to have data at each timepoint.

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

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyl transferase; LDH=lactate dehydrogenase.

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Clinically Significant Abnormal Laboratory Results

The determination of clinical significance was subjective, as deemed by the Investigator at each site. For protocols 62745-5, 62745-6, 62745-7, and 62745-8, investigators classified lab results outside of the normal range as clinically significant or not. For protocols 62745-2, 62745-3, and 62745-4, investigators classified changes from Baseline as clinically significant or not.

Percentage of Clinically Significant Laboratory Values

BUN and creatinine values were considered clinically significant in up to 40% of subjects pre-treatment, and the percentage did not substantially change with treatment.

Serum potassium values were considered clinically significant in up to 6% of subjects pre-treatment and the percentage did not increase to a clinically meaningful extent with treatment in any group.

Serum calcium values were considered clinically significant in 3.5% of subjects at Baseline for ferumoxytol first course subjects, and this increased to 4.6% at Day 35. There was no change in the proportion of subjects with clinically significant serum calcium from Baseline of the second course of ferumoxytol to Day 35 of the second course. For oral iron, 3.2% of subjects were considered to have clinically significant serum calcium values at Baseline with no change in percentage at Day 35 (3.0%).

AST, ALT, alkaline phosphatase, bilirubin, LDH, and total protein values were considered clinically significant in a small proportion (less than 3%) of subjects in any treatment exposure group with the following exceptions: alkaline phosphatase (7.7% of subjects) and GGT (9.2% of subjects) at Day 35 of the second ferumoxytol course.

Percentage of Grade 2 or Higher CTCAE Laboratory Values

The majority of these subjects with CKD had serum creatinine meeting CTCAE Grade 2 or greater criteria.

For serum potassium, 9.4% (ferumoxytol first course), 7.8% (ferumoxytol second course) and 7.6% (oral iron) of subjects met criteria at Day 35. For serum calcium, 7.8% (ferumoxytol first course), 10.8% (ferumoxytol second course) and 9.5% (oral iron) of subjects met criteria at Day 35. For serum phosphorus, 2.1% (ferumoxytol first course), 4.6% (ferumoxytol second course) and 5.4% (oral iron) of subjects met criteria at Day 35.

At Day 35, there were no meaningful differences between ferumoxytol first course and oral iron in incidences of CTCAE Grade 2 or higher values for AST (0.3% vs. 0%), ALT (0.3% vs. 0%), alkaline phosphatase (1.9% vs. 1.1%), or bilirubin (0.1% vs. 0.4%). There was a slightly higher

incidence of Grade 2 or higher GGT values in subjects treated with a first course of ferumoxytol (7.9%) and second course (13.8%) compared with subjects treated with oral iron (5.3%). There were no clinically meaningful increases in incidences of Grade 2 or higher in other liver function parameters following a second course of ferumoxytol.

Serum Phosphate

Serum phosphorus levels were obtained at baseline and at least one time following dosing in all ferumoxytol clinical studies. In the active-controlled Phase 3 trials (62,745-5, 62,745-6 and 62,745-7), serum phosphorus levels were obtained at baseline and Day 35, and in the placebo controlled cross-over trial (62,745-8), levels were obtained at baseline, Day 7 and Day 14. In Phase 1 and Phase 2 trials, serum phosphorus levels were obtained at baseline and either weekly or at the Day 7, 14 and/or 28 post-dose). Details of the schedule of serum phosphate evaluations by study and by visit are provided in the table below.

Summary of Evaluation Visits for Serum Phosphorus by Study

Protocol No	Study Population	Treatment Group	Pre Dose		Post Dose							
			Baseline	8h	Day 1	Seq Dialysis	Day 2	Day 3	Day 7 Wk 1	Day 14 Wk 2	Day 28 Wk 4	Day 35 Wk 5
7228-01	Healthy subjects	Ferumoxytol	X	X	X		X	X	X			
		Placebo										
62,745-9		Ferumoxytol	X						X			
		Placebo										
62,745-2	CKD subjects (stage 5D on HD)	1x125	X			X				X	X	
62,745-3	CKD subjects (stage 5D on HD)	Ferumoxytol	X						X		X	
	Oral iron	X										
62,745-4	CKD subjects (stages 1-5 and 5D on PD)	Ferumoxytol	X							X		
62,745-5	CKD subjects (stage 5D on HD)	Ferumoxytol	X									X
	Oral iron	X										

mg/dL				
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 21 Visit	14	1	4	0
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 28 Visit	26	0	6	0
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 35 Visit	756	65	261	0
phosphorus <2 mg/dL	8 (1.1%)	3 (4.6%)	4 (1.5%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)

Sponsor's table in Amendment 0007 submitted on June 23, 2008

At Day 7 visit, 6 (0.7%) subjects in the ferumoxytol group and 2 (0.3%) subjects in the placebo group had serum phosphate <2 mg/dL; 1 subject each in ferumoxytol and placebo group had serum phosphate <1 mg/dL. No phosphate data were available for oral iron group at Day 7 visit.

At Day 35 visit, 8 (1.1%) subjects in the ferumoxytol group and 4 (1.5%) subjects in the oral iron group had serum phosphate <2 mg/dL; 1 subject in the oral iron group had serum phosphate <1 mg/dL.

The following tables show the incidence of low serum phosphorus by treatment group by visit in CKD subjects. All subjects described above who had low serum phosphate were CKD patients.

Summary of Serum Phosphate <2 mg/dL and <1 mg/dL - by Treatment Group and Visit - CKD Subjects

	Ferumoxytol First Course (N=1562)	Ferumoxytol Second Courses (N=69)	Oral Iron (N=290)	Placebo (N=711)
Visit	Subjects N (%)	Subjects N (%)	Subjects N (%)	Subjects N (%)
Day -10 Visit	36	0	15	0
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day -5 Visit	1385	42	279	698
phosphorus <2 mg/dL	3 (0.2%)	0 (0.0%)	0 (0.0%)	2 (0.5%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 00 Visit	45	0	9	0
phosphorus <2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

mg/dL				
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 7 Visit	719	0	0	695
phosphorus <2 mg/dL	6 (0.8%)	0 (0.0%)	0 (0.0%)	2 (0.3%)
phosphorus <1 mg/dL	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Day 14 Visit	56	0	0	2
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 21 Visit	14	1	4	0
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 28 Visit	26	0	6	0
phosphorus <2 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Day 35 Visit	756	65	261	0
phosphorus <2 mg/dL	8 (1.1%)	3 (4.6%)	4 (1.5%)	0 (0.0%)
phosphorus <1 mg/dL	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)

Sponsor's table in Amendment 0007 submitted on June 23, 2008

The following table summarizes the incidence of hypophosphatemia by treatment group in all clinical studies. The incidence of any post-dose phosphorus 1.0 to <2.0 mg/dL was 0.9% with ferumoxytol (14 subjects during the first course of therapy, 3 during the second course of therapy), 1.4% with oral iron and 0.3% with placebo. All of the subjects with serum phosphorus <2.0 mg/dL had CKD, and all but one were on hemodialysis. Only one subject in each treatment group had a serum phosphorus <1.0 mg/dL; the incidence was 0.1% with ferumoxytol, 0.3% with oral iron and 0.1% with placebo; all of these subjects were on hemodialysis.

Among the 18 ferumoxytol-treated subjects who had serum phosphorus <2.0 mg/dL during the study, three had essentially no change from Baseline (decrease in serum phosphorus from baseline of 2.0 to 1.9 mg/dL, 1.8 to 1.8 mg/dL and from 1.5 to 1.6 mg/dL), and two subjects had a slight further decline following ferumoxytol after a more significant decline following placebo (3.0 to 2.0 mg/dL following placebo then had a slight further decline to 1.8 mg/dL following ferumoxytol) and oral iron (from 3.8 to 1.8 mg/dL with oral iron with a further decline to 1.6 mg/dL following ferumoxytol).

Summary of subjects with at least one post-baseline Phosphorus <2.0 mg/dL by Treatment Group – All subjects (CKD and non-CKD)

Preferred Term	Ferumoxytol (N=1795*)	Oral Iron (N=290)	Placebo (N=775)
	N (%)	N (%)	N (%)
Minimum phosphorus <2 and ≥1 mg/dL	17 (0.9)	4 (1.4)	2 (0.3)
Minimum phosphorus <1 mg/dL	1 (0.1)	1 (0.3)	1 (0.1)

*Includes 1726 first course and 69 second course ferumoxytol subjects
 Sponsor's table in Amendment 0007 submitted on June 23, 2008

In a cross-over study (62,745-8), nine subjects (1.2%) had low serum phosphorus levels. The following table shows the summary of subjects with serum phosphorus <2 mg/dL at Baseline, Day 7 prior to cross-over dose and at Day 14; the subjects with serum phosphorus <2 mg/dL at Day 7 in the ferumoxytol-treated group in the First Treatment Period are the same subjects listed under the Day 7 placebo-treated group in the Second Treatment Period after the cross-over, and vice versa. There were 10 instances in nine subjects of serum phosphorus <2 mg/dL in the cross-over safety study, 7 subjects following ferumoxytol and 3 subjects following placebo. Two of the 7 ferumoxytol-treated subjects had Baseline serum phosphorus <2 mg/dL, which did not decrease further on study. Baseline serum phosphorus among the other subjects ranged from 2.8 to 5.2 mg/dL. Only two subjects (0.3%) had serum phosphorus <1 mg/dL, one following ferumoxytol and one following placebo treatment.

Summary of Phosphorus <2 mg/dL in Study 62745-8, by Treatment Group and Visit -CKD Subjects

	Day 0	Day 7	Day 14
	N (%)	N (%)	N (%)
First Treatment Period			
Ferumoxytol (N=357)	2 (0.6)	4 (1.1)	---
Placebo (N=360)	0 (0.0)	1 (0.3)	---
Second Treatment Period (Cross-over)			
Ferumoxytol (N=354)	---	1 (0.3)	3 (0.8)
Placebo (N=355)	---	4 (1.1)	2 (0.6)

Sponsor's table in Amendment 0007 submitted on June 23, 2008

Iron Panel

Summary of Laboratory Values Over Time

Iron panel values at Baseline, Day 21 and Day 35 are summarized for the integrated analysis (all protocols) for CKD subjects and presented by treatment exposure in following table.

Mean serum ferritin increased with first and second ferumoxytol courses and decreased with oral iron. Mean transferrin saturation (TSAT) and serum iron concentrations increased with ferumoxytol more than with oral iron. Mean total iron binding capacity (TIBC) was decreased with ferumoxytol more than with oral iron.

**Summary of Iron Panel Values by Treatment Exposure at Baseline, Day 21,
 and Day 35 - CKD Subjects (Safety Population)**

Iron Panel (unit)	Ferumoxytol First Course N=1562		Ferumoxytol Second Course N=69		Oral Iron 200 mg/day N=290	
	n	Mean±SD	n	Mean±SD	n	Mean±SD
Serum Ferritin (ng/mL)						
Day -10	662	203.85±174.69		-*	279	249.34±194.19
Day -5	1404	199.43±163.80	44	299.29±167.14	280	234.55±181.76
Day 21	784	681.53±337.11	64	731.50±306.87	258	233.06±178.67
Day 35	796	543.77±313.32	65	600.97±301.07	272	220.37±174.53
TSAT (%)						
Day -10	663	12.93±8.06		-*	280	13.15±7.42
Day -5	1400	13.87±8.21	44	14.66±6.10	279	12.80±6.72
Day 21	784	22.76±12.69	65	25.60±17.89	256	15.30±9.94
Day 35	792	21.34±11.18	65	20.08±10.11	272	14.06±8.62
Serum iron (µg/dL)						
Day -10	656	47.13±22.57		-*	275	46.72±21.09
Day -5	1392	50.70±27.46	44	50.82±16.10	277	45.24±19.37
Day 21	783	67.93±33.05	65	68.91±30.60	252	52.92±27.45
Day 35	792	64.48±29.94	65	58.45±23.86	267	49.24±23.46
TIBC (µg/dL)						
Day -10	663	405.77±132.87		-*	280	389.48±126.28
Day -5	1400	403.43±130.60	44	373.48±102.02	280	385.00±125.84
Day 21	778	322.79±100.96	65	313.72±116.19	255	369.57±119.98
Day 35	788	322.83±99.19	65	319.78±108.00	270	378.63±116.82
Reticulocyte Count (%)						
Day -10	654	1.85±0.83		-*	276	1.89±0.93
Day -5	1376	1.74±0.83	44	2.00±0.92	274	1.87±0.85
Day 21	764	2.03±0.94	63	2.06±1.13	253	1.83±0.90

Day 35	776	1.82±0.92	62	2.11±0.93	271	1.73±0.78
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*Subjects readmitted for the second course within 8 days of Day 35 first course used their Day 35 laboratory values for their Readmission Baseline. Subjects who readmitted more than 8 days after Day 35 had laboratory values at Day -5R, which was used as their Readmission Baseline.

Note: Baseline was Day 00 for the First Course and Oral Iron and Day -5R for the Second Course; not all protocols required subjects to have data at each timepoint.

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

Abbreviations: TIBC=total iron binding capacity; TSAT=transferrin saturation.

Sponsor's table in summary of clinical safety

Clinically Significant Abnormal Laboratory Results

Percentage of Clinically Significant Laboratory Values

Serum ferritin was judged clinically significant at Day 21 (20.6%) and Day 35 (17.7%) following a first course of ferumoxytol, at Day 21 (26.2%) and Day 35 (16.9%) following a second course of ferumoxytol, and at Day 21 (6.9%) and Day 35 (6.8%) following oral iron treatment. TSAT and serum iron were judged clinically significant in 14 to 40% of subjects at various timepoints for all treatment exposure groups. TIBC and reticulocyte counts were judged clinically significant in less than 20% of subjects across treatment exposure groups.

Ferritin ≥800 ng/mL and/or TSAT ≥50%

The following table summarizes the subjects with at least one post treatment ferritin ≥800ng/mL and/or TSAT ≥50% by treatment in all subjects.

Summary of subjects with at least one post-baseline Ferritin ≥800 ng/mL, TSAT ≥50% or both Ferritin ≥800 ng/mL and TSAT ≥50% by treatment – All subjects (CKD and non-CKD)

	Ferumoxytol First Course (N=1726)	Ferumoxytol Second Courses (N=69)	Oral Iron (N=290)	Placebo (N=775)
	Subjects (N %)	Subjects (N %)	Subjects (N %)	Subjects (N %)
Maximum ferritin ≥800 ng/mL	448 (26.0)	28 (40.6)	4 (1.4)	71 (9.2)
Maximum TSAT ≥50%	169 (9.8)	5 (7.2)	4 (1.4)	23 (3.0)
Maximum ferritin ≥800 ng/mL and TSAT ≥50%	55 (3.2)	3 (4.3)	0	7 (0.9)

Sponsor's table in Amendment 0007 submitted on June 23, 2008

The overall incidence of any post-dose ferritin ≥800 ng/mL across all studies was 26.0% with ferumoxytol first course (N=1726); 41% with ferumoxytol second course (N=69); 1.4% with oral iron (N=290); and 9% with placebo (N=775).

The overall incidence of any post dose TSAT ≥50% was 10% with ferumoxytol first course; 7% with ferumoxytol second course; 1% with oral iron; and 3% with placebo.

The incidence of both ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ following treatment was 3% with ferumoxytol first course; 4% with ferumoxytol second course; 0% with oral iron; and 1% with placebo. The mean baseline ferritin among subjects who had post-treatment ferritin ≥ 800 ng/mL was 425 ng/mL (N=551), and ranged from 7 to 2778 ng/mL; 172 subjects had ferritin ≥ 500 ng/mL at baseline. The mean baseline TSAT among subjects who had post-treatment TSAT $\geq 50\%$ ng/mL was 34.5% (N=201), and ranged from 3% to 105%; 91 subjects had TSAT $\geq 25\%$ at baseline.

The following table shows the incidence of subjects (number of subjects and percent) with at least one postdose ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$ or both ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ in all study subjects in the safety database, who received ferumoxytol as 2x510 mg (N=750), 2 courses of 2 x 510 mg (4x510 mg; N=57), or a single 510 mg dose (1x510mg; N=708). All but 58 of the subjects who received these doses had chronic kidney disease (CKD); these 58 subjects were healthy volunteers who received 2x510 mg ferumoxytol within 24 hours in the thorough QTc study (62,745-9). The incidence of any post-dose ferritin ≥ 800 ng/mL was 35% with ferumoxytol first course (2x510mg); 42% with ferumoxytol second course (4x510mg); and 19% with single dose ferumoxytol (1x510mg). The overall incidence of any post dose TSAT $\geq 50\%$ was 11% with ferumoxytol first course (2x510mg); 7% with ferumoxytol second course (4x510mg); and 5% with single dose ferumoxytol (1x510mg). The incidence of both ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ following treatment was 5% with ferumoxytol first course (2x510mg); 5% with ferumoxytol second course (4x510mg); and 2% with single dose ferumoxytol (1x510mg).

**Summary of subjects with at least one post-baseline Ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$ or both Ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ by ferumoxytol dose group
 – All subjects (CKD and non-CKD)**

	Ferumoxytol 2x510 mg* (N=750)	Ferumoxytol 4x510 mg (N=57)	Ferumoxytol 1x510 mg (N=708)
	Subjects (N %)	Subjects (N %)	Subjects (N %)
Maximum ferritin ≥ 800 ng/mL	263 (35.1)	24 (42.1)	135 (19.1)
Maximum TSAT $\geq 50\%$	85 (11.3)	4 (7.0)	33 (4.7)
Maximum ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$	37 (4.9)	3 (5.3)	11 (1.6)

*This includes 58 healthy volunteers who received 2x510 mg ferumoxytol in the thorough QTc study (62,745-9) Sponsor's table in Amendment 0007 submitted on June 23, 2008

The following table shows the incidence of subjects (number of subjects and percent) with at least one postdose ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$ or both ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ in CKD patients (excluding 58 healthy volunteers from the table above). In CKD patients who received ferumoxytol first course (2x510mg), the incidence of any post-dose ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$, and both ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ was 35%, 11% and 3.3%, respectively.

Summary of subjects with at least one post-baseline Ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$ or both Ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ by ferumoxytol dose group in CKD patients

	Ferumoxytol 2x510 mg (N=692)	Ferumoxytol 4x510 mg (N=57)	Ferumoxytol 1x510 mg (N=708)
	Subjects (N %)	Subjects (N %)	Subjects (N %)
Maximum ferritin ≥ 800 ng/mL	246 (35.5)	24 (42.1)	135 (19.1)
Maximum TSAT $\geq 50\%$	38 (5.5)	4 (7.0)	33 (4.7)
Maximum ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$	23 (3.3)	3 (5.3)	11 (1.6)

Sponsor's table in Amendment 0007 submitted on June 23, 2008

Serum ferritin levels ≥ 800 ng/mL and/or TSAT $\geq 50\%$ following ferumoxytol administration were seen more often among subjects with significantly elevated levels of these indices at baseline. The mean (SD) serum ferritin at Baseline among CKD subjects who had at least one elevated serum ferritin ≥ 800 ng/mL following ferumoxytol doses of 1x510 mg, 2x510 mg and 4x510 mg was 357 ng/mL, 304 ng/mL and 487 ng/mL, respectively. In contrast, the mean (SD) Baseline ferritin for all CKD subjects in these dose groups was 208 ng/mL, 190 ng/mL and 291 ng/mL, respectively. The mean (SD) TSAT at baseline among CKD subjects who had at least one elevated serum TSAT $\geq 50\%$ following ferumoxytol doses of 1x510 mg, 2x510 mg and 4x510 mg was 28.1%, 18.4% and 20.5%, respectively. In contrast, the mean (SD) Baseline TSAT in all CKD subjects in these dose groups was 15.5%, 12.2% and 14.3%, respectively.

7.4.3 Vital Signs

For subjects with CKD receiving ferumoxytol, vital signs were obtained within 15 minutes predose and at 5, 10, 20, 30, and 60 minutes after dose administration. In addition, vital signs were obtained on Days -10, -5, 21 and 35 (or early termination). For CKD subjects on dialysis, the 15 minute pre-dose assessments were obtained 60 minutes into dialysis. For subjects receiving oral iron, vital signs were obtained on Days -10, -5, 0 (pre dose), 7, 14, 21 and 35 (or early termination). In addition, for subjects on dialysis receiving oral iron, vital signs were obtained at various times during dialysis.

Mean changes from Baseline in heart rate were small and similar between subjects receiving ferumoxytol (first and second courses), oral iron and placebo. Mean heart rate tended to decrease up to 3 beats per minute during the first hour post-dosing in both ferumoxytol and corresponding placebo subjects in the studies that included early time points post dosing. There were no clinically important differences in heart rate between treatment exposures over time.

The assessment of blood pressure focused on the potential for hypotension in the first hour after intravenous ferumoxytol and on any indication of an increase in blood pressure over time related

to the increase in hemoglobin and hematocrit. Over the first hour after ferumoxytol dosing (first course and second course) on Day 0 and Day 5, mean systolic and diastolic pressures decreased less than 4 mmHg. Blood pressure tended to decrease to a similar degree after oral iron, though the first assessment occurred at one hour post-dose. In subjects on hemodialysis, blood pressures decreased to a greater degree during dialysis which is consistent with observations during dialysis in general and with volume removal during the dialysis procedure.

Ferumoxytol-treated subjects had a higher incidence of SBP changes >30% of Baseline (3.7% in the first course) than subjects treated with oral iron (0) or placebo (1.8%). Subjects treated with a second course of ferumoxytol had a 2.9% incidence of hypertension.

In the ferumoxytol first course of treatment, there were no consistent effects on SBP increases >30% with increasing maximum hemoglobin concentrations; 2.4%, 5.6%, 2.6%, and 4.1% for <11 g/dL, 11 to <12 g/dL, 12 to <13 g/dL, and ≥13 g/dL, respectively. No consistent trends were observed for subjects treated with a second course of ferumoxytol, placebo, or oral iron. Most subjects, and most subjects with increases in SBP >30% of Baseline, had hemoglobin increase rates of <0.5 g/dL/week. No differences in the incidence of SBP increases >30% of Baseline among subjects with hemoglobin rate increases of 0.5 to 1.0 g/dL/week or >1.0 g/dL/week suggested an effect of hemoglobin rate of change on blood pressure in any treatment group.

Vital sign values at Baseline, Day 21 and Day 35 are summarized for the integrated analysis (all protocols) for CKD subjects and presented by treatment exposure in the table below.

**Summary of Vital Signs (Heart Rate and Blood Pressure) by Treatment
 Exposure at Baseline, Day 21, and Day 35 - CKD Subjects
 (Safety Population)**

Vital Sign Parameter (unit)	Ferumoxytol First Course 2 x 510 mg N=1562		Ferumoxytol Second Course 2 x 510 mg N=69		Oral Iron 200 mg/day N=290	
	n*	Mean±SD	n*	Mean±SD	n*	Mean±SD
HR (beats/min)						
Baseline	634	73.23±11.79	61	72.82±10.19	166	72.60±11.06
Day 21	361	75.32±11.23	26	71.35±10.54	262	74.21±11.95
Day 35	382	74.99±11.72	27	69.52±10.83	181	74.66±12.63
SBP (mmHg)						
Baseline	634	138.59±21.56	61	135.25±20.51	166	139.33±22.19
Day 21	361	143.05±24.72	26	142.81±25.39	262	143.03±23.30
Day 35	382	141.86±24.63	27	140.85±23.85	181	144.50±27.06
DBP (mmHg)						
Baseline	634	70.33±11.98	61	67.20±11.63	166	71.82±12.71

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Day 21	361	74.95±14.46	26	75.54±12.32	262	73.08±13.23
Day 35	382	74.80±14.34	27	72.52±12.64	181	74.39±14.99

*Varying subject numbers are due to varying vital signs collection times across protocols.

Note: Baseline was Day 00 (15 minute pre-dose) for the First Course, Day R00 (15 minute pre-dose) for the Second Course, and Day 00 (Not applicable) for Oral Iron. Ferumoxytol subjects also had vital signs collected at 30 minutes pre-dose and 5, 10, 20, 30 and 60 minutes post-dose; oral iron subjects also had vital signs collected at 15 minutes pre-dialysis and 60, 65, 70, 80, 90 and 120 minutes into dialysis.

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.

Abbreviations: DBP=diastolic blood pressure; HR=heart rate; SBP=systolic blood pressure.
 Sponsor's table in summary of clinical safety

7.4.4 Electrocardiograms (ECGs)

A Thorough QTc study (62,745-9) was conducted to evaluate the effect of ferumoxytol on the QTc. Only one phase 1 study (7228-01) had ECG monitoring in addition to the through QTc study. No ECG monitoring was performed in all phase 3 studies.

Summary of Thorough QT Study 62745-9

Study 62,745-9 was a Phase 1, active- and placebo-controlled, randomized, parallel group design study conducted in healthy volunteers, which investigated the effect of ferumoxytol on the QTc. The primary objectives of the study were to define the effect of a supratherapeutic regimen of ferumoxytol consisting of two doses of 510 mg (2 x 510 mg) administered IV within 24 hours on QT interval, QTcI, QTcB, QTcF, and heart rate, and to assess the pharmacokinetics (PK) of 2 x 510 mg ferumoxytol administered within 24 hours. The secondary objectives were to describe the relationship between exposure to ferumoxytol and ECG parameters (QT interval, QTcI, QTcB, QTcF, and heart rate), and to assess the safety and tolerability of 2 x 510 mg ferumoxytol administered within 24 hours. A total of 174 subjects (58 subjects in each treatment group) were enrolled. A parallel group design was utilized to study a supratherapeutic regimen of two 510 mg doses of ferumoxytol in a blinded fashion compared with two doses of placebo. Moxifloxacin was given as a positive control. The overall results are presented in Table 1.

The Through QT study was reviewed by the interdisciplinary QT review team (Joanne Zhang, et al, dated 7/15/08 in the DFS). The review concluded that no significant QT prolongation effect of ferumoxytol 2x510 mg was detected in this study. The upper two-sided 90% CI was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The results are shown below. There was no relationship between ferumoxytol concentrations and $\Delta\Delta\text{QTcF}$.

The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Ferumoxytol and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

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

Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment was 7.72 ms.

QT review team's table by Joanne Zhang, et al, dated 7/15/08 in the DFS

7.4.5 Special Safety Studies

A Through QT study was conducted. See Section 7.4.4 Electrocardiograms for the study results.

7.4.6 Immunogenicity

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

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was limited safety data in doses other than the proposed dosing regimen of 510 mg for 2 doses. No dose dependency was observed for adverse events based on available data.

7.5.2 Time Dependency for Adverse Events

The proposed dosing regimen of ferumoxytol injection is 510 mg for 2 doses. No time dependency was observed for adverse events based on available data.

7.5.3 Drug-Demographic Interactions

No study was specifically conducted to evaluate drug-demographic interactions.

The following are based on subgroup analyses from clinical trials.

Age

In subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were similar across all age subgroups: 35.1% in subjects <50 years; 33.1% in subjects 50 to <65 years; 31.0% in subjects 65 to <75 years; and 32.5% in subjects 75 years and older, and lower than with oral iron (56.1%, 53.0%, 50.0%, and 56.5%, respectively). There were no consistent increases or decreases in incidence rates across age subgroups and AE categories in subjects treated with a first course of ferumoxytol.

Gender

In subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were similar between gender subgroups: 32.1% in males; 33.3% in females. There were no consistent increases or decreases in incidence rates across gender subgroups and AE categories in subjects treated with a first course of ferumoxytol.

Race

In subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were similar across all race subgroups: 35.0% in Caucasian subjects; 29.7% in Black/African American subjects; and 32.6% in subjects of "Other" race. There were no consistent increases or decreases in incidence rates across race subgroups and AE categories in subjects treated with a first course of ferumoxytol.

7.5.4 Drug-Disease Interactions

No studies were specifically conducted to evaluate the interaction of ferumoxytol with co-existing disease factors.

The following are based on subgroup analyses from clinical trials.

Stage of CKD

In subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were similar across the following stages of CKD subgroups: 31.6% in the stage 3 subgroup; 36.1% in the stage 4 subgroup; 38.4% in the stage 5 subgroup; and 31.8% in the stage 5D on hemodialysis subgroup. Smaller numbers of subjects in the stages 1-2 subgroup (22 subjects with 13.6% TEAE incidence rate) and stage 5D on peritoneal dialysis (43 subjects with 18.6% TEAE incidence rate) limited subgroup comparisons.

7.5.5 Drug-Drug Interactions

No studies were conducted to evaluate the interaction of ferumoxytol with other medications.

The following are based on subgroup analyses from clinical trials.

ESA Dose

In subjects treated with a first course of ferumoxytol, there was a trend for increasing overall TEAE incidence rates with increasing average weekly ESA dose: 29.7% of 622 subjects not on ESAs; 41.9% of 370 subjects on <20,000 units/week; 55.5% of 128 subjects on 20,000 to < 40,000 units/week; 64.7% of 17 subjects on \geq 40,000 units/week.

For the TEAE and TESAE overview categories in which there were adequate numbers of subjects available for analysis, weekly ESA dose generally did not appear to impact the safety profile of ferumoxytol relative to oral iron (i.e., the incidence of events was lower in ferumoxytol-treated subjects vs. oral iron-treated subjects).

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

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

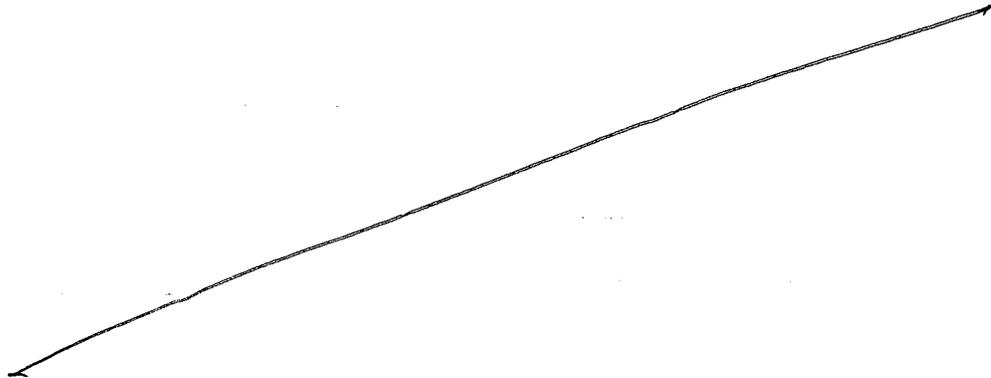
7.6.2 Human Reproduction and Pregnancy Data

No human reproduction and pregnancy data were available.

7.6.3 Pediatrics and Effect on Growth

No pediatric studies were conducted.

The sponsor is proposing two randomized, active-controlled studies in pediatric subjects (ages 2- <18 years) with iron deficiency anemia and chronic kidney disease (CKD) to support dosing and administration of ferumoxytol and assess its safety and effectiveness in the pediatric population. Only study synopses were provided.



A request for a full waiver from conducting a study of ferumoxytol in the neonate (birth to 1 month) and infant (1 month to 2 years) age groups was submitted. The waiver request is justified by the limited projected use of ferumoxytol in patients ≤ 2 years of age, which is based on the extremely low incidence and prevalence of CKD in this population, as well as the uncertain epidemiology of anemia and iron deficiency anemia in this population.

b(4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No formal studies have been conducted to evaluate the abuse potential, withdrawal and rebound serum iron decrease potential for ferumoxytol treatment.

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted on April 28, 2008. This submission contains a summary of ongoing physician-sponsored clinical studies for ferumoxytol and a report on gender analysis of pharmacokinetic (PK) parameters from Study 62,745-9. There are three physician-sponsored clinical studies ongoing evaluating the use of ferumoxytol in medical imaging. No new safety findings have been reported from these studies since the NDA submission in December 2007. No new clinical studies have been initiated by the sponsor between December 2007 and April 28, 2008.

8 Postmarketing Experience

N/A

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

The proposed labeling should be revised as follows.

12 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

9.3 Advisory Committee Meeting

N/A

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

/s/

Min Lu
10/7/2008 10:41:32 AM
MEDICAL OFFICER

Kathy Robie-Suh
10/7/2008 12:46:01 PM
MEDICAL OFFICER
Considerations for labeling are still being evaluated and will
be negotiated with the sponsor.

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22-180
Generic Name	Ferumoxytol
Sponsor	AMAG Pharmaceuticals
Indication	Iron-Deficiency Anemia in Patients with Chronic Kidney Disease
Dosage Form	Injection, Solution
Drug Class	Anti-anemia
Therapeutic Dose	2 x 510 mg given as a rapid IV injection days apart
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	2 x 510 mg given as a rapid IV injection within hours
Application Submission Date	December 18, 2007
Review Classification	Standard
Date Consult Received	March 27, 2008
Clinical Division	DMIHP / HFD 160
PDUFA Date	October 19, 2008

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1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of ferumoxytol 2x510 mg was detected in this study. The upper two-sided 90% CI was below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline.

This was a phase 1 active- and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women. A total of 174 subjects (58 subjects in each treatment group) were enrolled. A parallel group design was utilized to study a suprathreshold regimen of two 510 mg doses of ferumoxytol in a blinded fashion compared with two doses of placebo. Moxifloxacin was given as a positive control. The overall results are presented in Table 1.

3.2 PRECLINICAL INFORMATION

Source: IB-May 22, 2007

“The in vitro effects of ferumoxytol on the hERG (human ether-à-go-go-related gene) potassium channel current were examined. Inhibition of the hERG channel, which is responsible for the rapidly activating, delayed rectifier cardiac potassium current, is the most common cause of cardiac action potential prolongation by non-cardiac drugs. Ferumoxytol increased hERG currents by 17.3% and 9.1% at 100 and 500 µg/mL (n=3) compared with a 1.9% decrease (n=3) with vehicle control. The hERG results at 100 and 500 µg/mL were statistically significant when compared to vehicle control values. Because ferumoxytol did not inhibit hERG currents at the tested concentrations, the IC₅₀ could not be calculated. Under identical conditions, the positive control (60 nM terfenadine) inhibited hERG potassium current by 72.1% (n=2), which confirmed the sensitivity of the test system to demonstrate hERG inhibition.

“A study assessing both cardiovascular and respiratory responses was conducted in anesthetized beagle dogs. Infusion of ferumoxytol at doses up to 200 mg Fe/kg had no effect on cardiovascular function (arterial blood pressure, heart rate, femoral artery blood flow, left ventricular pressure) or respiratory function (respiratory rate, pulmonary flow and volume, blood pO₂, pCO₂, and pH) when compared to the control, mannitol vehicle. In particular, no treatment-related decreases in blood pressure or electrocardiogram (ECG) abnormalities were observed. Increased urinary flow rate was observed after vehicle and ferumoxytol administration at all doses, and was attributed to mannitol. No significant changes were seen in creatinine clearance, suggesting that ferumoxytol had no effect on glomerular filtration rate (GFR).”

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: IB-May 22, 2007

Approximately 1,740 subjects have been exposed to ferumoxytol in the entire clinical program, and approximately 1,509 subjects have been exposed to ferumoxytol in the Phase 3 studies.

Ferumoxytol was well tolerated following IV exposures up to 2 x 510 mg. In the Phase 3 studies in subjects with CKD (62,745-5, 62,745-6, 62,745-7, and 62,745-8, in which approximately 1,509 subjects were exposed to ferumoxytol), the most common adverse events following ferumoxytol administration included nausea, diarrhea, dizziness, headache, and peripheral edema.

There have been no deaths that were considered to be related to ferumoxytol treatment. There were 28 deaths in the clinical program, all of which have occurred in Phase 3 studies, with 16 deaths among the 1,740 subjects exposed to ferumoxytol (0.9%) and 8 deaths among the 296 subjects exposed to oral iron (2.7%). Four deaths occurred in subjects who had signed an informed consent for enrollment but did not receive any test article. All deaths in the clinical program

have been in subjects with CKD, who have a high risk of death due to cardiovascular and other causes.

In the randomized arm of the Phase 3 studies 62,745-6 and 62,745-7, the most common SAEs were congestive cardiac failure and chest pain (two ferumoxytol-treated subjects with each event in each study; one oral iron-treated subject had congestive cardiac failure in Study 62,745-6). In these studies and across the program, none of the events of congestive heart failure were considered to be related to treatment, and all of the subjects who experienced these events had significant pre-existing coronary risk factors, and in most cases, prior episodes of congestive heart failure.

Reviewer's Comment: There are no reports of QT prolongation. Reports of death due to cardiac arrest, ventricular tachycardia were in patients with CAD/CKD. Overall there does not appear to be any increased signal for adverse events related to QT prolongation.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of ferumoxytol's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1.1 Title

A phase I active- and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women.

4.1.2 Protocol Number

CSR-62745-9

4.1.3 Study Dates

22 May 2006 to 04 September 2006

4.1.4 Objectives

Primary Objectives:

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

Secondary Objectives:

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

4.1.5 Study Description

4.1.5.1 Design

This was a phase 1 active- and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women. A parallel group design with 3 arms was utilized to study a suprathreshold regimen of two 510 mg doses of ferumoxytol in a blinded fashion compared with two doses of placebo. Moxifloxacin was used as a positive control.

A total of 174 subjects (58 subjects in each treatment group) were enrolled.

4.1.5.2 Controls

The Sponsor uses both placebo and positive (moxifloxacin) controls.

4.1.5.3 Blinding

Two doses of 510 mg of ferumoxytol were compared in a blinded fashion with two doses of placebo. Moxifloxacin was unblinded.

4.1.6 Treatment Regimen

Treatment groups were as follows:

Treatment Group 1	400 mg moxifloxacin PO on Day 2
Treatment Group 2	510 mg ferumoxytol IV on Days 1 and 2
Treatment Group 3	Placebo (normal saline) IV on Days 1 and 2

4.1.6.1 Sponsor's Justification for Doses

“For a course of anemia treatment, ferumoxytol has been intravenously administered in two doses of 510 mg, typically within one week to replace iron stores. The usual IV dose for the repletion of iron deficiency is 1,000 mg of iron, which is typically administered over the course of a few weeks. The suprathreshold regimen chosen for this study, 1,020 mg ferumoxytol given in two 510 mg doses administered within 24 hours, was considered to be the maximal dose of iron that should be given to a healthy volunteer, who has normal pre-existing iron stores.”

Reviewer's Comments: As there are no major pathways of elimination for iron specifically the sponsor did not study drug-drug interactions. However, the lack of effect of ferumoxytol at 1.5 times the exposure (C_{max} after second dose of 301 µg/mL, C_{max} after first dose 206 µg/mL) in healthy volunteers who do not exhibit iron deficiency makes it difficult to conclude that ferumoxytol increases the QT interval. The number of doses and concentrations are thus limited to the single administration the sponsor provided. There is no way of knowing if other drugs influence the kinetics of ferumoxytol.

4.1.6.2 Instructions with Regard to Meals

Study medication was administered between 0800 hours and 1020 hours after an overnight fast. Timing of meals was controlled with respect to dosing (i.e., all doses administered fasting) to limit diurnal effects and post-prandial effects on the QTc data.

4.1.6.3 ECG and PK Assessments

(See Section 6.2-Table of Study Assessments)

4.1.6.4 Baseline

On Day -1, time-matched baseline ECGs were obtained using H12+ Holter recording device. In the analysis, pre-dose baseline was used.

4.1.7 ECG Collection

ECGs were obtained digitally in all subjects using a Mortara Instrument H-12 ECG continuous 12-lead digital recorder. Continuous 12-lead ECGs were obtained on Day 0 for 24 hours (baseline) and on Day 2 for 24 hours. Subjects were supine at 10 minutes pre and 10 minutes post continuous 12-lead ECG extraction time points.

Five 12-lead ECGs were downloaded from the H-12 flash card (at the central ECG laboratory) about every 10 seconds within 1 minute (providing 5 ECGs for each time point) on Day 0 (time matched baseline) and Day 2 at the following time points: 5, 15, 30, and 45 minutes post-dose and 1, 2, 3, 4, 8, and 23.5 hours post-dose. In addition, on Day 2, three (3) additional ECGs were downloaded at the following time points: within 15 minutes of dosing, 10 minutes post-dose and 12 hours post dose.

ECGs were read by an independent central lab using a high-resolution manual on-screen caliper method with annotations. Manual measurements of the RR, PR, QRS and QT interval durations were performed. The onsets of the QRS complex and of the T wave were identified by trained Cardiac Safety Specialists to define the QT interval. All ECG recordings from a given subject were read by a single reader blinded to time, treatment and subject identifier. Following the measurement and quality control process, all ECGs were reviewed by three independent cardiologists who were blinded to the treatment received by the subject.

Safety ECGs were performed on Days 1 and 2 at pre-dose, 15 minutes, and 1 hour post-dose and on Days 3 and 7.

4.1.8 Sponsor's Results

4.1.8.1 Study Subjects

174 healthy adult males (102) and females (72), 18-45 yrs of age with normal baseline ECG and BMI between 19-30 kg/m². Two subjects did not complete the study per protocol. Subject 170 was not administered the Day 2 ferumoxytol dose due to an adverse event. Subject 278 did not complete the 72, 96 and 120 hour return visits after Day 2 ferumoxytol drug administration and was considered lost-to-follow-up.

4.1.8.2 Statistical Analyses

4.1.8.2.1 Primary Analysis

Continuous ECG monitoring revealed that a suprathreshold regimen of two doses of 510 mg of ferumoxytol within 24 hours did not increase the QT interval or corrected QT interval. The Sponsor's results based on QTcF are provided in the following table.

No differences in the QTc results were observed between men and women.

Table 2: Placebo-Corrected Change from Baseline- Estimates from Mixed Model ANCOVA [1] for QTcF

Time	Moxifloxacin 400 mg		Ferumoxytol 2x510 mg	
	Estimate	Upper Bound[2]	Estimate	Upper Bound[2]
5 min	2.9	6.4	-1.1	2.4
15 min	1.6	5.0	-1.0	2.5
30 min	4.8	8.2	-0.5	3.0
45 min	8.5	12.0	-1.0	2.5
1 hour	9.0	12.5	-1.1	2.4
2 hour	10.2	13.6	-0.3	3.2
3 hour	13.2	16.7	-1.1	2.4
4 hour	11.9	15.4	-3.8	-0.3
8 hour	7.7	11.2	-4.4	-0.9
23.5 hour	6.5	10.1	-1.7	1.8
Time Ave.	7.7	9.1	-1.7	-0.3

[1] Mixed Model ANCOVA is used. The model included treatment, gender, time, and a time by treatment interaction

[2] Upper bound = upper one-sided 95% ANOVA model based confidence limit

Source: Table 14.2.3.2

Reviewer's Comments: For assay sensitivity, the lower bound instead of the upper bound should be considered.

4.1.8.2.2 Categorical Analysis

Except for more frequent tachycardic outlier events (7% of subjects for ferumoxytol as compared to 2% and 4% for moxifloxacin and placebo, respectively), there were no outliers in ECG measures (PR, QT, QRS, etc) noted in the ferumoxytol group. Moxifloxacin showed more outliers (≥ 30 ms increase in QTc from Baseline) compared to ferumoxytol and placebo.

4.1.8.3 Safety Analysis

There were no deaths or SAEs. One subject discontinued study treatment due to adverse events but completed all study assessments- a 39 yr old white male experienced head pressure, pruritis and hives soon after the first dose of ferumoxytol which resolved spontaneously.

Six subjects developed mild rashes and pruritus, with two subjects also developing hives (urticaria), within 7 to 30 hours of the Day 1 ferumoxytol dose. Five of the subjects were treated with medication, and the event resolved spontaneously in one subject. One subject who received ferumoxytol 510 mg i.v. experienced syncope. This was reported as unrelated to study drug.

Five percent of ferumoxytol treated subjects showed new T wave changes, a finding which has no known clinical relevance in this setting. No other morphological changes were observed.

4.1.8.4 Clinical Pharmacology

4.1.8.4.1 Pharmacokinetic Analysis

Table 3. Summary of Plasma Ferumoxytol C_{max} and T_{max} Values

Dose Number	Statistic	C _{max} (µg/mL)	t _{max} (hr)
1	n	58	58
	Mean	206	0.32
	SD	41.26	0.72
	%CV	19.99	222.5
	Median	204	0.17
	Geometric Mean	203	0.17
	Min	142	0.08
	Max	314	4.02
2	n	57	57
	Mean	301	0.60
	SD	52.17	1.244
	%CV	17.35	206.9
	Median	293	0.17
	Geometric Mean	297	0.27
	Min	221	0.08
	Max	459	8

Source: Sponsor's Table 8.

4.1.8.4.2 Exposure-Response Analysis

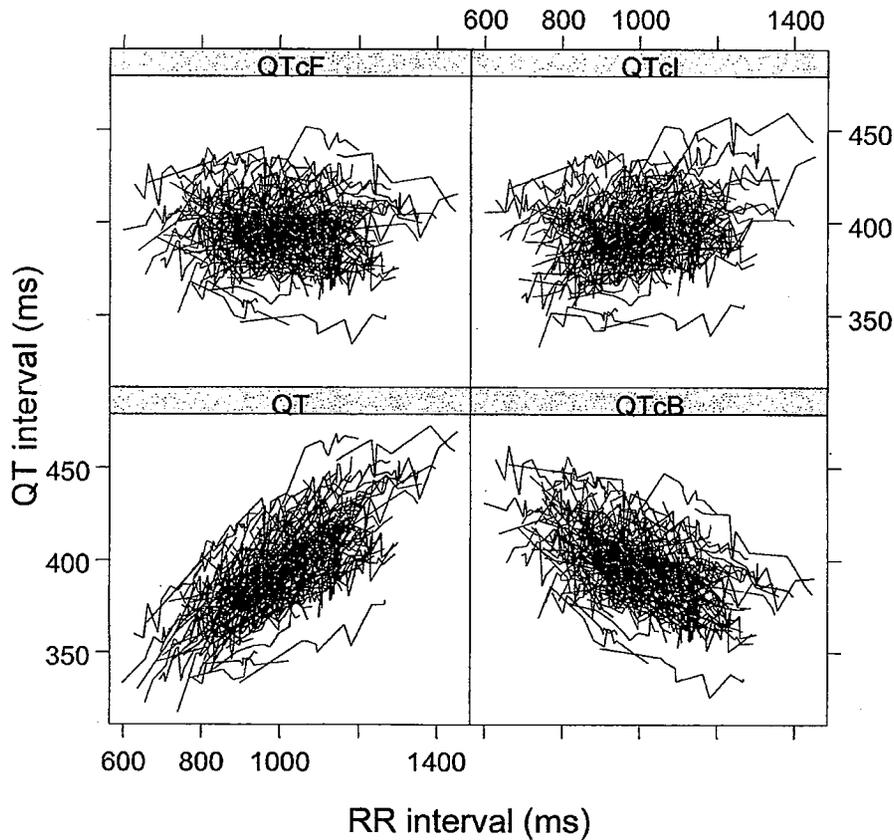
The sponsor did not evaluate any dose or concentration-QTcI or QTcF relationships.

5 REVIEWERS' ASSESSMENT

5.1 HEART RATE CORRECTION ASSESSMENT

The observed QT-RR interval relationship is presented together with the Bazett's (QTcB), Fridericia (QTcF), and the individual (QTcI) correction methods. It appears that QTcF is the most appropriate correction method.

Figure 1: QTcF, QTcI, QT and QTcB vs. RR



5.2 STATISTICAL ASSESSMENTS

The reviewer analyzed the Sponsor's SAS data provided in qtpk.xpt using ANCOVA.

The primary analysis was performed on all time points using analysis of covariance model. The moxifloxacin 400 mg was also compared with placebo using the same model. Only results for QTcF are reported. This reviewer also performed the same analysis for QTcI, and the results are very similar to those for QTcF.

As can be seen from Table 4, all the upper limits of the 90% confidence interval for the mean difference in QTcF change from baseline between ferumoxytol and placebo are below 10 ms, which indicates that this is a negative TQT study using the proposed dose.

For assay sensitivity, the largest lower 90% CI for the baseline adjusted mean difference of 400 mg moxifloxacin and placebo is 9.64 ms at hours 3 after dosing without multiple endpoint adjustment (Table 5). If Bonferroni multiple endpoint correction method is applied (corrected for 10 time points), the largest lower bound of $\Delta\Delta$ QTcF between moxifloxacin and placebo is 7.72 ms.

Since Bonferroni correction is the most conservative approach by assuming the independence of the data, we believe that assay sensitivity of the study has been established.

Table 4: Summary of $\Delta\Delta\text{QTcF}$ analysis: Ferumoxytol 2x510 mg versus Placebo

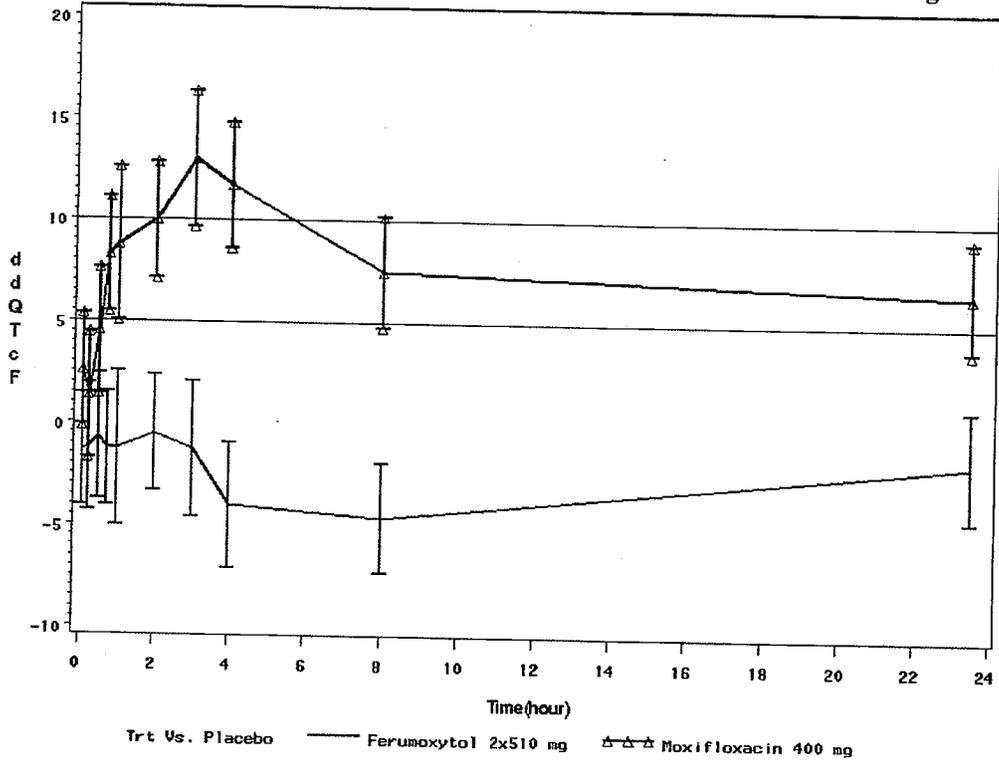
Day	Time	Mean ΔQTcF		Treatment Difference: $\Delta\Delta\text{QTcF}$		
		Ferumoxytol	Placebo	Estimate	S.E.	90% CI
2	5 min	-4.64	-3.29	-1.34	1.67	(-4.10, 1.41)
	15 min	-4.96	-3.77	-1.19	1.88	(-4.30, 1.91)
	30 min	-4.04	-3.36	-0.69	1.88	(-3.80, 2.42)
	45 min	-6.62	-5.38	-1.24	1.71	(-4.08, 1.49)
	1 hour	-5.29	-4.04	-1.26	2.30	(-5.05, 2.54)
	2 hour	-3.10	-2.59	-0.51	1.73	(-3.37, 2.34)
	3 hour	-3.50	-2.21	-1.29	2.01	(-4.62, 2.03)
	4 hour	-7.14	-3.11	-4.03	1.87	(-7.12, -0.94)
	8 hour	-6.09	-1.47	-4.62	1.63	(-7.32, -1.92)
23.5 hour	-1.66	0.16	-1.82	1.64	(-4.54, 0.89)	

Table 5: Summary of $\Delta\Delta\text{QTcF}$ analysis: Moxifloxacin 400 mg versus Placebo

Day	Time	Mean ΔQTcF		Treatment Difference: $\Delta\Delta\text{QTcF}$		
		Moxifloxacin	Placebo	Estimate	S.E.	90% CI
2	5 min	-0.68	-3.29	2.61	1.66	(-0.13, 5.36)
	15 min	-2.42	-3.77	1.35	1.87	(-1.75, 4.44)
	30 min	1.17	-3.36	4.53	1.87	(1.43, 7.63)
	45 min	2.90	-5.38	8.28	1.71	(5.46, 11.11)
	1 hour	4.76	-4.04	8.79	2.29	(5.01, 12.57)
	2 hour	7.37	-2.59	9.96	1.72	(7.11, 12.80)
	3 hour	10.75	-2.21	12.96	2.01	(9.64, 16.29)
	4 hour	8.58	-3.11	11.69	1.87	(8.60, 14.77)
	8 hour	5.98	-1.47	7.46	1.63	(4.75, 10.16)
23.5 hour	6.66	0.16	6.50	1.64	(3.78, 9.21)	

The time course of $\Delta\Delta\text{QTcF}$ for the study drug ferumoxytol 2x510 mg and moxifloxacin is displayed in Figure 2.

Figure 2: $\Delta\Delta$ QTcF for Ferumoxytol 2x510 mg and Moxifloxacin 400 mg



Our categorical analysis agrees with what the sponsor reported. Three subject's QTcF > 450 ms and all the three subjects are in the moxifloxacin group. Their corresponding QTcF values are 452, 451, and 451 ms, respectively.

Six out of 172 subjects (3.5%) had their QTcF change from baseline greater than 30 ms, and all the subjects are in the moxifloxacin group (Table 6).

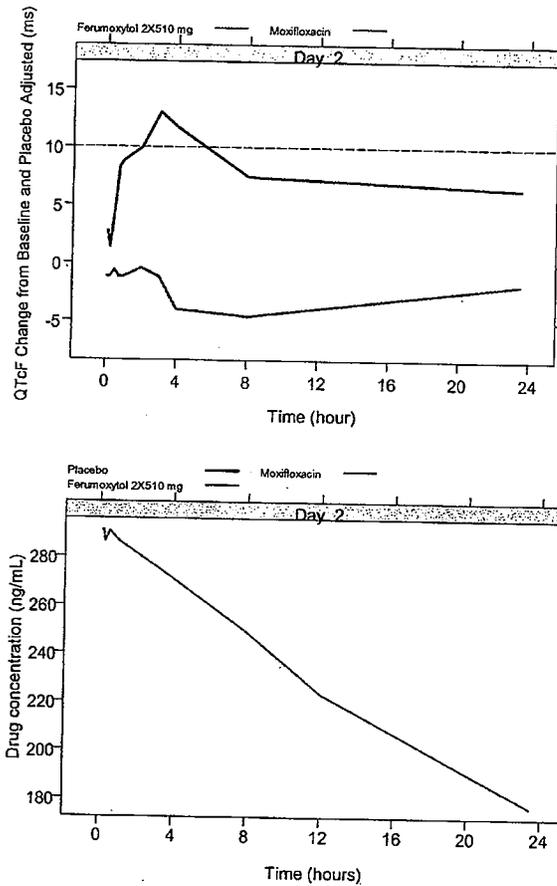
Table 6: QTcF Change from Baseline over 30 ms

ID	Treatment	Change: Δ QTcF (ms)
62745-9-117	Moxifloxacin 400 mg	30.4
62745-9-177	Moxifloxacin 400 mg	58.4
62745-9-239	Moxifloxacin 400 mg	30.6
62745-9-256	Moxifloxacin 400 mg	34.8
62745-9-274	Moxifloxacin 400 mg	42.0
62745-9-276	Moxifloxacin 400 mg	35.0

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 QTcF and Drug Concentration Time Profiles

Figure 3. Mean $\Delta\Delta$ QTcF (top), Ferumoxytol Concentration (bottom) Time Profiles for Ferumoxytol 2X510 mg (blue line) and moxifloxacin (green line)

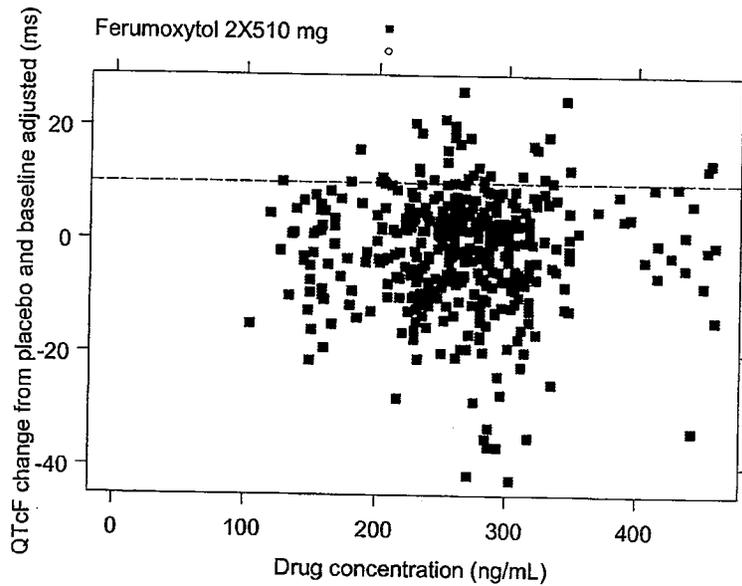


5.3.2 Drug Concentration-QTcF Analysis

The relationship between $\Delta\Delta$ QTcF and Drug concentrations is visualized in Figure 4 with no evident exposure-response relationship.

No exposure response relationship is evident based on the suprathreshold dose regimen.

Figure 4. $\Delta\Delta$ QTcF vs. Ferumoxytol Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

Three of the events identified to be of clinical importance per the ICH E14 guidelines i.e. sudden death, significant ventricular arrhythmias and seizure did not occur in this study. There was one case of syncope, but this was reported as unrelated to study drug and did not result in discontinuation from study.

5.4.2 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. 97% of waveforms were annotated in primary lead (II) with V5 as the back-up lead. According to statistics computed by the ECG warehouse, less than 0.5% of the ECGs had significant QT bias. Overall, ECG acquisition and interpretation in this study appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Parameters	Response
Therapeutic dose	<p><u>Include maximum proposed clinical dosing regimen:</u> Two doses of 510 mg each of ferumoxvtol given as a rapid IV injection (1 mL/sec) ———— days apart.</p> <p>Dose Rationale: Most chronic kidney disease patients require a cumulative repletion course of 1,000 mg of elemental iron to achieve a favorable hemoglobin response and to replenish iron stores.</p> <p>(Ref: Module 1, Section 1.14.1.3: Dosage and Administration)</p>
Maximum tolerated dose	<p><u>Include if studied or NOAEL dose:</u> Two doses of 510 mg of ferumoxvtol given as a rapid IV injection (1 mL/sec) within 24 hours was the maximum dose studied in Study 62,745-9.</p> <p>Maximum Dose Rationale: This dose was recommended by an iron metabolism expert to be the maximal dose of iron that should be given to a healthy volunteer, who was not anemic and has normal pre-existing iron stores.</p> <p>(Ref: Module 5, CSR-62,745-9, Section 9: Investigational Plan)</p>

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Parameters		Response																		
Principal adverse events		<p><u>Include most common adverse events; dose limiting adverse events:</u></p> <p>The most frequently occurring treatment-emergent adverse events ($\geq 5\%$ of subjects) were the expected laboratory increases in serum iron, ferritin, transferrin saturation and iron binding capacity; other events included headache, rash, pruritus and urticaria.</p> <p>All Adverse Events Occurring in $\geq 5\%$ of Ferumoxytol-Treated Subjects</p> <table border="1"> <thead> <tr> <th>Event</th> <th>Ferumoxytol (2x510 mg) N=58 N(%)</th> </tr> </thead> <tbody> <tr> <td>Blood iron increased</td> <td>43 (74.1)</td> </tr> <tr> <td>Serum ferritin increased</td> <td>55 (94.8)</td> </tr> <tr> <td>Transferrin saturation increased</td> <td>41 (70.7)</td> </tr> <tr> <td>Iron binding capacity total increased</td> <td>22 (37.9)</td> </tr> <tr> <td>Headache</td> <td>7 (12.1)</td> </tr> <tr> <td>Rash</td> <td>7 (12.1)</td> </tr> <tr> <td>Pruritus</td> <td>7 (12.1)</td> </tr> <tr> <td>Urticaria</td> <td>3 (5.2)</td> </tr> </tbody> </table> <p>(Ref: Module 5, CSR-62745-9, Table 16)</p>	Event	Ferumoxytol (2x510 mg) N=58 N(%)	Blood iron increased	43 (74.1)	Serum ferritin increased	55 (94.8)	Transferrin saturation increased	41 (70.7)	Iron binding capacity total increased	22 (37.9)	Headache	7 (12.1)	Rash	7 (12.1)	Pruritus	7 (12.1)	Urticaria	3 (5.2)
Event	Ferumoxytol (2x510 mg) N=58 N(%)																			
Blood iron increased	43 (74.1)																			
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Transferrin saturation increased	41 (70.7)																			
Iron binding capacity total increased	22 (37.9)																			
Headache	7 (12.1)																			
Rash	7 (12.1)																			
Pruritus	7 (12.1)																			
Urticaria	3 (5.2)																			
Maximum dose tested	Single Dose	<p><u>Specify dose:</u></p> <p>510 mg dose of ferumoxytol</p> <p>(Ref: Module 5, CSR-62,745-9, Section 9: Investigational Plan)</p>																		
	Multiple Dose	<p><u>Specify dosing interval and duration:</u></p> <p>A course of 1.02 g ferumoxytol given as two doses of 510 mg within 24 hours</p> <p>(Ref: Module 5, CSR-62,745-9, Section 9: Investigational Plan)</p>																		

Parameters		Response
Exposures Achieved at Maximum Tested Dose	Single Dose	<p><u>Mean (%CV) C_{max} and AUC:</u></p> <p>NCA - Observed data (N=58): C_{max} and AUC following single dose of 510 mg of ferumoxytol: Day 1: C_{max}: 206 µg/mL (20) $AUC_{(0-24)}$: 3450 µg·hr/mL (16.5) (Ref: Module 5, CSR-62,745-9, Table 8; Listing 16.2.6.6)</p>
	Multiple Dose	<p><u>Mean (%CV) C_{max} and AUC:</u></p> <p>NCA - Observed data (N=57): C_{max} and AUC following two doses of 510 mg each of ferumoxytol within 24 hours: Day 2: C_{max}: 301 µg/mL (17) $AUC_{0-\infty}$: 15400 µg·hr/mL (24.4)</p> <p>NCA - Population model simulated data: The estimated value for Day 2 C_{max} was 281 µg/mL and $AUC_{0-\infty}$ (across both Day 1 and Day 2 doses) was 14800 µg·hr/mL (Ref: Module 2, Section 2.7.2: Summary of Clinical Pharmacology Studies, Table 5; Module 5, CSR-62,745-9, Table 8; Listing 16.2.6.6)</p>
Range of linear PK		<p><u>Specify dosing regimen:</u></p> <p>With two 510 mg doses given within 24 hours, ferumoxytol pharmacokinetics exhibit nonlinear capacity limited elimination, due to the saturable uptake of ferumoxytol by the reticuloendothelial system.</p> <p>The nonlinear behavior was described by a pharmacokinetic model with $V_{max}=14.3$ mg/hr and $K_m=77.49$ mg/L (Ref: Module 5, CSR-62,745-9, Section 11.4.1.3: Structural Population PK Model, Table 11)</p>
Accumulation at steady state		<p><u>Mean (%CV); specify dosing regimen:</u></p> <p>Accumulation at steady state was not evaluated in Study 62,745-9.</p>

Parameters		Response
Metabolites		<p><u>Include listing of all metabolites and activity:</u> Metabolites were not evaluated in Study 62,745-9.</p> <p>Ferumoxytol is rapidly taken up into cells of the reticuloendothelial system and the iron is released from the polyglucose sorbitol carboxymethylether (PSC) coating. The metabolism of the iron in ferumoxytol parallels that of other iron oxides, via the iron metabolism pathway involving transferrin, ferritin and hemoglobin as evidenced by increases in these parameters post-dosing.</p>
Absorption	Absolute/Relative Bioavailability	<p><u>Mean (%CV):</u> Bioavailability of ferumoxytol is 100% because of its IV administration.</p>
	T _{max}	<p><u>Median (range) for parent:</u> T_{max} following two doses of 510 mg ferumoxytol within 24 hours: Day 1 (N=58): 0.32 hr (0.08 – 4.02) Day 2 (N=57): 0.6 hr (0.08 – 8) (Ref: Module 5: CSR-62,745-9, Table 8)</p> <p><u>Median (range) for metabolites:</u> T_{max} for metabolites was not evaluated in Study 62,745-9.</p>
Distribution	Vd/F or Vd	<p><u>Mean (%CV):</u> NCA - Observed data Estimated V_{ss} following two doses of 510 mg ferumoxytol within 24 hours was 3.16 L (15), which was consistent with plasma volume.</p> <p>NCA - Population model simulated data The estimated volume of distribution was 3.26 L. (Module 5, CSR-62,745-9, Listing: 16.2.6.6; Module 2, Section 2.7.2: Summary of Clinical Pharmacology Studies, Table 5)</p>
	% bound	<p><u>Mean (%CV):</u> Plasma protein binding was not evaluated in Study 62,745-9.</p>

Parameters		Response
Elimination	Route	<p><u>Primary route; percent dose eliminated:</u></p> <p>Elimination of ferumoxytol was not evaluated in Study 62,745-9.</p> <p>The metabolism of the iron in ferumoxytol parallels that of other iron oxides, via the iron metabolism pathway involving transferrin, ferritin, hemosiderin and hemoglobin. Humans maximally conserve iron and there is no physiologic mechanism of iron excretion.</p> <p><u>Other routes:</u></p> <p>Some iron is lost via the gastrointestinal tract and menses (approximately 1 mg per day in men and 2 to 4 mg per day in menstruating women), but this is minimal relative to typical iron stores of 2000 to 4000 mg.</p> <p>(Ref: Module 2, Section 2.5 Clinical Overview)</p>
	Terminal $t_{1/2}$	<p><u>Mean (%CV) for parent:</u></p> <p>NCA – Observed data Terminal $t_{1/2}$ following two doses of 510 mg ferumoxytol within 24 hours was 19 hr (24.3), which is calculated from terminal elimination plasma ferumoxytol concentrations after the second dose.</p> <p>NCA – Population model simulated data The estimated typical value for Day 2 terminal half-life was 15.8 hr.</p> <p><u>Mean (%CV) for metabolites:</u></p> <p>Terminal $t_{1/2}$ for metabolites was not evaluated in Study 62,745-9.</p> <p>(Ref: Module 2, Section 2.7.2: Summary of Clinical Pharmacology Studies, Table 5; Module 5, CSR-62,745-9, Listing: 16.2.6.6)</p>

Parameters		Response
	CL/F or CL	<p><u>Mean (%CV):</u></p> <p>NCA – Observed data Clearance of the intact ferumoxytol dosage form is concentration-dependent. Time-averaged clearance following two doses of 510 mg ferumoxytol within 24 hours was 69.1 mL/hr (20), which is calculated from the total dose of 1,020 mg ferumoxytol divided by the total AUC_{0-∞} from the time of the Day 1 dose to time infinity after the Day 2 dose.</p> <p>Population Model – The nonlinear clearance of ferumoxytol was described with a Michaelis Menton model with V_{max}=14.3 mg/hr and K_m=77.49 mg/L.</p> <p>NCA – Population model simulated data The estimated time-averaged clearance based on model predicted typical values was 69.1 mL/hr. (Ref: Module 2, Section 2.7.2: Summary of Clinical Pharmacology Studies, Table 5; Module 5, CSR-62,745-9, Listing: 16.2.6.6)</p>
Intrinsic Factors	Age	<p><u>Specify mean changes in C_{max} and AUC:</u> Effect of Age was not evaluated in Study 62,745-9. Subgroup analysis of the integrated clinical data showed no significant differences in pharmacodynamic parameters by age. (Ref: Module 5, Integrated Summary of Effectiveness, Section 8)</p>
	Sex	<p><u>Specify mean changes in C_{max} and AUC:</u> Effect of sex was not evaluated in Study 62,745-9. Subgroup analysis of the integrated clinical data showed no significant differences in pharmacodynamic parameters by sex. (Ref: Module 5, Integrated Summary of Effectiveness, Section 8)</p>
	Race	<p><u>Specify mean changes in C_{max} and AUC:</u> Effect of race was not evaluated in Study 62,745-9. Subgroup analysis of the integrated clinical data showed no significant differences in pharmacodynamic parameters by race. (Ref: Module 5, Integrated Summary of Effectiveness, Section 8)</p>

Parameters		Response
	Hepatic & Renal Impairment	<p><u>Specify mean changes in C_{max} and AUC:</u> Study 62,745-9 was conducted in healthy subjects and therefore, hepatic and renal impairment effects could not be evaluated.</p> <p>Pharmacokinetics of two dose levels (125 mg and 250 mg) of ferumoxytol were evaluated in subjects with chronic kidney disease stage 5D on hemo dialysis who were receiving supplemental erythropoietin therapy in Study 62,745-2.</p> <p>(Ref: Module 2, Section 2.7.2: Summary of Clinical Pharmacology Studies, Section 2.2)</p>
Extrinsic Factors	Drug interactions	<p><u>Include listing of studied DDI studies with mean changes in C_{max} and AUC:</u> Drug interactions were not evaluated in Study 62,745-9.</p>
	Food Effects	<p><u>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat):</u> Food effects were not evaluated in Study 62,745-9. Ferumoxytol is administered IV.</p>
Expected High Clinical Exposure Scenario		<p><u>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose:</u></p> <p>The dose chosen for 62,745-9 study, 1,020 mg ferumoxytol given in two 510 mg doses administered within 24 hours was a supratherapeutic dosing regimen. This was considered the highest dose that could be given to a healthy volunteer, who was not anemic and had normal pre-existing iron stores.</p> <p>The recommended treatment course for ferumoxytol consists of two 510 mg doses given _____ days apart; subjects in the 62,745-9 study received their second dose within 1 day (24 hr). For patients who are iron-deficient, high clinical exposures to iron would replete iron stores and not result in iron overload.</p> <p>A 510 mg vial is the largest vial size that would be made available for ferumoxytol, which limits the potential for clinical exposures to higher individual doses.</p>

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NCA: Noncompartmental analysis; V_{ss}: Volume of distribution at steady-state.

Source: Sponsor's Clinical Pharmacology Table.

6.2 TABLE OF STUDY ASSESSMENTS

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

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

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