Amsterdam, 15 September 2022
EMA/CHMP/7593382/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

FERAHEME

International non-proprietary name: ferumoxytol

Procedure No. EMEA/H/C/005974/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Invented name of the medicinal product:	**FERAHEME**
INN (or common name) of the active substance:	Ferumoxytol
Applicant:	Covis Pharma Europe B.V.
Applied Indication(s):	Intravenous treatment of iron deficiency anaemia (IDA): - who have intolerance to oral iron, or have had unsatisfactory response to oral iron, - in adult patients with chronic kidney disease (CKD)
Pharmaco-therapeutic group (ATC Code):	Iron, parenteral preparations (B03AC)
Pharmaceutical form(s) and strength(s):	Solution for infusion, 30mg/mL

List of abbreviations

ACE	angiotensin converting enzyme
AE	adverse event
ARB	angiotensin receptor blocker
AUB	abnormal uterine bleeding
AUC	area under the curve
CKD	chronic kidney disease
CS	clinically significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DHPC	Direct healthcare professional communication
ECG	electrocardiogram
EPO	erythropoietin
ESA	erythropoiesis stimulating agent(s)
FCM	ferric carboxymaltose
Fe	iron
GI	gastrointestinal
HD	haemodialysis
Hct	haematocrit
Hgb	haemoglobin
HSRs	Hypersensitivity reactions
HV(s)	Healthy volunteer(s)
IDA	iron deficiency anaemia

IS	Iron sucrose
IV	intravenous(ly)
K/DOQI	Kidney Disease Outcomes Quality Initiative
MR	magnetic resonance
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
ND (-CKD)	chronic kidney disease not on dialysis
PASS	Post-authorisation safety study
PD	peritoneal dialysis
PK	pharmacokinetic(s)
RBC(s)	red blood cell(s)
SD	standard deviation
t1/2	Half-life
TIBC	total iron binding capacity
TSAT	transferrin saturation

1. CHMP Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Feraheme in the treatment of iron deficiency anaemia (IDA):

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, or
- in adult patients with chronic kidney disease (CKD).

is **not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (see section VI).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

Major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies: Major objections are raised in relation to quality regarding the content of active substance on finished product and potential nitrosamines due to the application of ammonium hydroxide. In addition, amendment of the therapeutic indication wording claimed under 4.1 in the SmPC is requested.

1.1. Questions to be posed to additional experts

N/A

1.2. Inspection issues

1.2.1. GMP inspection(s)

N/A

1.2.2. GCP inspection(s)

According to information from the original MAA of Rienso, there had been FDA inspections in study sites of each of the pivotal CKD studies. The respective information has not been submitted within this procedure. At the time, the FDA inspections were reported to have not revealed any major issues that could have invalidated the study results.

1.3. New active substance status

As ferumoxytol is regarded as known active substance, no NAS is claimed.

2. Executive summary

Ferumoxytol was developed as an intravenous (IV) iron replacement therapy for the treatment of iron deficiency anaemia (IDA) in adults with chronic kidney disease (CKD), and in adults with IDA, e.g. abnormal uterine bleeding (AUB), cancer, gastrointestinal (GI) disorders and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.

The Applicant seeks approval of ferumoxytol for the treatment of iron deficiency anaemia (IDA)

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, or
- in adult patients with chronic kidney disease (CKD).

Regulatory history of the product

Ferumoxytol received a marketing authorisation in the European Union (EU) on 15 June 2012 under the brand name Rienso for the treatment of iron deficiency anaemia (IDA) in patients with chronic kidney disease (CKD). On 5 June 2013 a Type II variation (EMEA/H/C/002215/II/0008) was submitted to EMA to extend indication to adult patients with IDA from any underlying conditions (all-cause IDA patients with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used). During the assessment, a serious safety concern regarding anaphylaxis/hypersensitivity reports emerged, which led to several requests for supplemental clinical information. The MAH submitted a Periodic Safety Update Report dated 28 February 2014 (PSUR procedure EMEA/H/C/2215/01). The assessment of the submitted PSUR led to the conclusion that the use of Rienso was associated with a high rate of hypersensitivity reactions with fatal outcome. This issue was then referred to the PRAC. After discussion and assessment of the PSUR the PRAC concluded by majority decision (EMA/PRAC/404148/2014) that the benefit risk balance for Rienso remained positive; however, further risk minimisation measures and conditions were imposed such as a new contraindication, SmPC amendments, circulation of DHPC, new PASS and RMP amendments.

However, the CHMP concluded that the benefit/risk balance for the extension of indication to patients with all-cause IDA is considered negative until additional confirmative clinical data become available to support the claim of a similar (i.e. non-inferior) safety profile for the all-cause IDA population as compared to iron sucrose (especially regarding the incidence of serious hypersensitivity reactions).

In addition, a number of changes to the then existing product information (PI) were made as a way to mitigate the risk of hypersensitivity reaction i.e. including contraindication for patients with a history of drug allergy, a change in the method of administration (slower infusion over 15 minutes instead of hitherto recommended bolus injection in 17 seconds, which would allow timely recognition of signs and symptoms of hypersensitivity, drug interruption and an appropriate intervention), a warning in the product information that patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and 30 minutes at least after administration to further mitigate the risk of hypersensitivity reactions and a warning that fatal and life-threatening hypersensitivity reactions have been observed post-marketing. A DHCP was circulated to inform prescribers of these changes.

The PRAC requested an adequately powered study to further investigate the risk of hypersensitivity in EU CKD patients comparing ferumoxytol against iron sucrose. In addition, a study to investigate the mechanism of hypersensitivity with ferumoxytol (IgE or non-IgE mediated) was requested by the PRAC. The protocol for this study was never submitted to the EMA, and study was never initiated. Other actions requested by PRAC included an update on a controlled study against iron sucrose ongoing at the time. This study has been completed (CKD-401), however the objective of this study was investigation of comparative long term efficacy and safety in CKD patients on hemodialysis and not hypersensitivity reactions.

The FDA also requested that additional information be provided to better characterise the risk of the adverse event (AE) of anaphylaxis/hypersensitivity in the population. The additional information was supposed to be generated in one or more prospective clinical studies addressing mechanisms to reduce the risk for serious including fatal hypersensitivity reactions. According to the Applicant, the trials were to enrol patients with IDA without CKD. As a result of this recommendation, study IDA 304 was implemented. In a June 2014 during a meeting with the FDA, it was confirmed that this additional study (IDA-304) should only assess the 15-minute diluted IV infusion.

In the European Rienso risk management plan (RMP) dated 2014, there was agreement to participate in a joint PASS with other IV iron MAHs to further characterize the safety concern regarding hypersensitivity

reactions. However, upon MAH's decision, ferumoxytol was withdrawn from the market in Europe in February 2015, and further participation in the PASS did not occur.

In the United States (US) Ferumoxytol was granted marketing approval in June 2009 under the trade name Feraheme for the treatment of IDA in adult patients with CKD and subsequently, was approved in February 2018 also for the treatment of IDA in adult patients who have intolerance to oral iron or have had unsatisfactory response to oral iron with AMAG as MAH. Ferumoxytol is still marketed in the US.

Ferumoxytol was also approved in Canada in December 2011, for the same indication as in the EU. In September 2016, the product was withdrawn from the market.

Current Application:

The applicant has submitted the following data in support of efficacy and safety in the proposed indications:

CKD: The Applicant submitted the initial 11 studies including three pivotal clinical studies comparing a 2 x 510 mg ferumoxytol IV-treatment scheme administered 5 ± 3 days to a 21 day course of oral iron (200 mg of iron/day) in IDA patients with CKD stage 1-5D): studies **FER-CKD-62745-5**, **FER-CKD-62745-6** and **FER-CKD-62745-7**. Two additional clinical trials investigated the IV administration of ferumoxytol 2x510 mg against IV iron sucrose (10x 100 mg or 5x 200 mg in adult patients on HD and not on HD, respectively), i.e. phase 2 study **FER-CKD-201** in non-dialysis dependent (ND) and hemodialysis (HD) subjects and phase 4 study **FER—CKD-401** in HD subjects.

IDA: The clinical efficacy dataset of this marketing authorisation application supporting the second-line IDA indication in adult patients who have is based on the results of two pivotal and two supportive clinical trials investigating the IV administration of ferumoxytol at a dose of 2 × 510mg , i.e. pivotal Phase 3 trials **AMAG-FER-IDA-301** and **AMAG-FER-IDA-302** with supportive trials **AMAG-FER-IDA-303** and **AMAG-FER-IDA-304**.

With the current submission, the Applicant provided a dossier that was not updated as regards the List of Question (LoQ) and responses that were submitted during the original Rienso MAA. It should be noted that the pivotal studies were conducted more than 15 years ago and that the clinical treatment guidelines have evolved over time. Hence, the studies are not fully in line with the current clinical treatment recommendations, in particur from a European perspective.

The following is noted on the current assessment:

- Some Other concerns (OCs) are raised that were also raised (and resolved) previously, as the corresponding responses that were provided by the Applicant in the previous MAA are not included in the dossier.
- Some OCs are raised in light of the change of standard of care and treatment recommendations compared to the situation 15 years ago.
- Some OCs raised in relation to the new data provided that were not part of the previously submitted dossier.

2.1. Problem statement

2.1.1. Disease or condition

Iron is an essential component of the hemoglobin molecule. Anaemia is defined as a haemoglobin concentration below a specified cut-off point; that cut-off point depends on the age, gender, physiological

status, smoking habits and altitude at which the population being assessed lives. WHO defines anaemia in children aged under 5 years and pregnant women as a haemoglobin concentration <110 g/L at sea level, and anaemia in non-pregnant women as a haemoglobin concentration <120 g/L (WHO, 2011)

The most common cause of anemia worldwide is iron deficiency, which results in microcytic and hypochromic red cells on the peripheral smear. Several causes of iron deficiency vary based on age, gender, and socioeconomic status. The patient often will have nonspecific complaints such as fatigue and dyspnea on exertion. Treatment is a reversal of the underlying condition as well as iron supplementation. Iron supplementation is most often oral, but certain cases may require intravenous iron. Patients with iron-deficient anemia have been found to have a longer hospital stay, along with a higher number of adverse events (Warner MJ et al. 2021. Iron Deficiency Anaemia. StatPearls [Internet])

2.1.2. Epidemiology

The World Health Organization estimated worldwide prevalence of anemia to be 42% in children, 29% in non-pregnant women, and 38% in pregnant women in 2011. In 2013, iron deficiency (ID) was identified as the predominant cause of anemia among the 1.93 billion anemic people (27% of the world's population) globally, making iron deficiency anemia (IDA) a major global health issue. The people most at risk are women and children, regardless of socioeconomic status or geography. In 2017, the Global Burden of Diseases Study reported that dietary iron deficiency remains the fourth and twelfth leading cause of years lived with disability in women and men, respectively (WHO 2011; reviewed in Ning et al.; Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019 Dec 6;2019(1):315-322. doi: 10.1182/hematology.2019000034. PMID: 31808874; PMCID: PMC6913441).

2.1.3. Aetiology and pathogenesis

Iron deficiency anaemia (IDA) in CKD patients

Iron deficiency is an important and common cause of anaemia in patients with CKD and anaemia contributes to poor quality of life in these patients. The aetiology of iron deficiency is multi-factorial and can include decreased dietary intake or absorption of iron, iron sequestration due to inflammatory processes, blood loss during dialysis, and increased iron utilisation for red blood cell (RBC) production in response to erythropoiesis stimulating agents (ESA).

Anaemia may occur due to a number of anomalies in the regulation of the RBC lifecycle. In CKD, anaemia is predominantly due to iron deficiency and abnormalities in erythropoietin production. As renal function deteriorates in CKD patients, inadequate production of erythropoietin and/or inadequate bone marrow response to erythropoietin are major causes of anaemia, especially in end-stage renal disease (ESRD).

The correction of iron deficiency anaemia with iron replacement therapy is achieved through an increase in iron-dependent haem production, a component of haemoglobin necessary for red blood cell (RBC) synthesis. The pharmacological basis of iron replacement therapy for iron deficiency anaemia (IDA) is thus the efficient delivery of iron to erythroid precursors for haemoglobin synthesis.

All-Cause IDA

IDA develops for a variety of reasons but the main underlying causes can be classified as the following:

- Blood loss (e.g., AUB, a GI cause such as peptic ulcer, a hiatal hernia, a colon polyp or colorectal cancer), and from regular use of over-the-counter pain relievers, such as aspirin.
- A lack of iron in the diet.
- An inability to absorb iron (e.g., intestinal disorder, such as inflammatory bowel disease-IBD).

- Increased demand (e.g., pregnancy, during childhood development).
- A combination of factors (e.g., dietary insufficiency, malabsorption, chronic blood loss and parasitosis caused by parasitic worms such as hookworms, whipworms or roundworms).
- Chronic Heart Diseases.
- Iron-refractory iron deficiency anaemia (IRIDA). This is an inherited disorder of systemic iron balance in which both absorption and utilisation of iron are impaired

Distinction should be made between states of absolute and functional iron deficiency (ID). In absolute ID state, total body iron stores are reduced, while functional ID is characterized by the presence of apparently adequate iron stores, but with insufficient iron mobilization due to sequestration in the reticulo-endothelial system, blocking participation in erythropoiesis.

2.1.4. Clinical presentation and diagnosis

Anaemia is associated with fatigue, loss of stamina, shortness of breath, weakness, dizziness, pallor, impaired functional capacity, increased hospitalisation and mortality.

Anaemia in CKD is associated with decreased quality of life, increased risk of cardiovascular complications and increased morbidity and mortality. Cardiovascular complications such as left ventricular hypertrophy (LVH), left ventricular dilatation (LVD) and myocardial ischaemia result from adaptive mechanisms to maintain adequate tissue oxygenation (e.g., increased cardiac output) in response to anaemia.

Diagnostic criteria for iron deficiency anaemia vary between published studies, although the serum ferritin is largely regarded as the best noninvasive (and widely available) test. (Donaldson et al. 2019, https://doi.org/10.1177/2042098619854870) in combination with determination of transferrin saturation (TSAT). However, ferritin must be interpreted with caution since serum ferritin levels rise e.g. with ageing or chronic diseases. The diagnosis of iron defficiency becomes more challenging with concomitant inflammatory conditions and in the elderly because ferritin is an acute-phase reactant that increases with age. In these circumstances, low transferrin saturation (TSAT) (<16% or <20% with inflammation) can be used with higher ferritin thresholds (<100 ng/mL) for diagnosis. However, optimal thresholds remain unclear. In heart failure, ferritin<100 mg/L or ferritin <300 ng/mL with TSAT <20% has been recommended for the diagnosis of ID. In patients with chronic kidney disease, the Kidney Disease Improving Global Outcomes guideline recommends considering iron therapy if ferritin is ≤500 ng/mL and TSAT is ≤30%, whereas recent clinical trials in dialysis patients used ferritin <200 ng/mL or TSAT <20% as indications for iron therapy.

European clinical treatment guidelines generally recommend the use of lower thresholds. Distinction should be made between absolute and functional ID states and whether the patient receives concomitant ESA treatment and is on hemodialysis or not (Locatelli et al.; *Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement.* Nephrol Dial Transplant. 2013 Jun;28(6):1346-59. doi: 10.1093/ndt/gft033).

Other biochemical features of ID include low mean cell hemoglobin (hypochromia), mean corpuscular volume (microcytosis), and high red cell distribution width; these changes are slow to occur because of the long lifespan of red blood cells and are not specific for ID. An earlier marker of ID is the reticulated haemoglobin content (CHr), which is decreased (<29 pg) in ID (reticulated-Hb equivalent is provided instead of reticulated-Hb content on certain analyzers and the normal range may vary) or the use percentage of hypochromic red blood cells (% HRC; more than 6%), but only if processing of blood sample is possible within 6 hours. In certain cases, the diagnosis of ID is made only after a successful trial of iron supplementation. Bone marrow biopsy remains the gold standard for the diagnosis of ID but is infrequently pursued.

Regardless of the presence of symptoms, all patients with iron deficiency anemia should be treated with iron replacement therapy. The rationale is that there is risk for further organ damage/ischemia and progression of anemia unless the underlying cause of the deficiency is addressed and adequate iron stores are replenished.

2.1.5. Management

The usual approach in the treatment of iron deficiency anemia is the repletion of iron. Blood transfusion should not be used as treatment for iron deficiency unless the individual has severe anemia with hemodynamic instability.

The correction of iron deficiency anaemia with iron replacement therapy is achieved through an increase in iron-dependent haem production, a component of haemoglobin necessary for red blood cell (RBC) synthesis. The pharmacological basis of iron replacement therapy for iron deficiency anaemia is thus the efficient delivery of iron to erythroid precursors for haemoglobin synthesis.

The choice between oral and IV iron depends on a number of factors including the acuity of the anemia, costs and availability of different iron replacement products, as well as the ability of the patient to tolerate oral iron preparations. Most patients are treated with oral iron, however, up to 70 percent of patients for whom oral iron is prescribed report GI side effects. IV iron replacement provides an advantage over oral iron replacement because oral iron has limited absorption and is associated with GI side effects that may affect patient compliance (Kaltwasser 1991; Nielsen 2005). IV iron is also readily available for red blood cell production (Beshara 2003; Seligman 2004).

Decisions about the preferred route of iron supplementation should take into consideration severity of anaemia and iron deficiency, the response, tolerance and adherence to prior oral iron administration, costs, and ease of obtaining venous access, balanced against the desire to preserve venous access sites. Intravenous (IV) iron preparations currently approved in various countries in the European Union include iron dextran (e.g., CosmoFer), iron sucrose (e.g., Venofer), ferric gluconate (e.g., Ferrlecit), iron isomaltoside (e.g., MonoFer) and ferric carboxymaltose (e.g., Ferinject). All of these products are labeled for use as a second-line therapy in general IDA treatment, when oral iron preparations are ineffective, cannot be used or there is a requirement for rapid replenishment of iron stores. Some IV iron products are specifically approved for the second line treatment in patients with CKD or active IBD (SmPC Venofer, Sweden), however as these products are approved nationally, indications differ across EU countries. Iron sucrose is typically administered at doses of 100 to 200 mg, thus a full therapeutic course requires 5 to 10 injections or infusions, while the full course of ferric carboxymaltose (FCM) can be administered in 1-2 injections/infusions.

The efficacy of IV iron supplementation in the treatment of IDA has been studied in patients with a variety of underlying conditions including CKD, abnormal uterine bleeding (AUB), pregnancy, postpartum anaemia, cancer, and gastrointestinal (GI) disorders including inflammatory bowel disease and GI blood loss; studies have also examined its use for the pre-operative normalization of Hgb (Auerbach 2008; Gasche 1997; Gasche 1999; Gordon 2007; Al-Momen 1996; Schroder 2004). Doses of IV iron used to treat IDA in these studies have ranged from 800 mg to 2500 mg, and have resulted in mean increases in Hgb from baseline of 1.0 g/dL to 3.0 g/dL (Auerbach 2008; Gordon 2007; Van Wyck 2007). Treatment of IDA with IV iron has been shown to reduce the need for blood transfusions in AUB and cancer (Auerbach 2008; Diez-Lobo 2007).

For patients with IDA, several global treatment guidelines recommend a 1.0 g course of treatment (Hedenus 2008; Henry 2006; Gasche 2007). One gram of iron is also estimated to be within 20% of the calculated total iron deficit needed to achieve a Hgb of 11.0 g/dL to 12.0 g/dL for a wide range of body

weights (50 kg to 90 kg), starting from the range of baseline Hgb levels typical of adults with IDA (Ganzoni 1970).

2.2. About the product

Ferumoxytol is an aqueous colloidal suspension of polyglucose sorbitol carboxymethylether (PSC) coated ferric superparamagnetic iron oxide particles that has been developed as an intravenous (IV) iron replacement therapy for the treatment of iron deficiency in patients with CKD and IDA.

Ferumoxytol provides a source of bioactive iron, which is subject to the normal physiological pathways of iron homeostasis - principally involving transferrin, ferritin and haemoglobin (Hgb), and thus rapidly replenishes body iron stores. The PSC coating stabilises the colloidal iron oxide, controls the release of iron, and minimises free iron and immunological reactivity.

The proposed clinical dosing regimen for ferumoxytol is based on the patient's pre-treatment haemoglobin and body weight as detailed in the SmPC. The maximum dose is 1020 mg (2 vials). Each 510 mg dose is administered as an intravenous infusion for at least 15 minutes. For patients receiving two doses, the second 510 mg infusion is to be administered 2 to 8 days later.

The drug should only be administered by healthcare professionals and trained personnel and facilities for the treatment of anaphylactic reactions are a prerequisite for its therapeutic use.

The slow infusion over at least 15 minutes of dilutes ferumoxytol has been proposed following reports of severe and serious hypersensitivity/anaphylactic reactions with fatal outcome, that were associated with previously approved method of administration (undiluted, rapid injection).

Mode of action

The basic mechanism of action is well established for parenteral iron solutions and does not differ from the standard iron solutions for IV-administration. After injection the carbohydrate shell of the complex isolates the bioactive iron oxide core from plasma components until the whole iron-carbohydrate complex is taken up by reticuloendothelial system macrophages of the liver, spleen and bone marrow via phagocytosis. It enters the lysosomes where the trivalent iron is released from the carbohydrate shell. Iron then either enters the intracellular storage iron pool (e.g. ferritin) or is converted into Fe2+ which subsequently is released by divalent metal transporter (DMT1) then by ferroportin and taken up by plasma transferrin after oxidation by ceruloplasmin for transport to erythroid precursor cells for incorporation into haemoglobin.

Pharmacological classification

Pharmacotherapeutic group: Anti-anaemic preparation, iron, parenteral preparation, ATC code: B03AC

2.3. The development programme/compliance with guidance/scientific advice

The active substance was originally developed as a diagnostic contrast agent for magnetic resonance (MR) imaging by virtue of its superparamagnetic properties (using a dosage of ≤ 4mg/kg of Feraheme). The interference with MR-imaging is reflected in a warning in section 4.4 of the SmPC.

Before the initial MAA, the Applicant requested scientific advices from several national agencies.

National scientific advice on the development of the product for the originally intended indication in IDA patients with CKD was received from DE (BfArM, date: 10-30-2008), UK (MHRA, date: 08-08-2008), NL

(MEB, date: 09-23-2008) and SE (MPA, date: 08-27-2008). A Pre-Submission Meeting was held with DE on 05 November 2010.

The consulted agencies (except UK) requested a justification for the use of oral iron as the active comparator treatment especially for CKD-patients on haemodialysis and raised concerns about the lack of an IV iron comparator. DE and NL asked for a literature based comparison and NL suggested to generate supportive preclinical data. In response to the these recommendations a comprehensive literature-based review of the safety and efficacy of IV iron products approved in the EU has been submitted for comparison with the study data for Feraheme, and a head-to-head clinical study comparing the safety and efficacy of Feraheme with IV iron sucrose was designed and started (see below). The applicant did not conduct a preclinical comparative study (iron deficiency rodent model). All consulted agencies requested a justification for the lack of long-term efficacy and safety data. The proposed dose (fixed cumulative dose of ~1 g Fe) was acceptable to all agencies provided that it was adequately justified for all subsets of CKD patients, including pre-dialysis and dialysis patients.

SE in addition asked for a justification for not performing a PK study in patients with hepatic impairment and specified adverse effects of special interest: allergic/anaphylactoid reactions, risk of sensitisation, hypotension, peripheral oedema, infections, iron overload, pigmentation. UK asked for a robust pharmacovigilance plan and risk management plan including medium to long-term follow up due to lack of long-term safety data from clinical studies. NL asked for an accurate definition of patient subgroups with respect to the CKD-status, concomitant ESA-therapy etc., for a statement concerning the comparability of clinical practice in the USA vs. the EU and for more information on the metabolism of the PSC-coating. DE asked for a justification of the protocol amendments of the main clinical studies and a discussion of their impact on the analysis/results.

Prior to re-submitting the MAA, the Applicant requested a scientific advice from EMA (EMA/SA/0000061207, 22 July 2021). Main highlights of the received Advice:

- Suitability of the current clinical studies to support the efficacy and safety of ferumoxytol in the two pursued indications in the future MAA.

In principle, the final assessment of efficacy and safety should be based on thorough analysis of all data during regulatory review within the MAA procedure. However, with regards to efficacy, and based on the high-level information, which was provided, the CHMP concluded that the current clinical data package might suffice to support the marketing authorisation application (MAA) for ferumoxytol.

As to Safety, the CHMP concluded that the provided data is likely sufficient to determine the safety profile of ferumoxide. The proposed RMP could be acceptable. However, the precise wording of education material, SmPC and other details of the RMP will be reviewed and possibly revised during the MAA.

- Agreement with the proposed new paediatric clinical trials to support the registration of Ferumoxytol for the paediatric population.

The CHMP agreed that development in paediatric population should follow PIP agreement governed by EMA/PDCO, including the agreement for waiver for age group from 6 month to <2 years. Other specific comments are provided from scientific perspective regarding proposed paediatric studies, as e.g., suggestion of pooled safety between studies CKD-354 and IDA-352.

2.4. General comments on compliance with GMP, GLP, GCP

GMP:

Compliance to GMP is given, valid manufacturing authorisations for active substance manufacturer and QP-declaration is provided as well as FDA GMP certificate for the finished product manufacturer.

GLP:

The nonclinical development of ferumoxytol was predominantly performed in compliance with good laboratory practice (GLP). All GLP-compliant studies were conducted in accordance with Good Laboratory Practice for Nonclinical Laboratory Studies, Code of US Federal Regulations (21 CFR Part 58) and compliant under OECD GLP principles.

Pharmacodynamic and Pharmacokinetic studies were not conducted under GLP conditions. Safety pharmacology studies were conducted according to GLP with exception of two cardiovascular pilot studies (HHB-156, HHB-152B).

The nonclinical toxicological program consists of 27 toxicity studies, and all except eight studies that were conducted in full compliance with the Good Laboratory Practice (GLP) regulations and in accordance with the International Conference on Harmonization (ICH) guidelines. The eight non-GLP studies including the blood compatibility studies (HHB-154, HHB-153, HHB-157, HHB-158), immunotoxicity study (HHB-148B), exploratory repeat-dose toxicity study (HHB-178), and dose- finding embryo-foetal development studies (6782-106 and 6782-107) that did not fulfil the requirement to be considered GLP and were conducted as non-GLP studies.

GCP:

The Applicant claims that all clinical studies were conducted in concordance with applicable standards for the design, conduct, and analysis of clinical research, including the International Conference on Harmonization (ICH) consolidated guidelines on Good Clinical Practice (GCP) and the Food and Drug Administration (FDA) regulations in accordance with 21 CFR Parts 50, 54 and 56. All clinical studies met the ethical requirements of Directive 2001/20/EC.

For Clinical trials 62,745-5, 62,745-6 and 62,745-7 there is no identified signature of a principal or coordinating investigator in the final clinical study report as required by ICH E3 and Directive 2001/83/EC as amended. According to the ICH E3, "Structure and Content of Clinical Study Reports", the CSR should be signed by the "principal or coordinating investigator or Sponsor's Responsible Medical Officer depending on the regulatory authority's requirements". The regulatory authority's requirements are set out in Annex I, Part I, Module 5 of Directive 2001/83/EC, which lays down the "Format and Presentation" as well as the "Content: basic principles and requirements" of CSRs. In particular, Annex I, Part I, Module 5.2., indent d, of Directive 2001/83/EC provides that:

"The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made: […]

— final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator".

Directive 2001/83/EC as amended is the legal basis for this signature and for this reason the signature of the Sponsor's Responsible Medical Officer is not acceptable and the applicant must provide either the signature of all the investigators or to nominate one co-ordinating (principal) investigator to sign the clinical study report (**OC**). The intent of the legislation is to have a signature from the investigator community. We note that investigator's signature was requested and provided for the Rienso marketing authorisation application dossier.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

2.5.2. Orphan designation

Not Applicable.

2.5.3. Similarity with orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report, addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

2.5.4. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decisions P/0109/2022 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0109/2022 was not yet completed as some measures were deferred.

Paediatric subjects from 2 years to less than 18 years of age with iron deficiency anaemia (IDA) were deferred (Study AMAG-FER-IDA-352, study completion estimated in April 2025). A waiver was granted for children from birth to less than 2 years; for solution for infusion, on the grounds that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as solution for infusion containing "30 mg of iron and 30 mg polyglucose sorbitol carboxymethylether" as active substance.

Other ingredients are: mannitol, water for injection, hydrochloric acid, and sodium hydroxide

The product is available in 20 ml vials (type I glass) with stopper (chlorobutyl rubber) and aluminium crimp-on seal.

3.1.2. Active Substance

3.1.2.1. General Information

The active substance is described as a mixture of superparamagneticiron oxide crystals and polyglucose sorbitol carboxymethylether (PSC) with the iron oxide as core particle and PSC as coating. The active substance is manufactured in situ as a stable colloidal suspension.

3.1.2.2. Manufacture, process controls and characterisation

3.2.S.2

The manufacturing process is described, with starting materials, all in aqueous solution, pH adjusted. The manufacturing process ends with an ultrafiltrated suspension of PSC-coated iron oxide particles. For all relevant process steps sufficient in process controls are set. The information provided with regard to the manufacturing process description is mainly sufficient.

Information on batch size, respective on yield is missing 3.2.S.2.3

In the module "control of materials" most materials used in the process are listed, see list of questions.

Some questions have been raised to the starting materials and critical excipient (PSC).

Specifications from the starting material manufacturers and from the active substance manufacturer as well as respective CoAs are provided for starting materials within this module. These documents are acceptable.

The control of critical steps is described in detail (there are no intermediates in the process), all process steps are sufficiently under control and a comprehensive rational is presented for each control. Analytical tests for critical steps are separately listed and the respective analytical methods are described in the dossier.

Maximum holding times for all relevant process steps are provided. Maximum historical values have been used to define the acceptable holding times, which is in general acceptable, see list of questions.

The initial process was validated at one site and has than be transferred to the current manufacturing siteAll changes have been outlined in the dossier and equivalence studies have been performed. The documentation provided within the dossier shows that the current process is sufficiently under control and gives ann active substance with consistent quality. Nevertheless, there are some open issues.

After initial development of the active substance, several site transfers and changes in the manufacturing process have been made to get to the currently manufactured product.

The use of purified water in contrast to formerly used WFI is sufficiently justified and the sterile packaging system is controlled for appropriateness as well as for extractables and leachables. As the active substance is not declared to be sterile, no question is raised to the sterilisation method of the packaging material.

3.2.S.3

The active substance is a mixture of non-stoichiometric magnetite and polyglucose sorbitol carboxymethylether. The general and the average formula of iron oxide, as well as the formula of PSC are given in the dossier. The structures of both substances as well as for the mixture are elucidated, but further information is requested.

The impurity discussion is related to both iron sources, ferric chloride and ferrous chloride and the most likely impurities of these compounds, which is acceptable. No impurity discussion is given with regard to PSC, which should also be part of this module.

A brief outline of metal contaminants of ferric chloride and ferrous chloride is given, but no comprehensive risk evaluation with regard to ICH Q3D. This is acceptable as a respective risk evaluation is provided within module 3.2.P.5.5.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

3.2.S.4

The active substance specification contains most relevant parameters for this kind of active substance, but some parameter should be further evaluated, see list of questions.

Some parameters are indicated to be not tested for stability testing, which is acceptable as just non-stability indicating parameter "identity", "ammonium content" and "ethanol" are affected.

Analytical procedures are all described in detail, reference if in house or pharmacopoeial method is given.

If relevant all methods are validated with sufficient parameter, showing that the methods are fit for its intended purpose. Methods have been initially been validated at the original manufacturing site and transferred to the current manufacturing and testing sites Batch data are provided for twelve commercial batches manufactured at the current manufacturing site and several (supportive) batches manufactured at the original manufacturing siteand used in clinical trials. All data are in compliance to the proposed specification. Justification for specifications have been provided. Every parameter is justified, mainly on a statistical basis, using the mean value +/- three standard deviations as acceptable range. Due to the limited data, this approach is questionable and not generally sufficient for setting limits in specifications for active substances. See specific questions to respective parameter above.

3.2.S.5

All reference standards used for analysis of the active substance are described in sufficient detail, . Reference standards are either in house standards or USP standards.

3.2.S.6

The previously and currently used container closure systems are multi lamellar poly bags. They are differing just in the outer layer and are adequately described.

3.1.2.4. Stability

Stability studies have been performed on seven lots at long term conditions (2-8°C) and on three independent lots, at accelerated conditions(40°C/75%RH). Several questions with regard to stability have been raised.

The proposed expiration date with no retest date should be further explained, as it is not obvious to have no retest period.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

It is stated that Feraheme finished product is a sterile aqueous solution for infusion, which is packaged in 20 ml clear type I glass vials, closed grey chlorobutyl rubber stopper and sealed with an aluminium crimp-on seal. However, it seems that the finished product consists of nanoparticles suspended in a liquid. Thus, the term 'dispersion for infusion' should be applied instead of 'solution for infusion'. The dossier (including SmPC) should be updated/harmonised accordingly.

It contains ferumoxytol active substance (which consists of superparamagnetic iron oxide (corresponding to 30 mg iron) and 30 mg polyglucose sorbitol carboxymethylether) and excipient mannitol.

A short description of the finished product, a table with the composition (including amounts per-unit and % w/w basis) and a table with information on fill target volume, overfill, total volume and "Fe per target volume" is presented. Neverthless, the active substance is a solution that contains water for injection and whose pH is adjusted with sodium hydroxide. Thus, all excipients of the API mix and other ingredients that are optionally used, such as acids and alcalis for pH adjustment, should be included in the composition table. Additionally, the amount of PSC (as part of the API mix) should be indicated as free and bound PSC, respectively. Two other issues are raised regarding the presented composition table. A short description of the active substance is provided. However, a discussion on physicochemical properties of the active substance that can influence the performance of the finished product should be included. The active substance is compatible with excipient mannitol, which is sufficiently described. The purpose of mannitol is to raise the tonicity of the finished product (iso-osmotic). Discussion on product target profile is included. It is stated that "there has been only one formulation of ferumoxytol finished product developed since its use in clinical trials and through commercial lots distributed to the market". Further, formulation developmental considerations on iron concentration, terminal sterilisation, osmolality, and biodegradability and bioavailability have been included. There are no overages. Information on pH, viscosity, osmolality and particle size is provided. Development experimental results that led to the choice of the particle coating, magnetic character, and the proportion of ingredients in the active substance synthesis, as well as the formulation, bottling and sterilization process for the finished product, are presented.

Manufacturing process changes are described, such as, transfer of manufacturing from the former manufacturer responsible for DS and DP manufacture to the current manufacturing site.). Whereas the manufacturing process scale changed the latter change involved again a manufacturing scale up The container closure system is sufficiently described. Documents on stopper formulation characteristics, potential extractables in the stoppers, and a letter of conformity are presented. Integrity of the container closure system is discussed. However, there are two issues to be resolved. Compatibility with dosage devices and stability after reconstitution of the DP is discussed.

3.1.3.2. Manufacture of the product and process controls

Name, address and responsibility for each manufacturing site is listed. Nevertheless, one question remains.

The batch formula for the manufacturing scale batch size is presented. Nevertheless, two issues remain to be resolved.

A narrative description of the manufacturing process and a process flow-chart are provided. The manufacturing process involves active substance incoming inspection and testing, preparation of vials, stoppers and solutions, filtering, filling, stoppering and crimping, terminal sterilisation, vial drying, packaging and labelling. No reprocessing is proposed. However, several issues remain.

Critical process parameters, hold times and critical steps during manufacturing process are listed tabularly. Nevertheless, there are three questions to be resolved.

Manufacturing of the finished product is a non-standard manufacturing process (non Ph. Eur conformal terminal sterilisation). Transfer validation reports are provided. However, several issues remain.

Information on specification, CoA, analytical methods and validation of analytical methods is provided for excipient mannitol. Nevertheless, three questions remain regarding information provided on excipients.

3.1.3.3. Product specification, analytical procedures, batch analysis

The specified parameters for the control of the finished product have been set up primarily according to the Ph.Eur. requirements for this dosage form and according to respective ICH guidelines. Nevertheless, according to the respective directive the active substance content in a finished product should amount to at least 95 – 105%. As active substance, ferumoxytol, consists of iron and PSC, respectively, their acceptance limits in the finished product specification should be set (taking into account the target iron content and PSC content, respectively, to 95-105%. Importantly, the iron content should consistently be stated in % or in mg/ml and %, but not solely in mg/ml (MO). Additionally, several other issues remain to be resolved.

Method descriptions have been provided for all used methods (Ph.Eur. methods, in-house methods). However, there is one issue to be resolved. The analytical testing methods have been validated in accordance with ICH Q2. However, one issue remains.

Batch analyses data are provided for several commercial scale batches manufactured at the proposed finished product manufacturerand several batches used in pivotal clinical studiesmanufactured at the former finished product manufacturer . Information on batch number, manufacturing site, date of manufacture, and active substance batch numbers (used in respective finished product batches) is provided. The batch data comply with the proposed specification. Nevertheless, three issues remain to be resolved. Degradation products, elemental impurities and potential nitrosamines are discussed. However, one issue regarding potential nitrosamines remains (MO). Justification of each specified parameter is given. It is mentioned that test procedures and acceptance criteria have been established according to ICH-Q6A. Actually, every parameter is justified, mainly on a statistical basis, using the mean value +/- three standard deviations as acceptable range. Due to the limited data, this approach is questionable and not generally sufficient for setting limits in specifications for finished products. Accordingly, a number of questions remain to be resolved regarding the finished product specification.

Information provided for the used reference standards is mainly acceptable. Nevertheless, one issue remains. Information on specifications, CoAs and certificates of compliance has been provided for the proposed packaging material. However, there are several questions to be resolved.

3.1.3.4. Stability of the product

Up to 60 months long-term (25±2 °C/60% RH) and 6 months accelerated (40°C/75%RH) stability data are presented for three process validation batches and from several annual lots. All results are within specifications. In view of the presented stability data the proposed shelf life of 60 months and storage condition ("This medicinal product does not require any special storage conditions") is acceptable. Additionally, the "shelf-life after first opening and after dilution for infusion" as proposed in the SmPC, such as "Chemical and physical in-use stability has been demonstrated for 96 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not be longer than 6 hours at 25°C", is acceptable.

3.1.3.5. Post approval change management protocol(s)

N.A.

3.1.3.6. Adventitious agents

Ferumoxytol injection is an aqueous solution comprised of ferumoxytol active substance and mannitol. No excipients, components, or starting materials are derived from animal origin and all are synthetic, or plant based. TSE/BSE Statement for the product is provided.

3.1.3.7. GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The proposed finished product is not acceptable yet from a quality point of view as several OCs have been raised.

Please refer to the D80 Quality AR for detailed assessment.

3.1. Non-clinical aspects

3.1.1. Introduction

Ferumoxytol, the active ingredient of Feraheme, is an iron-carbohydrate complex comprised of polyglucose sorbitol carboxymethylether (PSC)-coated ferric iron oxide nanoparticles, which has been developed as an IV iron supplement for use in the treatment of iron deficiency in patients with chronic kidney disease (CKD). Feraheme is proposed to work in a manner similar to other parenteral iron products and it is indicated as episodic iron replacement therapy in the treatment of iron deficiency anemia in adult patients with chronic kidney disease and all-cause iron deficiency anaemia. It has been projected that PSC, derived from a dextran, coating would minimize free iron release being of decreased immunological reactivity.

Ferumoxytol contains iron in a form that is easily utilised by the body and is incorporated into the body's iron stores. The metabolism of iron in ferumoxytol follows the typical iron metabolism pathway involving transferrin, ferritin, hemosiderin and hemoglobin. Since the iron in ferumoxytol enters the normal body stores, its excretion is also expected to be minimal.

In the context of treatment of iron deficiency anaemia, please elaborate on potential positive or negative effects of the superparamagnetic properties of ferumoxytol, since it is anticipated that iron supplements are potentially sustained in the body for several months (**OC**).

3.1.2. Pharmacology

3.1.2.1. Primary pharmacodynamic studies

Intravenous administration of ferumoxytol (code 7228) was able to correct diet caused iron deficiency anaemia in rats by releasing bioactive iron and incorporating it into hemoglobin: a single administration of ferumoxytol (30 mg Fe/kg) over a three-week period resulted in a significant increase in hemoglobin levels (from 3.9 g/dL to 11.1 g/dL). Parameters such as erythrocyte count (RBC), Hct, serum iron and serum iron binding capacity were also increased.

Regarding the pharmacodynamic properties of Ferumoxytol, the Applicant provided a rather limited non-clinical developmental programme. However, since the concept is considered established, there are no fundamental objections to the nonclinical pharmacodynamic development of the colloidal iron-product submitted for approval.

3.1.2.2. Secondary pharmacodynamic studies

Two studies were performed to explore the suitability of Ferumoxytol in magnetic resonance spectroscopy in order to enhance the contrast of the acquired images. It was clearly shown, that Ferumoxytol may alter magnetic resonance images since the elemental iron in ferumoxytol retains magnetic properties.

3.1.2.3. Safety pharmacology programme

Ferumoxytol effects on general activity and behaviour, as well as autonomic and motor effects were investigated in mice, based on Irwin's method (Irwin, 1968). Observations were performed at 0-5, 15, 30, 60 and 120 minutes post-dose. No behavioural and physiological changes were observed in male mice following ferumoxytol administration at single doses of 100, 300 or 1000 mg Fe/kg. As such, no effects of Ferumoxytol on the CNS are to be expected from the non-clinical point of view.

The in vitro effects of Ferumoxytol on ionic currents in voltage-clamped human embryonic kidney cells (HEK293) that stably express the human ether-à-go-go-related gene (hERG), were determined. Ferumoxytol did not inhibit the peak-tail currents in cloned hERG potassium channels expressed in HEK cells at concentrations up to 500 µg/mL, indicating no risk for QT prolongation. In contrast, there was a significant increase in the peak-tail current recorded at all doses, which could possibly lead to reduced repolarization time and thus induce a shortening of the QT interval. According to Campuzano et al, 2018, the short QT syndrome is a highly malignant inherited cardiac disease characterized by ventricular tachyarrhythmias leading to syncope and sudden cardiac death.

The applicant should discuss the clinical relevance of the finding in the hERG assay and if the reduced repolarization time could be part of the mechanism behind the rapid cardio-respiratory collapse as observed in some patients experiencing severe/fatal hypersensitivity reactions (**OC**).

Three Code 7228 (ferumoxytol,120 mg Fe/kg) intravenously treated and two saline control anesthetized male CD (SD)BR rats (261-361 g) were evaluated for changes in mean arterial blood pressure (MABP), calculated from directly recorded the systolic and diastolic pressures in carotid artery in this pilot study. Each recording was evaluated for evidence of response which persisted for at least 1 minute during the initial 30 minutes post-injection. No reduction in MABP was measured in the 3 experimental animals receiving Ferumoxytol.

Male guinea pigs (anesthesised with Nembutal) were administered ferumoxytol IV at a dose of 120 mg Fe /kg. Guinea pigs were assessed for changes in pulse pressure (PP) and mean arterial blood pressure (MABP) for 1 hr after administration of Ferumoxytol, although it would have been an asset, if the blood pressure would have been measured within the first 10 minutes after application. However, short and transient changes in blood pressure can be straightforwardly determined in the clinical setup. Injection of saline resulted in an 8% reduction in MABP. 7/9 animals had no relative reductions in MABP after receiving ferumoxytol. 1/9 animal had a 25% reduction in MABP (mild). 1/9 animals was not included in the analysis due to fluctuating MABP readings over 1 hr post-dose.

In light of the serious/fatal adverse events in patients, the applicant should discuss if the two observations in the guinea pig (MABP decrease and highly variable MABP) could be induced by mechanisms of short QT interval and/or hypersensitivity reactions as observed in patients (**OC**).

Anaesthetized beagle dogs were administered ferumoxytol IV at doses of 4, 40 and 200 mg Fe /kg. Ferumoxytol had no effect on arterial blood pressure (systolic, diastolic and mean), heart rate, femoral artery blood flow and ECG parameters. An increase in dose volume and test article dose of ~ 10 to 50 fold had no effect on cardiovascular and respiratory parameters. No cardiac electrocardiographic deviations were detected.

However, there were vehicle associated increase in diuresis, minor effects on creatinine clearance, natriuresis and urinary potassium and chloride excretions. Due to the Applicant, these changes can be attributed to the mannitol composition of the vehicle. No further explanation was given on this finding. The Applicant is asked to provide a justification and/or a compilation of published data in order to support this statement with respective information (**OC**).

Summing up, Code 7228 had no effect on cardiovascular and respiratory measures and kidney function in anesthetized dogs relative to vehicle administration.

No biologically meaningful effects occurred as a result of PSC administration. No test article-related mortality; clinical observations; or effects on food consumption or body weight were noted. No heart rhythm abnormalities were attributable to PSC. Administration of PSC had no effect on PR interval, QRS duration, QT interval, QTc interval, heart rate, blood pressure (systolic, diastolic, and mean arterial pressures), pulse pressure, or intra-abdominal body temperature. With respect to the cardiovascular end points evaluated up to 25 hours postdose, a weekly intravenous bolus dose of the highest PSC dose administered (750 mg/kg) in beagle dogs caused no discernable effects when compared to those of vehicle control treated dogs.

3.1.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted based on the primary site of action of ferumoxytol which is the erythrocyte, and, in contrast to conventional drugs, no drug-receptor interaction takes place.

3.1.3. Pharmacokinetics

A total of 13 non-clinical in vivo PK studies (including two toxicokinetic studies) were conducted in support of the MAA of Feraheme. These studies comprised absorption of fermoxytol in rats, guinea pigs, rabbits and dogs, tissue distribution in rats and rabbits, evaluation of plasma catalytic iron released by ferumoxytol, urinary and faecal excretion of iron and of the PSC coating and its metabolites and excretion of ferumoxytol and ferumoxytol-derived ^{59}Fe and ^{14}C-radioactivity in milk.

In order to measure iron particles in different matrices as well as tissues, three complementary methods were employed, i.e. TD-NMR spectroscopy, ^{59}Fe-radioactivity measurements and ^{14}C-radioactivity measurements. It appears that the TD-NMR method is valid when used for serum, but cannot be used as a quantitative measure, when determining concentrations in tissues due to the close proximity of the nanoparticles in intracellular organelles. Hence, the distribution studies using radioactive labelled ferumoxytol is considered the most reliable and the study using TD-NMR can be observed as supportive studies.

Only the 13-week toxicity studies in rat and dog included toxicokinetics. These studies were conducted in 2007, prior to issuing of the EMA guideline for bioanalysis (2012). No individual bioanalytical report and no reporting of incurred sample reproducibility is available; however, this is accepted given the timing of the studies.

Of these three methods only the TD-NMR spectroscopy was validated. The method was validated for rat serum, dog serum, rat milk and rat plasma. Overall, all validation parameters complied and the method

can be regarded adequately validated. Lower limit of quantification was 17 µg/mL. It appears that serum concentrations much lower than 17 µg/mL were reported for toxicokinetics and were included in the toxicokinetics calculations in both the rat and dog 13-weeks toxicity study.

Results obtained with the non-validated methods can only be regarded supportive.

Five dedicated **absorption** studies were conducted in rats, guinea pigs and rabbits with doses ranging from 2.2 to 37 mg Fe/kg. In these studies animals received single doses administered i.v. corresponding to the intended clinical route of administration. $T_{1/2}$ ranged from 81 to 121 minutes after administration of 2.2 mg/kg in rats, guinea pigs and rabbits and was, thus, quite similar between species. Administration of 37 mg/kg lead to an $T_{1/2}$ increase to 3.9 and 4.4 hours in rats and rabbits, respectively. C_{max} values increased nearly dose-proportional in dogs that were administered single doses of 2, 6 and 12 mg/kg, whereas AUC_{0-24} increased in a more that dose-proportional manner. A slightly higher exposure was observed in male as compared to female animals.

Toxicokinetic evaluation in the scope of two 13-week repeat dose toxicity studies in rats and dogs (Covance 6782-114 and Covance 6782-115) revealed dose- and time-dependent increase of exposure. This increase was more than dose-proportional. The increase in AUC_{0-24} was more pronounced in rats and points towards accumulation. In addition, $T_{1/2}$ increased over time in the two higher dose groups. Clearance decreased with time and increasing dose in rats, whereas no such development was observed in dogs. T_{max} values of 0.25h were measured in both species at all time points. Of note, higher exposure was generally observed in males as compared to females.

Distribution was evaluated in six studies in rats and rabbits that received doses from 2.2 to 37 mg Fe/kg (Studies HHB-149B and HHB-173). The entities employed in these studies were unlabelled, ^{59}Fe- and ^{14}C-ferumoxytol in rats and ^{59}Fe-ferumoxytol in rabbits. Distribution of unlabelled ferumoxytol was evaluated over a period of 84 days and revealed highest uptake in spleen, liver, central and peripheral lymph nodes and bone marrow. Peak levels occurred 1 day post-dose and reached baseline levels at day 84.

Bioavailability was evaluated after administration of 2.2 mg Fe/kg (^{59}Fe-ferumoxytol) to rats (Study HHB-159) and monitored for 4 weeks post-dose. After initial large distribution of radioactivity to the plasma, levels declined within 1 day post-dose and increased again over the 4 week observation period. Detailed analysis revealed that the largest proportion of radioactivity was associated with red blood cells indicating incorporation of ^{59}Fe during red blood cell synthesis.

^{59}Fe-ferumoxytol was also used in **tissue distribution** studies in rats (37 mg Fe/kg) and rabbits (19 mg Fe/kg). 48 hours after administration in rats the tissues of major uptake were liver, spleen and central lymph glands, whereas rabbits had the highest levels in liver and bone marrow. The radioactivity detected in blood was virtually completely attributable to red blood cells.

Similar tissue distribution results were obtained after administration of 2.2 and 6 mg Fe/kg ^{14}C-ferumoxytol, intended to evaluate the distribution of the semi-synthetic carbohydrate component of ferumoxytol, to rats over the course of 84 days.

Distribution of iron to liver, lymph nodes and spleen was also confirmed by histopathological analysis in the scope of repeat-dose toxicity studies, where intracytoplasmatic brown pigmentation was found in macrophages or Kupffer cells of the indicated organs.

Metabolism of ferumoxytol was predominantly investigated regarding the availability of potentially cytotoxic catalytic iron, non-transferrin bound iron (NTBI), and the fate of the PSC coating.

NBTI levels were analysed in a comparative in vivo study in rats employing a bleomycin detectable iron assay. As a result, the formation of NBTI as compared to other colloidal iron preparations was comparable

or lower after administration of ferumoxytol. When observing NBTI levels over 24 hours, peaks were registered at 5 minutes and 6 hours after administration.

However, whether the amount of free iron determined in ferumoxytol could saturate transferrin at clinically relevant doses was not discussed.

Metabolism of PSC was not discussed. This should be justified (**OC**).

Excretion was evaluated after administration of ^{59}Fe-ferumoxytol to rats and rabbits (37 mg Fe/kg and 19 mg Fe/kg, respectively). The amount of ^{59}Fe was negligible in the urine and feces of both species (less than 2%) at 48 hours post-dose. The major part of recovered ^{59}Fe originated from the carcass, i.e. 18% in rats and 49% in rabbits.

Excretion of ferumoxytol via milk was investigated in lactating rats that were administered with 105 mg/kg ferumoxytol (control), 99.6 mg/kg ^{59}Fe-ferumoxytol and 99.5 mg/kg ^{14}C-ferumoxytol for 10 to 11 days after parturition and plasma and milk levels were observed 0.25, 8 and 72 hours after infusion (Covance 6782-119). Maximum plasma concentrations of ^{59}Fe and ^{14}C were detected 0.25 hours after infusion and continuously declined thereafter. In milk, highest levels of ^{59}Fe and ^{14}C were measured 8 and 24 hours after administration, respectively.

As for PSC, 90% of the ^{14}C-labelled dose was excreted via urine and feces 84 days after administration of a single dose of 2.2 mg Fe/kg to rats. The major part of excreted PSC was intact whereas 23% was excreted as low molecular weight structure indicating degradation.

Iron is anticipated to be incorporated and reused in the body and therefore not excreted except during bleeding and in cells lining the gastrointestinal tract.

No studies on pharmacodynamics drug interaction have been conducted. The Applicant's justification that ferumoxytol is not metabolized in the liver and not substantially excreted via the kidney and, thus, is not likely to interact with metabolism or urinary excretion of other drugs is supported.

3.1.4. Toxicology

3.1.4.1. Single dose toxicity

Single-dose toxicity studies employing doses of 0, 4, 40, or 450 mg Fe/kg to male and female beagle dogs did not reveal any severe drug effects. Some effects were observed in the highest dose group, however, not considered adverse. These observations included: an increase in liver and gallbladder weights that was related to iron uptake by Kupffer cells and associated hepatic sinusoidal distention. Mucous membranes and/or gums were discoloured along with lymph nodes that were also discoloured in two animals of the 40 mg dose group. Iron levels in the serum increased dose-dependently and peaked 3 days post-injection. Levels of the 40 mg and 450 mg dosing groups decreased after day 3 but remained significantly higher than control levels through day 15. Serum iron levels were slightly higher in female animals dosed 450 mg than in males of the same dosing group. Transient prolongation of activated partial thromboplastin times was observed at day 3 in the highest dose group. The NOAEL of 450 mg Fe/kg for single infusions is supported.

Administration of single doses of 0, 4, 40, or 450 mg Fe/kg to male and female Crl:CD (SD)BR rats in study 6782-103, was in generally well tolerated at all dose levels. Observations that were rated as non-adverse were limited to the high dose group and included: Transient limb swelling was observed, however, this was attributed to the dextran-sensitivity of the Sprague Dawley rat strain that has been reported to exhibit anaphylactoid reactions upon dextran infusion (L. Ivarsson et al.). Moreover, animals

of the high dose group exhibited discoloration of nose and limbs through day 4 that was very likely associated with the dark colour of the test material. Microscopic examination revealed brown pigmentation of macrophages/Kupffer cells in liver, spleen, lung, lymph nodes, thymus, testes, epididymes, ovaries, intestine and skin but also of hepatocytes.

The NOAEL determined at 450 mg Fe/kg for single administration to rats is agreed.

3.1.4.2. Repeat dose toxicity

In order to assess the dose range for the repeat-dose toxicity studies, ferumoxytol was repeatedly administered at doses of 30, 90, 180 or 360 mg Fe/kg/day (cumulative doses of 420, 1,260, 2,520 and 5,040 mg Fe/kg) for 14 consecutive days to rats aged 7 to 8 weeks to evaluate clinical signs and effects on body weight. No MTD was estimated in the dose-range study, as the doses were generally set too high.

At all doses, dose-dependent decreases in body-weight gain were noted for ferumoxytol groups compared to mannitol vehicle groups. Although body weight gain somewhat recovered after cessation of treatment, it did not completely return to normal levels until the end of the recovery period. Discoloration of ears, snout and paws was observed in the two high dose groups and persisted throughout the recovery period through day 35. Additionally, paw oedema was noted from doses of 180 mg Fe/kg/day. Piloerection and lacrimation were observed in all treatment groups after administration. Consequently, the doses were down-adjusted in the subsequent GLP compliant studies, which is supported.

A 4-week repeat-dose toxicity study with 4- and 26-week recovery was performed in 7-week old Crl:CD (SD)IGS BR rats that received doses of 6, 18, and 37 mg/kg/day (cumulative doses of 180, 540, or 1,110 mg Fe/kg) as an IV (tail vein) injection (Covance 6782-108). Body weight, body weight gain and food consumption were significantly decreased in the mid and high dose groups as compared to controls and persisted through the 4-week recovery period. Body weight gain returned to levels comparable to controls during the recovery period. Almost all organs including injection sites of animals of the high dose group showed yellowish-brown pigmentation that was attributed to the administered iron and persisted through week 26. Dose dependent haemorrhage, haemorraghic necrosis, chronic inflammation and bile duct hyperplasia was observed at week 26 in the majority of female 18 and 37 mg/kg animals. No such findings were made in male animals. Pigment-containing macrophages were found in spleens and lymph nodes as well as other organs and pigment was also detected in reticuloendothelial cells of many other tissues. These findings were largely dose-related and persisted through week 26 with a tendency of decrease over time. Total leukocyte, neutrophil and monocyte counts were significantly elevated in week 5 in the highest dose group and attributed to elimination of the test article as no signs of inflammation were noted. Significantly decreased mean prothrombin and activated partial thromboplastin time were observed at week 5 and other time points exclusively in male animals and attributed to potential optical interferences with the assay by plasma iron and considered to be of no biological relevance. Decreases in mean glucose concentrations in males of the 18 mg/kg and all animals of the 37 mg/kg dose group as well as increased cholesterol levels in both high dose groups were related to the decreases in body weight and body weight gain as well as reduced food consumption. Whereas glucose levels returned to normal within the recovery period, cholesterol levels remained elevated. The NOAEL was determined at the dose of 6 mg Fe/kg/day based on reduced body weight gain and food consumption as well as decreased glucose levels and increased cholesterol levels.

It should be noted that this NOAEL only provides a 1.7-fold change between the HED and the expected clinical dose.

A repeat-dose toxicity and toxicokinetics study was conducted in male and female rats that received doses of 0, 2, 6, and 12 mg Fe/kg/day for 13 weeks (Covance 6782-114). This dose-regimen resulted

in cumulative doses of 186, 558, or 1,116 mg Fe/kg, which was very similar to the cumulative dose from the 4-week study in rats. Body weight was statistically significantly reduced in male and female animals of the highest dosing group over the whole study period. Mean body weight gains were dose-dependently decreased at the termination time point. These observations were linked with decreased food consumption in all experimental groups that was statistically significant in the two highest dose-groups. Hematological changes included a slight, however, statistically significant decrease in red blood cell counts in the 6 and 12 mg/kg groups. Hemoglobin was slightly increased in all treatment groups. Male animals also exhibited increased mean cell volume, mean cell haemoglobin and mean cell haemoglobin concentration which was expected upon administration of colloidal iron. The decrease in red blood cells was considered to be of regenerative character which is supported by the increase in mean cell volume indicative for the presence of reticulocytes. White blood cell counts were increased in the highest dose group which was attributed to elimination of the product administered as signs of inflammation were absent. In this context, statistically significant increases in spleen and liver weights throughout all dose groups were considered to be related to iron disposition and associated mononuclear infiltrates. Iron-pigmented phagocytes were found in liver, kidneys, small intestine, spleen, lungs and lymphnodes. Iron pigment was also detected in hepatocytes. Pigment that was not confirmed to originate from the test article was also found in cells of other organs. Overall, pigmentation was dose-related and not associated with pathologic changes. Significantly increased serum iron levels were noted on all treated animals. Cholesterol was statistically significantly increased in animals of the two high dose groups and a dose-related decrease in mean glucose was observed in all treated male animals. Aspartate aminotransferase and alanine aminotransferase were statistically significantly increased in animals of the 12 mg/kg group, gamma glutamyltranspeptidase was only elevated in males of the highest dose group and alkaline phosphatase levels were increased in 6 mg/kg females and 12 mg/kg males and females. Based on the fact that no histopathologic or toxicological changes were associated with iron dispositions in cells or organs as well as with the decreased body weight gain the NOAEL was determined to be 12 mg Fe/kg/day.

A 4 week repeat-dose toxicity study was conducted in beagle dogs that were administered 0, 6, 18 or 37 mg Fe/kg (cumulative doses of 0, 192, 576 and 1,184 mg Fe/kg) and were observed for 4 or 26 weeks after dosing (Covance 6782-109). Ferumoxytol was well tolerated at all doses administered. Serum iron levels increased in a dose-dependent manner, decreased during the 4 week recovery period but remained elevated relative to control animals. No changes in haematological or clinical chemistry parameters were noted in relation to elevated serum iron levels. Iron-related pigmentation was observed in tissues and organs, predominantly liver, spleen, lymph nodes, kidneys and small intestine, of all dose groups and remained through the 26-week recovery period, albeit with decreasing intensity. Cellular localisation of iron pigmentation was mainly in phagocytic reticuloendothelial cells. An increase in liver/gallbladder weights with statistically significant elevation of organ-to-body weight ratios was observed in the 18 and 37 mg/kg groups after the 4-week treatment period. Liver/gallbladder weights remained elevated in these dosing groups predominantly in males throughout recovery with organs weights twice of those of controls after 4 weeks and 26 weeks in the highest dose group. Microscopic examination did not reveal cell injury or signs of inflammation. No signs for immune toxicity became apparent. Thus, the Applicant determined the NOAEL for ferumoxytol in dogs at 37 mg Fe/kg/day, which is acceptable.

A second repeat-dose toxicity study was conducted in dogs which received doses of 0, 2, 6, and 12 mg Fe/kg/day over 13 weeks (Covance 6782-115). This dose-regimen resulted in cumulative doses of 186, 558, or 1,116 mg Fe/kg, which was very similar to the cumulative dose from the 4-week study in dogs. Ferumoxytol administration was generally well tolerated and did not affect food consumption or body weight. Yellow discoloration of the conjunctiva was evident in all animals of the 12 mg/kg group starting from day 70 of treatment. This was attributed to iron deposition as no signs of jaundice were detected in livers. In this context also yellow gums were observed in the mid and high dose groups. Discoloration

was also noted in gastric mucosa and lymph nodes upon necropsy. Microscopic examination revealed iron-containing phagocytes in many tissues including liver, lymph nodes spleen and choroid plexus with dose-dependent incidence. Liver weights were statistically significantly elevated in a dose-dependent manner. Serum iron levels were elevated, but no related adverse changes in haematological or clinical chemistry parameters were detected. Liver weights were increased in male and female animals of all dose levels, except for the lowest dose that only affected liver weights of females. In addition, spleen weights were increased in males of all dosing groups and in females of the 2 and 6 mg/kg group. Based on these results the NOAEL was determined at 12 mg Fe/kg/day, which is acceptable.

3.1.4.3. Genotoxicity

A total of three in vitro and in vivo studies were conducted in order to investigate potential genotoxicity of ferumoxytol. In vitro genotoxicity was assessed in a bacterial reverse mutation assay (Covance 19860-0-409OECD) and a chromosomal aberration assay in CHO cells both in presence and absence of metabolic activation (Covance 19860-0-437OECD). Both assays were conducted in line with OECD recommendations, i.e. OECD test 471 and OECD test 473. No evidence for genotoxic activity or induction of chromosomal aberration was obtained. An in vivo genotoxicity test was conducted in mice. Animals were dosed at 200, 500, 800, 1000, and 1500 mg Fe/kg and observed for 2 days after dosing (Covance 19860-0-455OECD). A statistically significant decrease in the PCE:NCE (polychromatic erythrocytes: normochromatic erythrocytes) ratio in animals of the highest dose group was observed 24 hours after administration and returned to normal levels after 48 hours which demonstrated a cytotoxic effect at this dose. The percentage of micronuclei was very slightly increased at the 24 hour time point and decreased to levels comparable to the vehicle group at 48 hours. Thus, no evidence for clastogenic activity of ferumoxytol was observed.

3.1.4.4. Carcinogenicity

Carcinogenicity studies were not conducted which is in line with guideline ICH S1 stating that such studies are only indicated for pharmaceuticals that are intended to be administered for at least 6 months or for which cause of concern exists based on the results of the genotoxicity studies. As this does not apply to fermuoxytol the omission of carcinogenicity studies is accepted.

Additionally, no carcinogenic potential was expected as genotoxicity was not seen for Ferumoxytol in vitro or in vivo, no preneoplastic lesion were seen in the conducted in vivo studies and no history of carcinogenicity was noted for other iv iron product.

3.1.4.5. Reproductive and developmental toxicity

A **fertility and early embryonic development** study was conducted in rats. Male rats were administered doses of 6, 12 and 18 mg Fe/kg/day for at least 28 days prior to mating, through the mating period of three weeks until terminal sacrifice (mean cumulative doses of 450, 900 and 1350 mg Fe/kg) (Covance 6782-113). Female animals received the same doses starting from at least 14 days prior to mating, throughout the mating period up to gestation day 7 (mean cumulative doses of 150, 300 and 450 mg Fe/kg). In males body weight and body weight change were significantly decreased as compared to controls in the 12 mg and 18 mg/kg/day dose groups. A similar effect was observed in females of the same dose groups, however, limited to the gestation period only. Treatment-related clinical observations were limited to hyperpigmentation of the skin (ears, paws and tail) of 12 and 18 mg/kg/day males as well as pigmented lymph nodes that was observed in male and female animals of all dosing groups. No effect on mating behaviour, pregnancy rates, number of corpora lutea and viability of foetuses was observed in relation to ferumoxytol treatment. No changes were noted in male fertility

parameters. An apparent increase in testicular weight compared to BW was described in the study report, however, it is agreed with the study director that this more likely reflected a reduction in BW in males that an effect on testes, as no correlating histopathological changes was seen. Due to the effects noted on parental body weight the NOEL for parental toxicity was determined at 6 mg Fe/kg, which is endorsed. The NOEL for fertility, general reproductive performance and early embryonic development was set at 18 mg Fe/kg/day, as no treatment related differences were seen in any of the factors determining these parameters.

A dose-range finding study in preparation for a **developmental toxicity** study was performed in rats. Mated females were dosed 6, 18, 50, and 100 mg Fe/kg/day (cumulative doses of 72, 216, 600 and 1200 mg/kg) for 12 days from GD 6 through 17 (Covance 6782-107). Maternal toxicity was noted by reduced weight gain and decreased food consumption from doses ≥50 mg Fe/kg (cumulative dose of 600 mg/kg). However, no correlating findings of in utero toxicity were detected. For the definitive embryo-foetal toxicity study time-mated females received doses of 10, 31.6 and 100 mg Fe/kg/day (cumulative doses of 120, 379 and 1,200 mg Fe/kg) for 12 days from GD 6 through 17 (Covance 6782-111). Mean body weights of high dose females were statistically significantly decreased to 89% of controls from GD 8 through GD 20. The mean total food consumption was reduced to 68% of controls in the highest dose group and transiently significantly reduced in the 31.6 mg/kg/day group. Related to that uterine weights of females of the 100 mg/kg/day group were statistically significantly reduced which was also owed to statistically significantly decreased foetal body weights in the 100 mg/kg/day group indicative for delayed development. No adverse findings were made in maternal animals at terminal necropsy at any dose levels. Animals of the highest dose group displayed iron-related discoloration of livers, spleens and adipose tissue as well as skin hyperpigmentation. The foetal and litter incidence of wavy/bent ribs in foetuses was statistically significantly increased in a dose-dependent manner and reached levels of 30% of foetuses and 76% of litters in the highest dose group. The incidence of unossified vertebral centrum as well as unossified 6th sternebrae was elevated in the highest dose group and both high dose groups, respectively. On the other hand ossification of pubis and vertebral arch was accelerated as compared to controls.

A dose-range finding study was performed in support of a planned developmental toxicity study in rabbits. Animals received 6, 18, 50, and 100 mg Fe/kg/day (cumulative doses of 84, 252, 700 and 1,400 mg Fe/kg) for 14 days through GD 24 (Covance 6782-106). Iron-related discoloration of the skin was observed in dams starting from the 50 mg/kg dose. Decreased food consumption, body weight and body weight gain was observed in the 100 mg/kg group starting from GD 15. Necropsy revealed accumulation of ferumoxytol in various organs in all except for the lowest dosing groups. Brown discoloration of the amniotic fluid was observed in the two highest dose groups. An increased number of resorptions, decreased number of live foetuses in the context with decreased uterine weights were noted in the 100 mg/kg dose group. One drug-related abortion occurred in the 50 mg/kg group and in the 100 mg/kg group.

For the definitive developmental toxicity study in rabbits doses of 6, 16.5 and 45.3 mg/kg/day were administered for 14 days (cumulative doses of 84, 231 and 634 mg Fe/kg) through GD 29 (Covance 6782-110). Abortion was noted in two animals dosed with 45.3 mg Fe/kg. Evidence of foetal toxicity and teratogenic effect was observed as dead foetuses (3/12 in one litter) and a cluster of malformations consisting of absent brains (anencephaly, 6/133 foetuses from 3/16 litters), dome shaped head (5/133 foetuses from 4/16 litters) and malrotated/flexed limbs/paws (7/133 foetuses from 4/16 litters) at doses of 45.3 mg Fe/kg. Additionally, one fetus had cleft palate and microglossia. Three other foetuses had hydrocephalus (3/133 foetuses from 3/16 litters) without any other malformation. Incomplete ossification of the skull was noted for two 45.3 mg Fe/kg/day foetuses with dome-shaped heads and/or absence of the brain. Other observed skeletal variations in vertebra, sternebra and ribs were within historical reference and therefore not considered drug related but correlated with findings from the rat

study. In addition to the observed malformations, mean foetal weight was significantly decreased for the whole group compared to both control and historical data. No adverse effects on number of implantations, resorptions or viability of foetuses were noted in the other dosing groups. The NOAEL were set to 16.5 mg/kg with a cumulative dose of 231 mg/kg and a safety margin to HED of 4.4-fold.

No overt maternal toxicity was observed. Food consumption and body weight gain were generally unaffected by the treatment, but a non-significant tendency of reduced BW gain and food consumption were noted at doses of 45.3 mg Fe/kg. Hyperpigmentation (ears, nose, lip, eyes and organs including ovaries, amniotic sac and uterus) were seen at doses ≥ 16.5 mg Fe/kg.

Thus, it can be concluded that doses of 6 or 16.5 Fe mg/kg administered during organogenesis did not affect dams or foetal development. Maternal effects in the 45.3 mg/kg group were limited to decreased body weight gains, however, clear teratogenic or foetotoxic effects were observed. The safety margin to the teratogenic cumulative dose is 11.9-fold.

A **pre- and post-natal development** study including maternal function was conducted in rats that were administered 10, 30 and 60 mg/kg/day (cumulative doses of 350, 1050 and 2100 mg Fe/kg) for 35 days from gestation day 6 through lactation day 20 (Covance 6782-118). In order to determine potential effects on the fertility of the offspring, F1 males were mated with F1 naïve females and F1 females were mated with F1 as well as naïve males due to decreased reproductive indices of F1 females. Observations in the F0 generation were limited to statistically significant decreases in maternal body weight gains during gestation and at the beginning of the lactation period in the 60 mg/kg group that was accompanied by significantly decreased food consumption. Transient decreases in food consumption were also observed in the 30 mg/kg group. No effects on maternal delivery and survival of the offspring were reported. However, a dose-related decrease in the body weights of neonates of both genders that persisted through the lactation period was observed in the 30 and 60 mg/kg groups. Survival as well as clinical and developmental parameters were unaffected by ferumoxytol treatment in offspring of the F1 generation except for sexual maturation parameters, i.e. delayed vaginal opening and preputial separation, in the highest dose group. F1 females of the 30 and 60 mg/kg dose group had lower reproductive indices as compared to the other dose groups. Thus, time to confirmation of pregnancy and copulation as well as fertility and fecundity indices were delayed. In addition, maternal body weights of F1 females of the highest dose group were reduced by 5% throughout the gestation phase. F1 males of the 30 and 60 mg/kg dosing groups as well as F1 females that did not deliver were rebred with naïve partners in order to distinguish between male and female fertility effects. Decreases in body weights were settled at the time point of the second mating. Reproductive indices of naïve females mated with F1 males of the highest dose group were lower but no effects on the duration of gestation and the number of pups per litter was observed. No other findings on reproductive performance were noted. F1 females of the 30 and 60 mg/kg group rebred with naïve males exhibited reduced reproductive indices, i.e. reduced copulation index and reduced fertility index. Fertility indices were similar (60%) in both dosing groups and the reproductive index was 0% in the 30 mg/kg and 40% in the 60 mg/kg group. In addition, two females of the 60 mg/kg group experienced prolonged gestation with or without delivery, respectively. Of note, due to the rebreeding approach chosen for this experiment, interpretation of data is somewhat hampered by different group sizes. An increased incidence of dilated renal pelvis was observed in F1 females of the highest dosing group and was likely to be dose-related.

3.1.4.6. Toxicokinetic data

Toxicokinetic evaluation is included in section 3.2.3 Pharmacokinetics.

3.1.4.7. Tolerance

Local tolerance was assessed in rabbits after single i.v. (0.42 mL/kg), perivenous (0.1 mL/kg) or intra-arterial injection (0.42 mL/kg) of ferumoxytol at a 30 mg Fe/mL concentration (Covance 6782-105). No systemic adverse findings were made in this study. Local effects were limited to haematomas at the injection sites. No erythema or oedema were noted during the in-life phase of 15 days duration. Necropsy revealed residual iron at the injections sites but this was not associated with inflammatory processes. Thus, ferumoxytol can be considered non-irritating for the intended route of administration.

3.1.4.8. Other toxicity studies

Potential **immunomodulatory effects** of ferumoxytol were analysed in an in vitro assay employing human peripheral blood leucytes (PBLs) that were exposed to concentrations of 75, 150 and 300 µg Fe/kg over 20 hours (IITRI 1555, Study 1). PBLs were used under unstimulated as well as PHA- or LPS-stimulated conditions. Concentration-related, however, statistically not significant upregulation of IL-1β and IL-6 was observed in unstimulated PBLs. In PHA- and LPS-stimulated cells IL-1β, IL-2, IL-6 or TNF-α and IL-1β, IL-6 and TNF-α, respectively, were significantly upregulated. Ferumoxytol did not add to cytokine production in stimulated cells. The slight increase of of IL-1β and IL-6 production by ferumoxytol alone was attributed to phagocytic activity of macrophages which is considered conceivable based on in vivo observations.

It should be noted that the concentrations repeatedly are reported as mg/ml in the non-clinical overview and in toxicology-written-summery, which is misleading as it is µg/ml according to the study report IITRI-1555-1. However, the highest concentration of 300 µg Fe/mL only reflected an approximately 2-fold safety margin to the clinically relevant dose of 510 mg dissolved in 3,5 l blood.

Potential immunomodulatory effects were additionally investigated in vivo in female B6C3F1 mice that received single doses of 0.6, 6 or 60 mg Fe/kg (IITRI 1555, Study 3). Endpoints analysed were an antibody-forming cell assay (AFC), a NK assay, a TNF-α assay and Listeria host resistance. A statistically significant decrease in AFCs per million spleen cells was noted in the 60 mg Fe/kg group on day 8. No differences between treatment groups and vehicle control group were observed at the remaining time points and therefore, no effect on antibody-forming cells was attributed to ferumoxytol. With regard to cytotoxic activity to tumor cells (NK assay) statistically significant increases in cytotoxicity were observed on day 8 in two different effector-target cell concentrations in the 60 mg and 0.6 mg Fe/kg groups. Cytotoxicity of all ferumoxytol dose groups was decreased in a single effector-target cell concentration group on day 90. Of note, the effector-target cell concentrations employed on day 90 were completely different to those employed at the other time points. TNF-α production by peritoneal macrophages was not affected by ferumoxytol of any dose if unstimulated. LPS-stimulated macrophages upregulated TNF-α production throughout all dose levels as well as vehicle controls statistically significantly as compared to unstimulated cells. Statistically significantly elevated TNF-α levels were noted occasionally at day 2 and day 90 in the 0.6, 6 and 60 mg Fe/kg groups. The effect was not clearly dose-dependent but apparently higher at earlier time-points after administration. Overall, the ability of macrophages to produce TNF-α in response to stimulation was not impaired.

Host resistance to Listeria monocytogenes was investigated in vivo in B6C3F1 mice that received single doses of 0.6, 6 and 60 mg Fe/kg and were challenged with Listeria monocytogenes 89, 28, 7 and 0 days after ferumoxytol treatment (IITRI Number 1555, Study 4). Mortality was dose-dependent and at the same time decreased with increasing time intervals between ferumoxytol administration and Listeria challenge. Whereas mortality was between 20 – 40% in the vehicle group, it raised up to 80% in the highest dose group 0 or 7 days after ferumoxytol infusion. At the highest time interval no difference between ferumoxytol and vehicle groups were noted. Thus, ferumoxytol appears to have a transient effect on host resistance at the highest dose tested.

In order to evaluate whether the dextran-related PSC coating of ferumoxytol potentially leads to paw edema reaction in rats a respective study was conducted (HHB-148B). Rats received a single dose of 100 mg Fe/kg of three different batches. Minimal swelling was produced by PSC, i.e. maximal 3%, as compared to 58% in animals injected with the positive control dextran T10.

Potential hypersensitivity inducing activity of ferumoxytol was assessed employing passive cutaneous anaphylaxis (PCA), passive haemagglutinin and active systemic anaphylaxis (ASA) tests in guinea pigs (IITRI 1555, Study 2). In none of the tests signs of hypersensitivity or anaphylactic reactions were observed in the ferumoxytol groups as compared to positive controls. Thus, no potential to induce hypersensitivity or anaphylaxis can be attributed to ferumoxytol.

A number of studies was conducted to evaluate the **compatibility with human blood**. Potential influence of ferumoxytol on clotting time was determined in vitro by incubation pooled human plasma for 60 minutes with 0.2, 1.1 and 2.2 mg Fe/mL (HHB-153). These concentrations were indicated to represent 1 to 11 times human plasma concentrations after infusion of 510 mg. Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), and Thrombin Clotting Time (TCT) were determined. All parameters were in the normal range for the 0.2 mg/mL concentration. For the 1.1 and 2.2 mg Fe/mL concentrations, APTT ranged from 22% to 68% prolongation, TCT from 7% to 29% prolongation and PT was maximally prolonged by 5%.

The haemolytic potential of ferumoxytol was evaluated in human whole blood in vitro with concentrations representing the 15- or 30-fold clinical blood concentration, i.e.1.5 and 3.0 mg Fe/mL (HHB-157). The observed haemolytic effect was dose-dependent, however, minimal with 4.5% at the higher dose. No data with the actual estimated clinical blood concentration were generated.

In vitro incubation of ferumoxytol with human plasma and serum did not cause visible flocculation, precipitation or sedimentation at concentrations of up to 15 mg Fe/mL (HHB-158).

In vivo evaluation of potential effects on clotting time in rats revealed after administration of 50 mg Fe/kg a slight prolongation of APTT but no changes in PT and TCT (HHB-154) after administration of a clinically relevant dose of 50 mg Fe/kg (HED= 8.06 mg Fe/kg).

The potential **toxicity of PSC** was evaluated in vivo in rats that received doses of 50, 400, 800, or 1600 mg/kg/day (cumulative doses of 750, 6000, 12,000 or 24,000 mg/kg) for 15 days *(Covance 8245738)*. Body weight and food consumption were not affected by the treatment. Transient swelling of feet, nose and perioral region as well as reddening of feet and ear skin was observed in all but the lowest dose groups. A statistically significant decrease in uterine weights relative to body weight was observed in the highest dose group, however, without morphologic changes. Again in the highest dose groups lung weights were statistically significantly increased. Histology revealed alveolar histiocytosis, perivascular lymphocyte infiltrates, chronic inflammation and haemorrhage. Alveolar histiocytosis and perivascular lymphocytes infiltrates were observed in virtually all dosing groups with dose-dependent severity. An increase in macrophages of mesenteric and mandibular lymph nodes was observed in all but the 50 mg/kg dose group. Vacuolation of renal cortical tubules was observed in all but the lowest dose group, however, without evidence of inflammation or functional impairment. Similarly, periportal vacuolation and slight hepatocellular necrosis were occasionally observed in the highest dose group without correlation in any clinical chemistry parameters.

Further evaluation of the toxicity of PSC in beagle dogs that received doses of 15, 120, 375, or 750 mg PSC/kg/day (cumulative doses of 210, 1680, 5250 or 10,500 mg PSC/kg) for 14 days did not reveals any adverse clinical signs or effects on body weight and food consumption (Covance 8245739). Occasional increased weight of pituitary glands in relation to body weights was observed, however, without related histopathologic findings. Renal tubular vacuolation was observed in the two high dose

level but again without pathological correlates. Thus, the NOAEL for PSC in dogs was determined at 750 mg/kg/day.

3.1.5. Ecotoxicity/environmental risk assessment

The Applicant provided a justification for not performing specific **ERA** studies. A calculation of the predicted environmental concentration was performed that resulted in a PEC value of 0.014 µg/L, which is slightly above the action limit of 0.01 µg/L. The Applicant argues that this calculation is based on the assumption that all infused iron is excreted via urine or feces which is obviously not the case. Nevertheless, it is emphasized that the environmental risk assessment categorically does not take into account metabolism or similar processes but always assumes 100% excretion. It is also stated the iron contained in Ferheme is present in its electrolytical form, which is not supported as the major part of iron is present in a bound form. Thus, the reference to electrolytes listed in the Guideline along with other substance classes not requiring an ERA is not supported. Further, the Applicant argues that iron is ubiquitously present in the environment. This is agreed and iron is regarded a naturally occurring substance. Thus, the use of ferumoxytol is not considered to substantially increase environmental iron concentrations or to pose a risk to the environment. The polyglucose sorbitol carboxymethylether (PSC) coating is not naturally occurring, however, consists of the natural carbohydrates glucose and sorbitol. The α-1,6 glycosidic linkages of the PSC molecule be cleaved by glycosidases both of which are found in a wide variety of organisms. Thus, PSC is considered to pose no risk to the environment.

Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}			N/A
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.014	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)

3.1.6. Discussion on non-clinical aspects

Pharmacodynamic:

The mode of action of ferumoxytol is well-established and similar in principle to other i.v. formulations on the market. However, ferumoxytol is also developed for imaging and is actually administered in its superparamagnetic form. This has not been discussed by the applicant in terms of clinical safety (**OC**).

Iron deficient diet induced anaemia in rats was shown to be corrected by bioactive iron released from intravenously administered ferumoxytol. No harmful CNS, pulmonary and renal effects were detected in the provided safety pharmacology studies.

Ferumoxytol had no effect on arterial blood pressure (systolic, diastolic and mean), heart rate, femoral artery blood flow and ECG parameters in the safety study (E992-920) with anaesthetized beagle dogs (ferumoxytol IV at doses of 4, 40 and 200 mg Fe/kg). However, in light of the incidents of both serious

and fatal cases of hypersensitivity in clinical practice, the rodent and hERG cardiovascular safety assays did show some minor observations, which should be further discussed by the applicant (**OC**)

Moreover, there were vehicle associated increases in diuresis, minor effects on creatinine clearance, natriuresis and urinary potassium and chloride excretions. Due to the Applicant, these changes can be attributed to the mannitol composition of the vehicle. No further explanation was given on this finding. The Applicant is asked to provide a justification and/or a compilation of published data in order to support this statement with respective information (**OC**).

In regard of the nature of ferumoxytol as an iron preparation and its basic similarity to other parenteral iron medicinal products used in clinical practice nowadays, the preclinical pharmacology programme provided by the Applicant is deemed sufficient.

Pharmacokinetics:

The validation of the TD-NMR spectroscopy for rat serum, dog serum, rat milk and rat plasma took place before issuing of the current guideline. Hence deficiencies such as lack of incurred sample reproducibility can be accepted. However, it appears that serum concentrations much lower than 17 µg/mL were reported for toxicokinetics and were included in the toxicokinetics calculations in both the rat and dog 13-weeks toxicity study. that the inclusion of data below lower limit of quantification for toxicokinetic evaluation should be justified (**OC**).

Exposure after single or repeated i.v. administration was dose dependent in all species investigated. Whereas C_{max} increased generally dose-proportional, AUC_{0-24} increased in a more than dose-proportional manner, especially in rats, pointing towards accumulation.

Ferumoxytol was initially mainly distributed to the plasma followed by rapid decline in plasma levels and finally an increase in iron levels due to redistribution to red blood cells. The main target organs for tissue distribution were spleen, liver, lymph nodes and bone marrow or, more precisely to phagocytic cells residing in these tissues.

The only studies under "Metabolism" are studies comparing amount of free iron in ferumoxytol with other parenteral iron products on the market. These are important safety studies, since free iron can induce free radical reactions. The amount of free iron in ferumoxytol appears to be in the low end comparable to dexferrum, the first coated iron treatment for infusion (dextran). Whether the amount of free iron determined in ferumoxytol could saturate transferrin at clinically relevant doses was not discussed (**OC**).

Metabolism of PSC was not discussed. This should be justified (**OC**).

Excretion of iron via urine and feces was negligible over the first 48h after administration. Terminal examination revealed that a considerable amount of iron was retained in the carcass in various tissues presumably including red blood cells.

The Applicant states that iron excreted via milk has not been separated from PSC. This is not really comprehensible as maximum levels of ^{14}C and ^{59}Fe have been observed at different time points after administration, i.e. 8 hours and 24 hours post-dose, respectively, an should be further clarified (**OC**).

Toxicology:

Single- and repeat-dose toxicity studies were conducted in rats and dogs. The most apparent finding related to ferumoxytol-administration was discoloration of various parts of the skin and internal organs secondary to iron disposition. In internal organs iron disposition was confined to reticuloendothelial and other phagocytic cells. No information was provided on the tissue type iron was retained in in the skin. In addition, the fate of the iron taken-up by phagocytes has not been addressed in the dossier and should

be further discussed (**OC**). Associated with the iron-disposition and clearance by phagocytic cells a significant increase in organ weights of liver, gallbladder and spleen was observed. These phagocytic infiltrations were not associated with signs of inflammation and, therefore, not considered adverse. In study Covance 6782-108 female rats administered 18 and 37 mg Fe/kg/day for 4 weeks haemorrhage, haemorraghic necrosis, chronic inflammation and bile duct hyperplasia were observed. The Applicant is invited to explain how the causality of these dose-dependent events relates to the test article and discuss the clinical relevance of the finding (**OC**). Adversity was attributed to the test-article related effects on food consumption, body weight gain and body weight that were dose-related and often persisted through the recovery period. In this context it was noted that in study Covance 6782-114 significantly decreased body weight throughout the recovery period was not considered adverse as compared to other repeat-dose toxicity studies. This is not agreed. Additionally, significant increases in liver enzymes (ALT, AST, ALP and GGT) were noted at 12 mg/kg in all animals. In the light of the liver findings from the 4-week study in female rats, this could be predictive of initial hepatotoxicity even though no histopathology were noted. Thus, the NOAEL of 12 mg/kg in rats is not supported and the NOAEL for this study should therefore be set at 6 mg Fe/kg (**OC**). Lowering the NOAEL to 6 mg Fe/kg would provide a safety margin of approx. 5-fold to the human clinical doses, which is acceptable.

No organ or tissue toxicities were observed upon long term daily administration of ferumoxytol of doses largely exceeding the clinical dose, i.e. a cumulative dose of 5,040 mg/kg over 14 days in rats vs. approximately 40 mg/kg within 2 to 8 days as maximum dose in humans.

Cumulative doses have been used for the repeat-dose studies throughout the dossier for comparison to human equivalent doses, which is an unusual approach. In the non-clinical overview, the following was stated regarding this approach: Since iron is highly conserved, values of Cmax and AUC underestimate systemic exposure, and cumulative doses provide a better index of exposure. This was, however, not substantiated by data or further discussed by the applicant. In order to substantiate this approach, the applicant is asked to provide a comparison of cumulative dose from the 13-week repeat-dose studies in rats and dog to human clinical doses (HED) using the specific animal scalation factor (FDA Guidance for industry, estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult heathy volunteers, July 2005, Pharmacology and toxicology). Additionally, a comparison between systemic exposure in humans and systemic exposure in the animals from the 13-week TK studies based on AUClast measurements should be provided. The two methods of comparing data should be held against each other and safety margins should be discussed and compared for both approaches (**OC**).

No evidence for in vitro genotoxicity and in vivo clastogenic activity was observed for ferumoxytol and the conduct of carcinogenicity studies is not warranted considering the non-chronic dosing schedule.

Reproduction and early embryo-fetal development were not affected by doses of up to 18 mg Fe/day, however, as already observed in the repeat-dose toxicity studies parental food consumption and body weight were adversely influenced by ferumoxytol in the rat. Developmental toxicity was observed starting from doses of 31.6 mg/kg/day and involved skeletal malformations as well as delayed or accelerated ossification in rats. Similarly, skeletal as well as more severe brain malformations were observed in rabbit foetuses at a maternal dose level of 45.4 mg/kg/day. The Applicant states that the observation of wavy ribs in rats in study Covance 6782-111 is a common variation considered to be reversible or transitory and consistent with smaller foetuses which is in principle agreed. However, wavy ribs were accompanied by accelerated and delayed ossification of various sites, and teratogenicity of ferumoxytol was clearly demonstrated in rabbits. The Applicant is therefore asked to determine and justify a NOAEL for the Covance 6782-111 study and to reconsider to extend the following SmPC wording to include the observed changes in ossification: Administration of <Invented Name> during organogenesis in rats at maternally toxic doses of 100 mg Fe/kg/day caused a decrease in foetal weights and doses from X mg Fe/kg/day resulted in foetal changes characterized by wavy ribs, accelerated and/or delayed ossification at various sites (e.g. vertebra, sternebra, pubis and vertebra arch) (**OC**).

In the EFD study in rabbits (Covance 6782-110), abortions and clear teratogenic or foetotoxic effects was noted at doses of 45.3 mg Fe/kg. The cluster of malformations consisted of absent brains (anencephaly), hydrocephalus, dome shaped head and malrotated/flexed limbs. Additionally, cleft palate and macroglossia was also noted. Incomplete ossification of the skull and skeletal variations in vertebra, sternebra and ribs correlated with findings from the rat study. In addition to the observed malformations, mean foetal weight was significantly decreased for the whole group compared to both control and historical data.

It can be concluded that clear teratogenic or foetotoxic effects were observed at dose of 45.3 mg/kg, while the maternal effect was limited to decreased body weight gains. Results indicated that especially the developing foetal brain is a major target organ for Ferumoxytol and this should be further addressed by the applicant (**OC**). Doses of 6 or 16.5 Fe mg/kg administered during organogenesis did not affect dams or foetal development. Thus, NOAEL were set to 16.5 mg/kg with a cumulative dose of 231 mg/kg, however, this only provided a safety margin to HED of 4.4-fold.

Relevant data and warnings have been included in the SmPC section 4.6 and 5.3, however, due to the severe character of the teratogenic effect it must be ensured that the EFD findings are clearly communicated in the SmPC and do not drown in other study information. Additionally, safety margin to HED should be presented in section 5.3 instead of just HEDs, as these are concerningly low compared to the severity of the findings (absent brains, hydrocephalus, dome shaped head, malrotated/flexed limbs) (**OC**).

Administration of ferumoxytol through gestation and lactation statistically significantly reduced maternal weight during the gestation and lactation period at doses of 60 mg/kg. Additionally, a dose-related decrease was seen in neonatal body weight at doses of 30 and 60 mg/kg. F1 pups of both genders exhibited delayed sexual maturation (i.e. vaginal opening and preputial separation) and reduced reproductive performance in the 60 mg/kg group for males and the 30 and 60 mg/kg group for females. Furthermore, disruption of the oestrus cycle was noted in F1 females at doses ≥10 mg Fe/kg, however, only a limited number of animals were examined, making it difficult to conclude on the prevalence. The overall NOAEL for the PPND was set to 10 mg Fe/kg, which provides a safety margin of 3,3-fold to HED. However, the potential underlying mechanisms and the clinical relevance of the effect of ferumoxytol on delayed sexual maturity, prolonged oestrus and reduced reproduction competence in the F1 offspring was insufficiently addressed by the applicant. Also, in the non-clinical overview results from PPND studies in other iv iron-products (Ferrlecit and Ferinject) has been presented, however, with the exception of a delayed vaginal opening for Ferrlecit, these products do not appear to cause similar effects on oestrus cycle and reproduction competence and this should be discussed by the applicant (**OC**).

The effects on immune cells or function were examined in the scope of various assays and studies conducted on immunotoxicity without any apparent effect according to applicant. However, in the study evaluating cytokine release from peripheral blood leukocytes (PBL) (IITRI-1555-1) a slight but non-significant increase in IL-1β and IL-6 was noted at the highest concentration of 300 µg Fe/mL, which only reflected an approximately 2-fold safety margin to the clinically relevant dose of 510 mg dissolved in 3,5 l blood. As a higher concentration of ferumoxytol potentially could be expected at the site of injection, the applicant was asked to address the choice of doses in the context of the clinical history of anaphylactic reactions (**OC**).

A transient reduction of host resistance to Listeria monocytogenes infection were noted in study 4 (IITRI Number 1555) at the highest dose tested. However, the doses with which the study was conducted, appear to be much lower than the human clinically relevant dose questioning the relevance of the study (the highest dose of 60 mg Fe/kg corresponds to a HED of 4.8 which is lower than the human single dose of 8.5 mg Fe/kg). This also applies for study 3 (IITRI 1555). Moreover, in light of the apparent increased risk for infections with ferumoxytol as compared to iron sucrose (e.g. clinical study CKD-401,

clinical safety OC), the mechanism of action and clinical relevance of these data should be further discussed (**OC**).

In the paw edema study (HHB-148B), a small swelling did occur even though it was less (3%) than for Dextran T70 (58%). Since paw swelling was also observed in the single-dose study at doses of 450 mg Fe/kg and cases of anaphylaxis and hypersensitivity was seen in the clinical history of ferumoxytol this should be further addressed. Additionally, the translational value of the study should be discussed with respect to the animal species, choice of dose, lack of multiple escalating dose levels and safety margins to expected human exposure of a possible anaphylactoid response of ferumoxytol (**OC**). Ferumoxytol did not appear to influence coagulation parameters at the intended dose level and slightly prolonged coagulation time at concentrations up to the 10-fold clinical dose.

PSC alone did not cause adverse events at doses of up to 1600 mg/kg administered daily for 15 days. Swelling of paws is a finding consistent with study HHB-148B, where the immunotoxicity of PSC was evaluated after a single administration of 100 mg Fe/ kg. Oedema is a known side effect of dextran-related compounds and with regard to paw swelling, as observed in study Covance 8245738, subject to adaptive compensation over a longer administration period. Nevertheless, lung weights were increased in a dose-dependent manner with signs of inflammations. Lung oedema as a consequence of iron dextran administration is occasionally observed in dialysis patients (Freter et al., 1997). The Applicant should therefore specify, whether signs of lung oedema in addition to paw oedema were observed in rats. Furthermore, the NOAEL of 1600 mg PSC/kg/day should be re-evaluated (**OC**).

In all repeat dose studies in both rats and dogs, discoloration and accumulation of iron pigment in eyes (conjunctiva, sclera) and skin were seen. These changes should be addressed with respect to a potential need for phototoxicity testing (**OC**).

3.1.7. Conclusion on non-clinical aspects

No major objections regarding the non-clinical aspects of Ferumoxytol were identified. Several other concerns are implemented in the "List of questions". There are no objections to authorisation of this medicinal product providing there is adequate resolution of the outstanding concerns.

3.2. Clinical aspects

- **Tabular overview of clinical studies**

Table 1 Synopses of Individual Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Studies in Healthy Volunteers									
Phase I, PK and safety	7228-01 "A Phase I clinical investigation of Code 7228" Start date: 09-June-1999 Completion date: 04-August-1999	Module 5.3.3.1	To evaluate the PK and safety of ferumoxytol at increasing dose levels and at various rates of administration	Randomised, double-blind, placebocontrolled, single center, ascending dose	Ferumoxytol. 1 mg Fe/kg 2 mg Fe/kg 4 mg Fe/kg; IV	N=41 (randomised) Ferumoxytol- 35; Placebo - 6	Healthy volunteers M: 22 F: 19	Single dose	Complete. Full report CSR 7228-01
Phase I Thorough QTc and PK	62,745-9 "A Phase I active and placebocontrolled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women" Start date: 22-May-2006 Completion date: 4-September-2006	Module 5.3.4.1	To define the effect of ferumoxytol on the QT interval; to assess PK and tolerability	Active- and placebocontrolled, randomised, double-blind (with respect to ferumoxytol and placebo), parallel group, single-center	Ferumoxytol: Two 510 mg doses of ferumoxytol administered on two consecutive days Placebo (saline): IV Moxifloxacin (400 mg) as active control: Oral	174 Total (randomised) Ferumoxytol - 58; Moxifloxacin - 58; Placebo-58	Healthy volunteers M: 102 F: 72	2 x 510 mg doses of ferumoxytol administered on two consecutive days	Complete. Full report CSR-62745-9
Studies in Patients with Chronic Kidney Disease									
Phase I	62,745-2	Module	The objective	Open-label,	Ferumoxytol.	20 Total	Patients	Single dose	Complete.

PK and safety	"A Phase I open-label, rate administration, pharmacokinetic study of the safety of Code 7228 as an iron replacement therapy in chronic haemodialysis patients who are receiving supplemental EPO therapy" Start date: 26-Sep-2001 Completion date: 10-Apr2002	5.3.3.2	of this study was to evaluate the safety and PK of two doses (125 and 250 mg) of ferumoxytol in subjects with CKD stage 5D who were on HD and receiving supplemental EPO therapy	single center; Uncontrolled	1 x 125 mg 1 x 250 mg; IV	(enrolled) Ferumoxytol 125 mg – 10; Ferumoxytol 250 mg - 10	with CKD stage 5D on haemodialysis M: 10 F: 10		Full report CSR-62745-2
Phase II, Safety/ Efficacy	62,745-3 "A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Code 7228 (Compared With Oral Iron) as an Iron Replacement Therapy in Chronic Haemodialysis Patients Who Are Receiving Supplemental EPO Therapy"	Module 5.3.5.1	To evaluate the safety and efficacy of two parenteral dose regimens of ferumoxytol compared with oral iron	Multicentre, open label; Active control	Ferumoxytol: 8 x 128 mg 2 x 510 mg; IV Oral iron: 325 mg per day	36 Total (enrolled) Ferumoxytol 8 x 128 mg - 15; Ferumoxytol 2 x 510 mg – 11; Oral iron - 10	Patients with CKD stage 5D on haemodialysis M: 21 F: 15	8 x 128 mg doses of ferumoxytol within 4 weeks; 2x 510 mg of ferumoxytol within 2 weeks; daily oral iron for 8 sequential dialysis sessions (approx. 3 weeks)	Complete; Full report CSR-62745-3

	Start date: 20-Jan-2003 Completion date: 19-June-2003								
Phase II, Safety/ Efficacy	62,745-4 "A Phase II, Open-Label Study of the Safety and Efficacy of Two Parenteral Dose Regimens of Code 7228 (Ferumoxytol) as an Iron Replacement Therapy in Chronic Kidney Disease Patients or Patients on Peritoneal Dialysis" Start date: 07-Oct-2002 Completion date: 27-Dec-2002	Module 5.3.5.2	To evaluate the safety and efficacy of two parenteral dose regimens of ferumoxytol in subjects with chronic renal failure (not on dialysis), or who were on PD	Multicentre, open label; Uncontrolled	Ferumoxytol; 4 x 255 mg 2 x 510 mg; IV	21 Total (enrolled) Ferumoxytol 4 x 255 mg - 10; Ferumoxytol 2 x 510 mg - 11	Patients with CKD stages 1-5 not on haemodialysis M: 9 F: 12	4 x 255 mg of ferumoxytol each separated by 2-3 days: 2 x 510 mg doses of ferumoxytol each separated by 2-3 days	Completed; Full report CSR-62745-4
Phase III, Safety/ Efficacy	62,745-5 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron as an iron replacement therapy in subjects with CKD stage 5D	Randomised, multicentre, open label; Active control	Ferumoxytol: Post-amendment: 2 x 510 mg; Pre-amendment: 4 x 255 and 2 x 510 mg IV	378 Total (randomised) Post-amendment: 230 Total; Ferumoxytol 114; Oral Iron-116	Patients with CKD stage 5D on haemodialysis Post-amendment: M: 130	2 x 510 mg doses ferumoxytol within 7 days; 4 x 255 mg doses of ferumoxytol, within 14 days; or oral iron for 21	Complete; Full report CSR 62745-5

	Therapy in Haemodialysis Patients who are Receiving Supplemental Erythropoietin Therapy" Start date: 09-Aug-2004 Completion date: 24-Apr-2007		on HD who were receiving supplemental ESA therapy		Oral iron: 200 mg per day	Pre-amendment: 148 Total; Ferumoxytol 4 x255 mg – 62; Ferumoxytol 2x510 mg - 64; Oral Iron - 22	F: 100 Pre-amendment: M: 63 F: 85	consecutive days	
Phase III, Safety/ Efficacy	62,745-6 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in chronic kidney disease patients not on dialysis" Start date: 10-May-2004 Completion date: 25-Sep-2006	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in subjects with CKD stages 1-5	Randomised, multicentre, open label; Active control	Ferumoxytol; 2 x 510 mg; IV; Oral iron: 200 mg per day	304 Total (randomised) Ferumoxytol - 228; Oral Iron - 76	Patients with CKD stages 1-5 M: 118 F: 186	2 x 510 mg doses of ferumoxytol within 5±3 days, or 21 consecutive days of oral iron	Complete; Full report CSR-62745-6
Phase III, Safety/ Efficacy	62,745-7 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron	Module 5.3.5.1	To evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in	Randomised, multicentre, open label; Active control	Ferumoxytol; 2 x 510 mg; IV Oral iron: 200 mg per day	304 Total (randomised) Ferumoxytol - 227; Oral Iron – 77	Patients with CKD stages 1-5 M: 125 F: 179	Two IV doses of ferumoxytol within 5±3 days, or 21 consecutive days of oral iron	Complete; Full report CSR-62745-7

	Replacement Therapy in chronic kidney disease patients not on dialysis" Start date: 02-June-2004 Completion date: 20-Dec-2006		subjects with CKD stages 1-5						
Phase III, Safety	62,745-8 "A Double Blind, Placebo Controlled, Crossover Design, Multicentre Study of Intravenous Ferumoxytol Compared with Placebo" Start date: 27-Jan-2005 Completion date: 6-Sep2006	Module 5.3.5.1	To compare the safety of a single 510 mg dose of IV ferumoxytol versus a single dose of IV saline placebo in subjects with all stages of CKD	Randomised, multicentre, double-blind, placebo controlled, crossover design	Ferumoxytol; 1 x 510 mg; IV Placebo (saline) IV	N=750 (randomised)	Patients with CKD stages 1-5 and 5D M: 347 F: 403	A single dose, followed by the crossover dose 7±2 days later	Complete; Full report CSR-62745-8
Phase II	FER-CKD-201 "Ferumoxytol Compared to Iron Sucrose Trial (FIRST): A Randomised, Multicentre, Trial of Ferumoxytol Compared to Iron Sucrose for the Treatment of	Module 5.3.5.1	To evaluate safety and efficacy of intravenous (IV) ferumoxytol compared to IV iron sucrose for the treatment of IDA in subjects with CKD	Randomised, open-label, active-controlled, multicentre clinical trial	Ferumoxytol: 510 mg (17 mL) at Day 1 and a second injection of 510 mg (17 mL) 5±3 days after Dose 1 IV Iron Sucrose: Subjects on	162 subjects randomised 80 subjects received ferumoxytol 82 received iron sucrose	Adult subjects with IDA and CKD	Maximum length of subject participation in the study was 7 weeks, which included a 2- week (14-day) Screening Period and 5-week (35±2	Complete; Full report: CSR FER-CKD-201

	Iron Deficiency Anaemia in Adult Subjects with Chronic Kidney Disease" First subject randomised: 01Mar2010 Last subject completed (last visit): 19Jul2011		Primary Objective • To evaluate the safety of a 1.02 g course of IV ferumoxytol compared to a 1.0 g course of IV iron sucrose Additional Objective • To evaluate the efficacy of ferumoxytol compared to iron sucrose by assessing changes in haemoglobin from Baseline to Week 5		HD received either slow IV injection or IV drip infusion of 100 mg at Day 1 and at following 9 consecutive HD sessions for total cumulative dose of 1.0 g Subjects not on dialysis received either slow IV injection or IV drip infusion 200 mg at Day 1 and at 4 subsequent visits on nonconsecutive days over a 14- day period for a total cumulative dose of 1.0 g			days) Treatment Period	
Phase IV	CKD-401 "Ferumoxytol for Anaemia of CKD Trial (FACT): A Phase IV, Open-Label, Multicentre Trial, with MRI Substudy, of Repeated Doses of Ferumoxytol Compared with Iron Sucrose for	Module 5.3.5.1	To evaluate safety and efficacy of repeated doses of intravenous (IV) ferumoxytol compared to IV iron sucrose for the treatment of IDA in subjects	Randomised, open-label, active-controlled, multicentre clinical trial	Ferumoxytol: 2 x 510 mg; IV. Iron sucrose: Total cumulative doses of 1.0 g mg per day (10 administrations of 100 mg IV)	293 subjects randomized 196 subjects received ferumoxytol 97 received iron sucrose	Adult subjects with IDA and CKD in HD	Following the initial 5-week TP, subjects entered the 11-month Monthly Observation Period during which they were serially evaluated for IDA. Subjects who had	Complete; Full report: CSR FER-CKD-401

	the Treatment of Iron Deficiency Anaemia (IDA) in Chronic Kidney Disease (CKD) Patients on Haemodialysis"		with CKD					persistent or recurrent IDA, at any Monthly Observation Visit or final visit (Week 5) of any TP, entered another TP and were treated again with an additional course of their randomised treatment.	
Studies in Medical Imaging Subjects (Patients and Healthy Volunteers)									
Phase I/IIA, Safety	58,254-2 "A Phase I/IIa Pilot Investigation Of Code 7228 As A Magnetic Resonance Angiography Contrast Agent" Start date: 01-Nov-2001 Completion date: 11-May-2002	Module 5.3.5.4	To evaluate the safety and imaging feasibility of ferumoxytol	Open label, single center, Uncontrolled	Ferumoxytol; ≤4 mg Fe/kg; IV	17 Total (enrolled) Healthy volunteers – 10; Imaging patients – 7	Healthy volunteers and imaging patients M: 12 F: 5	Single dose	Complete; Abbreviated report CSR-58254-2
Phase II, Safety	58,254-5 "A Phase 2 Investigation of Code 7228 as a Magnetic Resonance Angiography Contrast Agent" Start date:	Module 5.3.5.4	To evaluate the safety and imaging feasibility of ferumoxytol	Open label, single center; Uncontrolled	Ferumoxytol; ≤4 mg Fe/kg; IV	49 Total (enrolled) Healthy volunteers - 15; Imaging patients – 34	Healthy volunteers and imaging patients M: 29 F: 20	Single or incremental dose within the same imaging session	Complete; Abbreviated report CSR-58254-5

	7-Aug-2002 Completion date: 6-Sep2005								
Phase II	FER-PAD-001 A Phase II, Open Label, Randomised, Multicentre Trial Comparing Noncontrast MRA versus Ferumoxytol Vascular Enhanced MRI (VE-MRI) for the Detection of Clinically Significant Stenosis or Occlusion of the Aortoiliac and Superficial Femoral Arteries in Subjects with Peripheral Arterial Disease Scheduled for Digital Subtraction Angiography (DSA)	N/A – Study ongoing	To assess the sensitivity and specificity of ferumoxytol vascular enhanced magnetic resonance imaging (VEMRI) and noncontrast magnetic resonance angiography (MRA) in detecting ≥ 50% stenosis of the aortoiliac and superficial femoral arteries as seen on digital subtraction angiography (DSA)	Open label, randomised, multicentre Uncontrolled	Ferumoxytol 1.0 Fe mg/kg 2.5 Fe mg/kg 4.0 Fe mg/kg IV	108 Planned	Subjects with PAD (based on an anklebrachial index ≤ 0.90)	Single dose	Ongoing N/A
Studies in Patients with All-Cause Iron Deficiency Anaemia									
Phase III	AMAG-FER-IDA-301 "A Phase III Randomised, Double-Blind, Placebo-Controlled Trial of Ferumoxytol	Module 5.3.5.1	The objective of this study was to evaluate the efficacy and safety of a 1.02g course of intravenous	Phase III, randomised, double-blind, placebo-controlled, multicentre clinical	Ferumoxytol: Two separate injections of 510mg, the first at Baseline (Day 1) and the second 2 to 8	808 subjects randomised and treated, in a 3:1 ratio into one of two Treatment Groups: ferumoxytol (608 subjects) or	Adult patients with IDA and with a history of unsatisfactory oral iron	The maximum length of subject participation was 7 Weeks, which included up to a 14-day	Complete; Full report: CSR-AMAG-FER-IDA-301

	for the Treatment of Iron Deficiency Anaemia" First subject enrolled: 19-Jun-2010 Last subject completed : 27-Feb-2012		(IV) ferumoxytol administered as two doses of 510 mg each, compared with placebo (normal saline) for the treatment of iron deficiency anaemia (IDA) in adult patients with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.	study	days later. IV Placebo: Two separate injections, the first at Baseline (Day 1) and the second 2 to 8 days later. IV	placebo (200 subjects)	therapy or in whom oral iron could not be used	Screening Period and a 35- day (±2 days) Treatment Period	
Phase III	AMAG-FER-IDA-302 "A Phase III, Randomised, Open- label, Active-Controlled Trial Comparing Ferumoxytol with Iron Sucrose for the Treatment of Iron Deficiency Anaemia" First subject enrolled: 10Aug2010	Module 5.3.5.1	The objective of the study was to evaluate the efficacy and safety of a 1.02 g course of IV ferumoxytol, administered as 2 doses of 510 mg each, compared with 1.0 g of IV iron sucrose, administered as 5 doses of 200 mg each for the	Phase III, randomised, open-label, active-controlled, multicentre clinical trial	Ferumoxytol: One dose of 510 mg (17 mL) on Day 1 followed by a second dose, 2 to 8 days later, for a total cumulative dose of 1.02 g IV injection iron sucrose: One dose of 200 mg (10 mL) on 5 non-consecutive	605 subjects were randomised in a 2:1 ratio into one of two Treatment Groups: ferumoxytol (406 subjects) iron sucrose (199 subjects).	Adult patients with IDA and with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used	The maximum length of subject participation was 7 Weeks (51 days), which included up to a 14-day Screening Period and a 35- day (±2 days) Treatment Period.	Complete; Full report: CSR-AMAG-FER-IDA-302

	Last subject complete d: 09Nov20 11		treatment of iron deficiency anaemia (IDA) in patients with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.		days over a 14- day period, for a total cumulative dose of 1.0 g. IV injection				
Phase III, Extensi on	AMAG-FER-IDA-303 "A Phase III, Open- Label Extension Trial of the Safety and Efficacy of Ferumoxytol for the Episodic Treatment of Iron Deficiency Anaemia" First subject enrolled: 27Jul201 0 Last subject complete d: 24Sep20 12	Module 5.3.5.1	The purpose of this study was to evaluate the safety and efficacy of ferumoxytol for the episodic treatment of IDA over a 6-month period in adult patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used	Phase III, open- label Extension Study of the Phase III study AMAG-FER- IDA-301	Ferumoxytol: Two doses given as 1 dose of 510 mg (17 mL) at Baseline followed by a second one 2 to 8 days after the first and then as needed over a 6 month observation period, IV injection	A total of 634 subjects enrolled in the Extension Study and comprised the Safety Population; 337/634 (53.2%) subjects received ferumoxytol (ITT Population) and 297/634 (46.8%) did not receive ferumoxytol	Adult patients with IDA and with a history of unsatisfact ory oral iron therapy or in whom oral iron could not be used	The maximum length of subject participation was approximately 6 months, which included a 14-day Screening Period and 6-month Observation Period	Complete; Full report: CSR-AMAG-FER-IDA-303
Phase III	AMAG-FER-IDA-304 "A Phase III, Randomised, Multicentre, Double- Blind,	Module 5.3.5.1	To evaluate the safety of 1.020 g of intravenous (IV) ferumoxytol,	Phase III, randomised, double-blind, active-controlled, multicentre	Ferumoxytol: IV infusion of 510 mg diluted (17 mL) in 233 mL 0.9% sodium	A total of 2014 subjects were randomised in a 1:1 ratio to study drug (1997 subjects received	Adult patients with IDA in whom intravenou s iron	The maximum length of study participation was 9 weeks,	Complete; Full report: CSR-AMAG-FER-IDA-

	Safety Study of Ferumoxytol Compared to Ferric Carboxymaltose for the Treatment of Iron Deficiency Anaemia (IDA) First subject enrolled: 29Feb2016 Last subject completed: 16Jan2017		administered as 2 doses of 510 mg each, compared to 1.500 g of IV ferric carboxymaltose (FCM), administered as 2 doses of 750 mg each for the treatment of IDA in subjects with a history of unsatisfactory oral iron therapy or in whom oral iron could not be tolerated, or in whom oral iron was considered medically inappropriate	clinical trial	chloride injection, USP (normal saline) to a final volume of 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.020 g. FCM: IV infusion of 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) to a final volume 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.500 g.	study drug). Prior to administration of study drug, 9 (0.9%) subjects randomised to ferumoxytol and 8 (0.8%) subjects randomised to FCM withdrew from the study. Both the Safety- and ITT-populations comprised 997 subjects in the ferumoxytol group and 1000 subjects in the FCM group	treatment was indicated and had a documented history of unsatisfactory oral iron therapy or in whom oral iron cannot be tolerated, or for whom oral iron is considered medically inappropriate.	which consisted of 5 study visits for subjects randomised: Screening (up to 30 days prior to Day 1 or on Day 1 prior to any procedures), Day 1 (Baseline, Dose 1), Day 8 (+1) (Dose 2; 7 to 8 days post Day 1), Week 2 (Day 14±2 days post Day 1), and Week 5 or Early Termination Visit (Day 35±2 days post Day 1).	304

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

3.2.1. Clinical pharmacology

3.2.1.1. Pharmacokinetics

Ferumoxytol is an aqueous colloidal solution of polyglucose sorbitol carboxymethyl ether (PSC)-coated iron oxide particles that has been developed as an intravenous (IV) iron supplement for the treatment of iron deficiency anaemia (IDA) in patients with chronic kidney disease (CKD) as well as in patients with all cause IDA when oral iron preparations are ineffective or cannot be used.

A single formulation containing 30 mg/mL of elemental iron and 44 mg/mL of mannitol was used via IV administration in all clinical studies to-date and represents the to-be-marketed formulation, which will be available in a single use, 20 ml vial size.

The PSC coating stabilizes the colloidal iron oxide, controls the release of iron and minimizes free iron and immunological reactivity, thus providing a form of bioavailable iron that can be administered rapidly at high doses without dilution.

The clinical pharmacology of ferumoxytol was assessed in three Phase I studies. Studies 7228-01 and 62,745-9 (a thorough QT Study) were conducted in healthy volunteers; Study 62,745-2 was conducted in subjects with CKD stage 5D on haemodialysis. The studies examined doses ranging from 1 mg/kg (about 85 mg) to two doses of 510 mg (the intended clinical dosing regimen) in healthy volunteers and single doses of 125 mg to 250 mg in subjects with CKD 5D on haemodialysis. Together, these studies investigated:

• single and multiple IV doses of ferumoxytol in healthy volunteers,

• increasing rates of IV administration of a fixed dose of ferumoxytol in healthy volunteers,

• single IV doses of ferumoxytol in HD patients receiving erythropoietin (EPO) therapy, and

• the pharmacodynamic (PD) effect of ferumoxytol on cardiac electrophysiology (specifically, QT/QTc prolongation) subsequent to the administration of a supratherapeutic dosing regimen to healthy volunteers (see PD section).

The three clinical pharmacology studies were performed in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and the protocols approved by the responsible Institutional Review Board (IRB).

There was no requirement for other Clinical Pharmacology trials (ie, drug-drug interaction studies) owing to its IV route of administration, thus bypassing absorption processes and related variability, and its lack of potential for metabolic liability: for example, via conventional phase 1 and 2 metabolic enzymes and/or transporters.

No other Clinical Pharmacology or clinical PK studies were conducted since the original submission, which focused on the CKD indication.

However, an additional population PK analysis was completed using all of the available ferumoxytol PK data, allowing potential differences across the HV and CKD populations to be explored. This analysis expanded upon the previous population PK analysis performed on data from a single study (Study 62,745-9) as reported in the previously approved registration dossier.

As the PK in the all-cause IDA population was not expected to differ from that of HVs or CKD patients, no further Clinical Pharmacology or clinical PK studies were conducted.

Table 2 Summary of Mean (SD) ferumoxytol Pharmacokinetic Parameters from all Pharmacokinetic Studies

Parameter	**Study 7228-01**			**Study 62,745-9**			**Study 62,745-2**		**Population PK model**
Subjects	HV			HV			CKD 5D on HD		All
Dose	1 mg/kg (85.3 mg[b])	2 mg/kg (152 mg[b])	4 mg/kg[a] (316 mg[b])	Two 510 mg doses			125 mg	250 mg	All
Analysis Method	NCA	NCA	NCA	NCA (individual data)	NCA (popPK-model simulated data)	NONMEM[c] v6	NCA	NCA	NONMEM[c] v7
N	8	8	17	58	1	58	10	10	91 HVs, 20 CKD
AUC0–∞ (µg·hr/mL)	365 (128)	996 (313)	2930 (685)	15400 (3750)[d]	14800[d]	--	--	--	CKD HD: 5000 non-HD: 5840 HVs: 6040
Cmax (µg/mL)	27.0 (7.7)	62.2 (12.0)	138 (34)	206 (41), 301 (52)[f]	187, 281[f]	--	40.0 (13.27)[e]	85.8 (27.06)[e]	CKD: HD: 188 non-HD: 203 HVs: 209
t½ (hr)	9.7 (2.0)	11.4 (1.6)	14.9 (2.0)	19.0 (4.6)[g]	15.8[g]	49.6, 10.2[h]	--	--	CKD HD: 19.9 non-HD: 20.3 HVs: 20.2
CL (mL/hr)	265 (118)	164 (56)	110 (24)	69.1 (13.9)[g]	69.1[g]	37.9, 185[h]	--	--	--
CL/weight (mL/hr/kg)	3.15 (1.52)	2.18 (0.66)	1.44 (0.32)	0.901 (0.156)[g]	0.901[g,i]	0.494, 2.41[h]	--	--	--
Vd (L)	3.45 (0.81)	2.62 (0.67)	2.36 (0.55)	3.16 (0.48)	3.26 (V1)	V1: 2.71. V2: 0.44[j]	3.44 (1.08)	3.20 (1.06)	V1: 2.78, V2: 0.34[j]
Vd/weight (mL/kg)	41.5 (11.8)	34.8 (7.9)	30.8 (7.8)	41.8 (6.6)	42.5[i]	--	--	--	--
Vmax (mg/hr)	--	--	--	--	--	14.3	--	--	5.77
Km (mg/L)	--	--	--	--	--	77.49	--	--	150
Q (mL/hr)	--	--	--	--	--	22.1	--	--	29.0

Abbreviations: HV=Healthy Volunteers, CKD=Chronic kidney disease, NCA=Non-compartmental analysis, HD= Haemodialysis

a. Results for all administration rates were combined for 4 mg Fe/kg dose
b. Mean dose amount administered
c. Population predicted parameters from a two-compartment model with capacity-limited elimination from the central compartment and weight as a covariate on volume of the central compartment
d. Represents total AUC from time 0 of the first dose to infinity after the second dose
e. Estimated from 5-minute serum ferumoxytol concentration
f. Dose 1 Cmax, Dose 2 Cmax
g. Represents time-averaged values
h. Calculated at two plasma ferumoxytol concentrations: (i) 300 µg/mL and (ii) much less than Km (<<77.49 µg/mL)
i. Calculated using mean subject weight (76.6 kg)
j. V1 and V2 represent the volumes of distribution of the central and peripheral compartments, respectively

Population PK model

A cross-study population analysis of ferumoxytol PK data using a population approach was completed. This analysis expanded upon previous population PK analyses performed on 62,745-9 in healthy volunteers. Additional PK data in healthy volunteers, from 7228-01, and in patients with CKD stage 5D on haemodialysis, from 62,745-2, were pooled together in the new analysis. The inclusion of these 2

studies enabled a better characterization of the PK, the exploration of the differences between healthy volunteers and CKD patients and a better understanding of the sources of variability influencing the PK of ferumoxytol.

Ferumoxytol PK was studied at doses ranging from 1 mg/kg (approximately 70 mg) to 510 mg in healthy subjects and 125 to 250 mg in subjects with CKD stage 5D on HD. In total, 1686 observation records from 91 HVs and 20 CKD patients were available in the pooled dataset.

A 2-compartment model with zero-order input and capacity-limited elimination from the central compartment was able to describe the observed more than dose-proportional PK of ferumoxytol and provided the best fit to the data. Remarkably, results from this model supported the hypothesis that the PK in healthy volunteers and CKD patients is comparable. This was due to the fact that the observed differences in PK between these 2 groups could actually be explained by accounting for the effects of haemodialysis on the central volume of distribution which resulted in altered concentration-time profiles in CKD patients undergoing this procedure.

Figure 1 Two-compartment PK model with Zero-Order Input and Michaelis-Menten Elimination

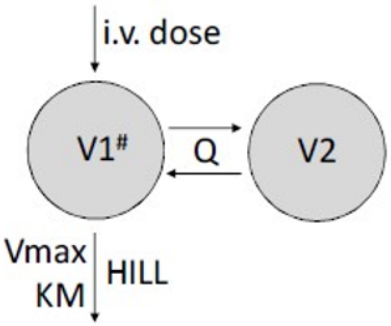
$$\frac{dA1}{dt} = -Q/V1 * A(1) + Q/V2 * A(2) - \frac{V\max \cdot A(1)^{HILL}}{Km^{HILL} + A(1)^{HILL}} \quad \text{(Eq. 1)}$$

$$\frac{dA2}{dt} = Q/V1 * A(1) - Q/V2 * A(2) \quad \text{(Eq. 2)}$$

(a) WithoutHD: $\frac{dA3}{dt} = 0$ (Eq. 3)

(b) During HD: $\frac{dA3}{dt} = VSLOPE$ (Eq. 4)

(c) Within 3h after HD: $\frac{dA3}{dt} = -VSLOPEUP$ (Eq. 5)



A(1): Amount of drug in the central; A(2): Amount of drug in the peripheral compartment; A(3) is initialized to correspond to V1. V1: Central volume of distribution; V2: Peripheral volume of distribution; Q: Intercompartmental clearance. Vmax: Maximum elimination rate of ferumoxytol; HILL: Sigmoidal hill factor; Km: Amount of ferumoxytol leading to half-maximum elimination rate; VSLOPE: rate of decline in V1. VSLOPEUP rate of recovery in V1 set to be equal to VSLOPE.

A number of covariates relating to baseline characteristics of subjects, including demographic and iron metabolism laboratory parameters, were selected for testing based on their physiological plausibility and/or due to observed trends in plots of their individual model parameters vs covariate values. These analyses confirmed body weight is a significant predictor of the central volume of distribution, with sex also having an additional effect. Statistically significant effects of the CKD specific extrinsic factors 'HD' and 'body weight loss due to HD' on V1 were also identified. No other tested intrinsic factors were found to be of significance for explaining the variability in PK of ferumoxytol. Therefore, variability in these non-significant parameters across the various CKD and all-cause IDA populations would not lead to significant changes in ferumoxytol PK. Overall, the effect of the tested statistically significant covariates on the PK was regarded to be small and not clinically relevant, and so dose adjustment on the basis of the PK differences is not warranted.

In summary, the model adequately described the PK of ferumoxytol in both HVs and in CKD stage 5D patients for all studied dose groups. The inclusion of weight, subject sex and weight loss during HD (for the CKD patients only) significantly improved the fit of the model to the observed data. These results are consistent with normal physiology and with published information for other compounds with similar distributional patterns. The data analysis supports hypothesis that CKD patients and HVs have similar PK, and that differences between the populations can be explained by the hemodynamic changes affecting the central volume of distribution during and after HD. This also supports the previous assertion

of a lack of an effect of renal impairment, characteristic in the CKD population, on the PK of ferumoxytol. Overall, results from this population PK model indicate that there are no differences in the disposition of ferumoxytol in CKD patients as compared to HVs.

Table 3 Final Parameter Estimates and Standard Errors of the Final PK Model

Parameter	Final Parameter Estimate		Interindividual Variability / Residual Variability	
	Typical Value	%SEM	Magnitude	%SEM
V1 (L)	2.78	3.14	16.6%CV	16.1
V2 (L)	0.344	11.0	53.3%CV	33.9
Q (L/hr)	0.0290	8.26	NE	NE
Vmax (mg/h)	5.77	5.09	19.5%CV	16.8
KM (mg)	150	8.99	NE	NE
HILL	0.778	FIXED	NE	NE
VSLOPE (L/h)	-0.191	7.84	NE	NE
WGT on V1 (%/kg)	0.613	23.5	NE	NE
V1 reduction for females (%)	-18.2	16.9	NE	NE
WLO on V1 (%/kg weight loss)	6.99	23.3	NE	NE
add.error (µg/mL)	1.18	9.18	NE	NE
prop.err (SD)	0.0784	0.649	NE	NE
	Minimum value of the objective function = 10032.754			

NA: Not Available; NE: Not Estimated; SD: standard deviation; CV: coefficient of variation; SEM: standard error of the mean; WGT: body weight; WLO: Body weight loss due to HD

Simulations

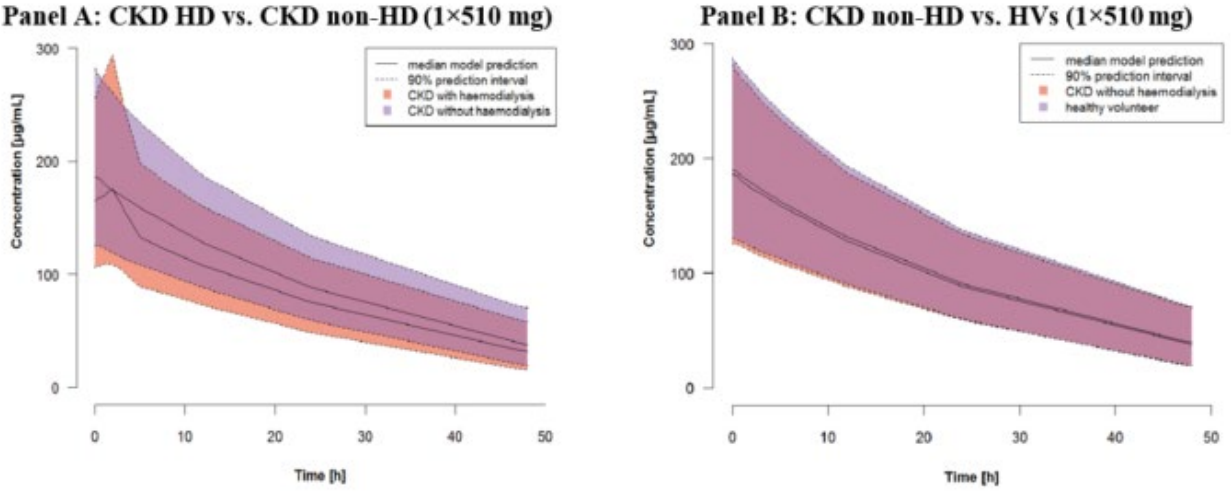
Simulations have been performed based on:

- Status: HV vs HD and non HD CKD patients
- Dosing intervals: 2,5 and 8 days between both administrations (Please refer to section time dependency below)

Results from the popPK model supported the hypothesis that the PK in HVs and CKD patients is comparable after accounting for changes occurring in the central volume of distribution during the HD procedure.

The final PK model was used to generate simulations of concentration-time profiles with the intention of comparing the ferumoxytol exposures between CKD patients and HVs. For this evaluation, simulations were performed following a single IV dose of 510 mg. The same populations as in studies 62,745-2, for CKD, and 62,745-9, for HVs, were simulated. Each sampled subject was simulated 100 times. For the CKD patients on HD (CKD HD), PK profiles were simulated such that drug administration took place after completion of one hour of HD, as per the ferumoxytol Summary of Product Characteristics (SmPC). In addition, simulations were also performed on the CKD patient population without the effect of HD (CKD non-HD group), for which the body weight loss due to fluid loss during HD was assumed to be zero. The simulated profiles are shown in Figure 2 and the non- compartmental (NCA) derived PK parameters are shown in Table 4.

Figure 2 Simulated Single 510 mg Dose Ferumoxytol Conc. vs. Time (first 48 hours)



As shown in Figure 2 (Panel A), initial concentrations at time zero (t=0) were ~13% higher for CKD patients on HD. This is in part due to the fact that CKD non-HD patients were simulated using their corresponding weight post-HD (or 'dry weight'), and not their initial 'wet weight'. The latter is typically due to fluid retention, and so this would not be expected to occur in patients not requiring HD. For this reason, the CKD HD group would tend to present with slightly larger initial central volumes of distribution (V1) thus influencing their initial concentrations. In addition, other small differences between the two PK profiles result from the interplay between the time-dependent changes in V1, occurring during HD, and the saturable Michaelis-Menten elimination behaviour of ferumoxytol. For example, the marginal transient changes in peak exposure are a result of the effect of fluid retention and subsequent fluid loss occurring during HD. This is reflected by the lack of a decline in the ferumoxytol plasma concentrations in the CKD HD population within 3 hours post-dose, consistent with the end of the HD procedure.

Table 4 Simulated Ferumoxytol Median Single Dose PK Parameters with 90% Prediction Intervals

Group	Percentile	C_{max} (µg/mL)	AUC_{inf} (µg·hr/mL)	$AUC_{(0-48h)}$ (µg·hr/mL)	$T_{1/2}$ (hr)
CKD HD	Median	188	5000	4030	19.9
	5th	*121*	*3150*	*2690*	*13.7*
	95th	*302*	*8060*	*6060*	*29.8*
CKD non-HD	Median	203	5840	4700	20.3
	5th	*140*	*3830*	*3250*	*13.8*
	95th	*305*	*9600*	*6940*	*29.9*
HVs	Median	209	6040	4800	20.2
	5th	*145*	*3840*	*3310*	*13.7*
	95th	*310*	*9590*	*7110*	*29.5*

The predicted median peak exposure (Cmax) in the CKD non-HD group is approximately 10% higher when compared to CKD HD, with the predicted median Cmax (90% Prediction Interval) values of 203 (140-302) vs. 188 (121-302) µg/mL, respectively. The small differences predicted for total exposure (area under the plasma concentration-time curve from time 0 to infinity (AUCinf)) are again due to the saturable Michaelis-Menten elimination behaviour of ferumoxytol. The simulated typical AUCinf for CKD HD patients and non-HD patients would be 5000 (31508060) and 5840 (3830-9600) µg·hr/L, respectively.

For the purposes of investigating differences in exposure between CKD patients and HVs the simulated profile from HVs was compared to that of non-HD CKD patients. As shown in Figure 2 (Panel B), differences between the two populations are minimal as the profiles for the two groups clearly overlap. This is also reflected in the results from the median (90% Prediction Interval) PK parameters which are

similar between the two population groups, with a Cmax of 209 (145-310) vs. 203 (140-302) µg/mL, and AUCinf of 6040 (3840-9590) vs. 5840 (38309600) µg·hr/mL. Due to the comparable PK between the two groups, subsequent simulations treated HVs and CKD non-HD patients as a single group, henceforth referred to as the 'ALL' group.

Overall, the results from the simulations confirm that, as a result of the extrinsic factor 'HD', there is a slight increase in Cmax and AUC in the CKD HD patients when compared to the CKD non-HD population. Transient changes in peak exposure occurring during the HD procedure, due central volume loss, accurately represented the observed CKD HD data from Study 62,745-2. In practice, these differences in exposure are considered to be marginal and are judged to be non clinically relevant. Comparisons of the simulations for CKD non-HD and HVs support the hypothesis that there is no difference in the PK between these two populations, particularly after removing the effect of the time dependent V1 loss. Indeed, if V1 is kept constant (as performed for the simulations in the CKD non-HD group) then the PK profile overlays that of the HVs, as shown by the almost identical simulated exposure parameters (Cmax and AUC). Given that differences in PK profiles between CKD and HVs are not related to intrinsic factors, it is therefore expected that the PK of these two groups is indeed representative of that of other populations provided there are no other extrinsic factors causing clinically significant perturbations on the PK parameters, in particular V1 (i.e., extreme losses of blood).

Absorption

Ferumoxytol achieves 100% bioavailability since it is administered intravenously. Consequently, no influence of food is expected.

A Cmax of approx. 200 µg/mL has been achieved for HV and CKD-patients.

Distribution

The volume of distribution is in line with plasma volume, which was also observed for other IV iron products. According to the population PK model, the central (V1) and peripheral (V2) volume of distribution were 2.8 L and 0.3 L, respectively.

Elimination

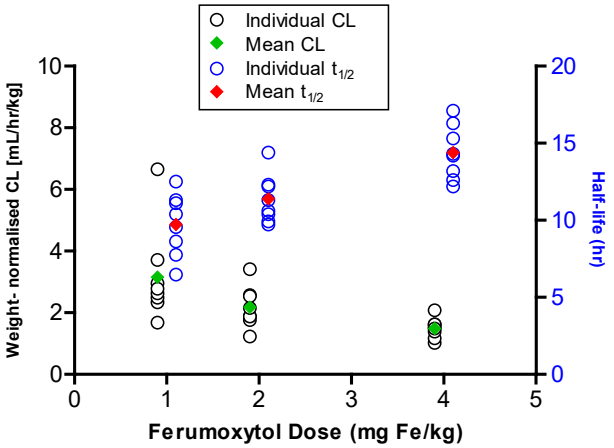
IV iron products, including ferumoxytol, do not undergo the 'typical' metabolism of other drugs by the liver or kidney, nor do they undergo gastrointestinal excretion. Instead, intact ferumoxytol is taken up by macrophages of the reticuloendothelial system, where the iron is released from the iron-carbohydrate complex and is transported to the marrow for incorporation into erythrocytes, or transferred to storage sites (principally involving transferrin, ferritin and Hgb). Therefore, the rate of elimination of ferumoxytol from plasma is not affected by intrinsic factors such as renal or hepatic insufficiency.

Overall, the results of the three PK studies consistently demonstrated that the elimination of ferumoxytol from plasma was nonlinear.

Estimated clearance values varied substantially depending on the dose of ferumoxytol administered. Administration of higher doses of ferumoxytol resulted in slower clearance. This is consistent with the modeled capacity-limited elimination. Clearance values calculated from the population-predicted parameters for the final model in Study 62,745-9 substantiate this capacity-limited elimination of ferumoxytol from plasma. The estimated clearance at a plasma ferumoxytol concentration of 300 µg/mL (near Day 2 C_{max}) was only 38 mL/hr whereas the estimated clearance approached 185 mL/hr at very low concentrations. Consistent with the estimated clearance values are the estimated half-life values for ferumoxytol in Study 62,745-9. Apparent half-life becomes longer with increasing concentrations. Estimated apparent half-life at 300 µg/mL was about 50 hours and approached about 10 hours as concentrations declined. This lower estimated half-life is similar to the value calculated in

Study 7228-01 for the 1 mg Fe/kg dose group. Exploratory data from Study 62,745-2 suggest that the rate of clearance of ferumoxytol in subjects with CKD stage 5D on HD is similar to that in healthy volunteers.

Figure 3: Ferumoxytol Plasma t1/2 and Weight-normalised CL (Study 7228-01)



Overall, the PK data indicate dose-dependent, capacity-limited elimination of Ferumoxytol from plasma. The population PK analysis in Study 62,745-9 was best described using a two-compartment model with capacity-limited elimination from the central compartment. This is most likely a result of saturable uptake into the RES, where iron is released from Ferumoxytol for uptake by storage and transport proteins.

Dose proportionality and time dependencies

Dose proportionality
Cmax increased proportionally with dose as a reflection of the consistent Vd.
In single dose studies, peak plasma levels of ferumoxytol (Cmax) increased proportionately to dose (see study -01 below), but plasma clearance decreased non-linearly with increasing dose as a result of capacity-limited elimination, resulting in longer half-lives (t1/2) with increasing dose.
The PK profile of ferumoxytol after multiple dosing at higher concentrations was best described using a two-compartment model with non-linear elimination, and is similar to the profiles described for certain other IV iron products: (iron(III)hydroxide sucrose complex or iron dextran.

Study 7228-01: Mean plasma ferumoxytol concentrations increased with dose in subjects receiving 1, 2, or 4 mg Fe/kg and the rate of decline appeared to follow first-order kinetics in each of the three dosage groups. Increasing rates of injection (2 to 60 mL/min) had no effect on the PK of ferumoxytol at a dose of 4 mg Fe/kg.

Figure 4: Dose-normalised AUC0-∞ vs. Dose (Study 7228-01)

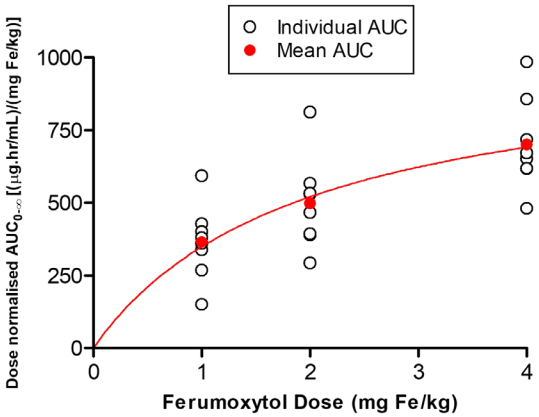


Figure 5: $t_{1/2}$ and Weight-normalised CL vs. Dose (Study 7228-01)

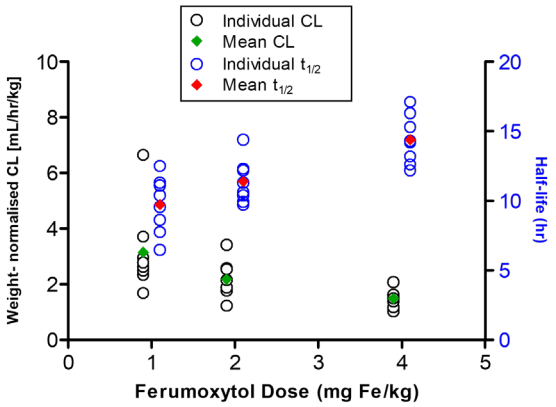


Table 5 Summary of Mean (SD) Pharmacokinetic Parameters for Increasing Doses Given at the Same Rate of Administration (Study 7228-01)

Parameter	Increasing Dose at Same Rate of Administration			P-value
Dose (mg Fe/kg)	1	2	4	NA
Rate (mL/min)	2	2	2	NA
N	8	8	8	NA
$AUC_{0-\infty}$ (µg·hr/mL)	365 (128)	996 (313)	2,800 (625)	<0.0001*
Dose-Normalized $AUC_{0-\infty}$ ((µg·hr/mL)/(mg Fe/kg))	365 (128)	498 (157)	700 (156)	0.0007*
C_{max} (µg/mL)	27.0 (7.7)	62.2 (12.0)	134 (36)	<0.0001*
Dose-Normalized C_{max} ((µg/mL)/(mg Fe/kg))	27.0 (7.7)	31.1 (6.00)	33.5 (9.0)	0.2534
λz (hr-1)	0.074 (0.017)	0.062 (0.008)	0.049 (0.006)	0.0002*
$t_{½}$ (hr)	9.7 (2.0)	11.4 (1.6)	14.4 (1.7)	0.0001*
CL (mL/hr)	265 (118)	164 (56)	114 (15)	0.0014*
CL/weight (mL/hr/kg)	3.15 (1.52)	2.18 (0.66)	1.49 (0.32)	0.0011*
V_z (L)	3.45 (0.81)	2.62 (0.67)	2.38 (0.44)	0.0097*
V_z/weight (mL/kg)	41.5 (11.8)	34.8 (7.9)	31.1 (8.4)	0.1103

ANOVA used for parametric data and Kruskal-Wallis Test used for nonparametric data *Indicates an overall statistically significant difference in PK parameter by dose group.

Time dependency

Simulations based on the 'ALL' population were generated at the labelled dosing regimen of 510 mg given twice within 2 to 8 days. The simulations were based on 20 CKD patients and 58 HVs, which reflects the actual number of subjects in the original clinical trials, and covariate information was also obtained from these trials. For the purposes of illustrating various possible dosing regimens with regards to the administration times, simulations were provided following administration 2, 5 and 8 days apart. A plot depicting the three different regimens is provided in Figure 6 with their respective PK parameters shown in Table 6. As expected, based on the estimated ~20-hour half-life for Ferumoxytol, the simulations confirmed that exposure following redosing at 5 and 8 days was similar due to the negligible accumulation. Due to the shorter dosing interval, the peak and total exposure of ferumoxytol when given two days apart is marginally higher, with the median Cmax of the second dose and Total AUCinf being 1.2- and 1.1-fold higher, respectively, compared to doing 5 to 8 days apart.

Figure 6 'ALL' Group Simulated Ferumoxytol Conc. vs. Time at Labeled Dose Regimens

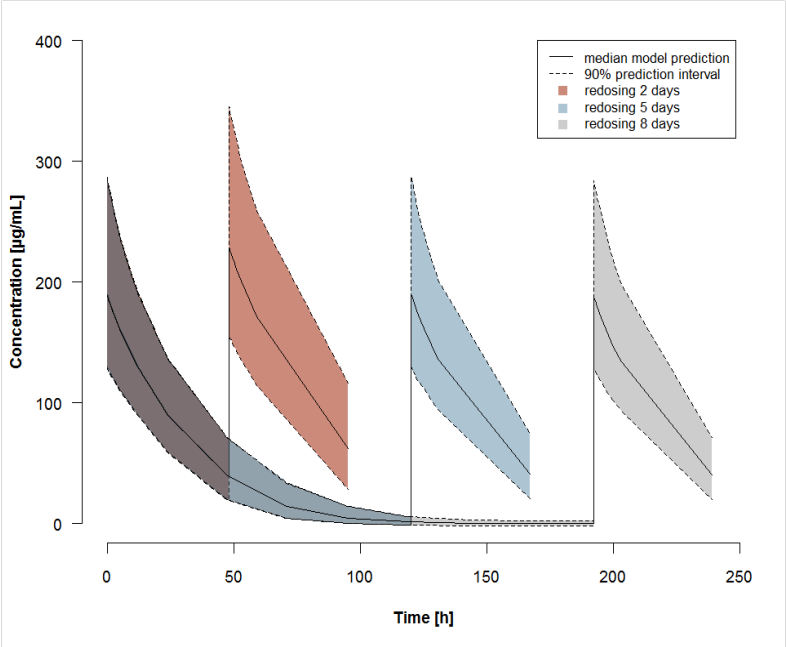


Table 6 'ALL' Group Simulated Ferumoxytol Median (90% Prediction Interval) at Labeled Dose Regimens

Dosing Schedule	Percentile	Cmax (µg/mL)	Total AUCinf (µg·h/mL)	AUC(0-48h) (µg·h/mL)	T1/2 (hr)
1×510 mg - Single Dose	Median *5th* *95th*	207 *144* *309*	5990 *3840* *9590*	4770 *3290* *7070*	20.2 *13.7* *29.7*
2×510 mg – 2 Days Apart [Cmax and T1/2 after second dose]	Median *5th* *95th*	250 *171* *370*	13500 *8500* *22200*	4770 *3290* *7070*	24.9 *16.5* *37.7*
2×510 mg – 5 Days Apart [Cmax and T1/2 after second dose]	Median *5th* *95th*	207 *144* *307*	12000 *7800* *18900*	4760 *3280* *7020*	21.3 *15.0* *31.1*
2×510 mg – 8 Days Apart [Cmax and T1/2 after second dose]	Median *5th* *95th*	204 *142* *307*	11900 *7760* *18700*	4760 *3260* *7060*	21.0 *14.9* *30.1*

Note: For the 1×510 mg regimen, Total AUCinf equates the single dose AUCinf. For the 2×510 mg regimens, Total AUCinf is the sum of the AUC(0-48h) after the first dose, and the AUCinf from the second dose.

Special populations

Impaired hepatic function

No PK data is available for patients with impaired hepatic function.

Since ferumoxytol is not metabolised in the liver and no differential effect was expected in subjects with impaired hepatic function, a separate study was not conducted in this patient population. However, a subpopulation analysis identified a total of 8 patients exposed to ferumoxytol (2 x 510 mg) in the pivotal studies who had a history of liver cirrhosis. In these subjects, the incidence of abnormal liver function serology was slightly higher compared to those subjects without a history of cirrhosis

Gender
In Study 7228-01, the PK parameters of Vd and CL for ferumoxytol were observed to be higher for male subjects compared to female subjects at higher single doses (4 mg Fe/kg). However, no significant differences were seen between males and females when Vd and CL were weight-normalised.

In the new population PK model analysis, the covariate analysis showed that females had an 18.2% lower V1 than males.

These results are consistent with normal physiology, as central volume typically increases with body weight, and are also comparable with results reported for other compounds which are principally distributed in the central compartment (as commonly observed for highly water-soluble drugs). As described in the literature, differences between sexes have been attributed to factors such as body composition. This is because for the same given weight, percentage body fat is higher in females compared to males, and so water-soluble compounds would tend exhibit a relatively lower volume of distribution in females.

The effect of weight on exposure was not explored as this is already dealt with the dose adjustment indicated for patients with weights of less than 50 kg (please refer to the posology section of the SmPC).

Race: No effect of race/ethnicity was identified in any analysis.

Weight: Both Studies 7228-01 and 62,745-9 demonstrated a relationship between the volume of distribution and body weight, consistent with the physiological proportionality between body weight and plasma volume. In the new population PK model analysis, the covariate analysis showed that V1 increased by 0.613% per kg of body weight.

Elderly: No data on elderly subjects was provided.

Children: No PK data for the paediatric population is available.

Pharmacokinetic interaction studies

No interaction studies were performed.

3.2.1.2. Pharmacodynamics

Mechanism of action

Ferumoxytol is a colloidal iron-carbohydrate complex. It includes iron oxide particles with an iron oxide core surrounded by a polyglucose sorbitol-carboxymethylether shell. The shell isolates the bioactive iron from plasma components until the iron-carbohydrate complex enter reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is then released intracellularly from the iron-carbohydrate complex within vesicles in macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into haemoglobin.

Primary and Secondary pharmacology

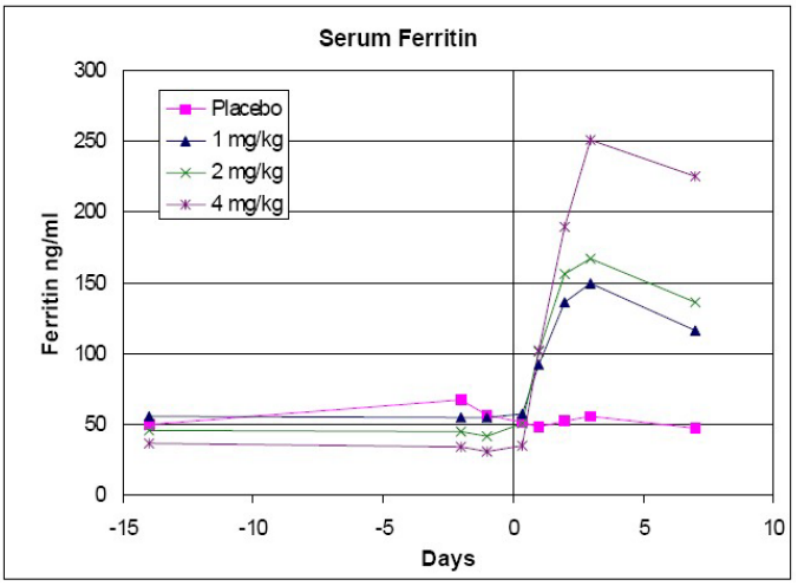
Ferumoxytol is an IV iron replacement therapy, which has been designed to provide bioactive iron for uptake by storage and transport proteins (ferritin and transferrin) and utilisation for Hgb production within erythroid precursors in patients with iron deficiency. The intended effect of iron repletion is to restore impaired erythropoiesis and to correct iron deficiency and increase Hgb. Ultimately, therefore, the elemental iron contained in ferumoxytol is transferred through a series of steps to Hgb within red blood cells. As a result, measures of Hgb together with those of serum iron, serum ferritin and transferrin

saturation (TSAT) provide a direct evaluation of both the pharmacological effect and therapeutic efficacy of ferumoxytol.

Because of the potential interference of plasma ferumoxytol levels with the serum iron assay, serum ferritin was a better indicator of iron status during these short-term studies. Increased serum ferritin levels, which were sustained for at least one-week post-dosing in both ferumoxytol treated healthy volunteers and haemodialysis patients, were indicative of ferumoxytol metabolism and increased availability of iron for incorporation into iron stores.

As expected iron parameters (serum iron, total iron binding capacity (TIBC), transferrin saturation (TSAT) and serum ferritin) increase after administration of ferumoxytol in all three studies, consistent with the intended PD effect.

Figure 7 Mean Serum Ferritin Levels versus Time Profiles after Administration of Varying Doses of Ferumoxytol in Study 7228-01



The PD effect on cardiac electrophysiology (QT/QTc prolongation) subsequent to the administration of a supratherapeutic dosing regimen to healthy volunteers was investigated in the PK / PD-study 62,745-9.

The administration of a 1.02 g (2 x 510 mg) dose of ferumoxytol within a period of 24 hours did not affect atrioventricular (AV) conduction, as measured by the PR and QRS intervals.

Furthermore, ferumoxytol was not associated with an increase in the corrected QT interval, QTcI (using the individual correction method). Although a slight decrease in QTcI (2 msec) was noted, this was not considered to be clinically relevant. There was no clinically relevant relationship between change from baseline in QTcI and the plasma concentration of ferumoxytol. The slope of the relationship was nearly zero and slightly negative, suggesting a lesser change in QTcI with increasing plasma ferumoxytol concentrations.

Ferumoxytol did not affect heart rate. T wave changes in ECG waveform morphology were identified in 5% of subjects receiving ferumoxytol and were deemed to be of no clinical importance.

3.2.2. Discussion on clinical pharmacology

Pharmacokinetics

Ferumoxytol is an aqueous colloidal solution of polyglucose sorbitol carboxymethyl ether (PSC)-coated iron oxide particles that has been developed as an intravenous (IV) iron supplement for the treatment

of iron deficiency anaemia (IDA) in patients with chronic kidney disease (CKD) as well as in patients with all cause IDA when oral iron preparations are ineffective or cannot be used.

The clinical pharmacology of ferumoxytol was assessed in three Phase I studies. Studies 7228-01 and 62,745-9 (a thorough QT Study) were conducted in healthy volunteers; Study 62,745-2 was conducted in subjects with CKD stage 5D on haemodialysis. The studies examined doses ranging from 1 mg/kg (about 85 mg) to two doses of 510 mg (the intended clinical dosing regimen) in healthy volunteers and single doses of 125 mg to 250 mg in subjects with CKD 5D on haemodialysis. Study -01 investigated increasing doses up to 4mg/kg and in a second part the PK of different rates of IV administration.

The presented studies were already submitted with the initial MAA and no other clinical pharmacology studies were conducted since the original submission. The Applicant did however submit an **additional population PK analysis** using all of the available ferumoxytol PK data (1686 PK samples from three studies: Study 7228-01 (HVs, n = 33), Study 62,745-9 (HVs, n = 58) and Study 62,745-9 (CKD stage 5D on HD, n = 20)), which is endorsed and preferred over the previous submitted data (popPK model only for study -9 I HVs). 29 observations were BLQ and set to missing. It is unclear whether missing data were excluded but omittance of BLQ samples would be considered acceptable since BLQ was low (1.7%). The applied methods are state of the art and are acceptable.

The population PK could be described by a two-compartment model with sigmoidal Michaelis-Menten elimination with a combined additive and proportional error model. An additional parameter accounted for rate of change in the central volume (V1) during haemodialysis. Sex and body weight (on V1) were identified as the only significant covariates. V1 was estimated to be increased by 0.613% per kg of body weight and females were estimated to have an 18.2% lower V1 than males.

Overall, the model seems to fit the data well, and the results are overall in line with the separate analyses of each study. However, some limitations have been identified as discussed below. Consequently, interpretation of modelling results and respective simulations have to be interpreted with care.

All fixed and random-effects were estimated with adequate precision. Low interindividual variability were identified on Vmax (19.5 %CV) and V1 (16.6 %CV) whereas interindividual variability was high on V2 (53.3 %CV). Information on shrinkage was not presented. The statistical significance of PK parameters was confirmed based on the 95% confidence interval of the bootstrap. However, out of 1000 bootstrap runs performed, only 175 minimized successfully whereas 825 runs terminated due to rounding errors which could indicate poor model stability. However, run termination based on rounding errors is not an important indicator of quality of bootstrap parameter estimates and the issue is not pursued.

No major model misspecifications were noted in the goodness-of-fit (GOF) plots. A local regression line in addition to the line of identity would have served the model evaluation. Several outliers were noted in the GOF-plots but no steps were taken in order to assess the influence of these data points. In general, treatment stratified VPCs indicated good predictive performance of the model. However, the nature of scatter VPCs does not allow for good direct comparison of the observed and predicted distributions. Concentrations also seemed to be overpredicted in the 1 mg/kg treatment group (TRT == 70).

In order to avoid anaphylactic reactions due to the administration of ferumoxytol, a different administration is recommended as has been used in the initial MAA studies. A slower IV infusion over 15 minutes is recommended instead of a rapid injection. Consequently, PK parameters might differ slightly. While the overall PK properties will not be affected, the Applicant is asked to discuss respective differences caused by the now recommended slower administration (**OC**).

The **presented data is overall rather limited** and mainly based on data from healthy volunteers (91 HV, 20 CKD-patients on haemodialysis). No data for all-cause IDA patients is available. Further, data from the only study in CKD patients is limited to max 180 min since concentrations in the majority of the later timepoints (48 and 96 hour) are not quantifiable. The Applicant claims that in total 1686

observation from different dose level are available and have been integrated in the population PK analysis, it is however not clear how these are distributed over doses, time points and HV/CKD-patients. The Applicant is asked to provide a respective table indicating how many observations are available and above LLOQ, for each dose and timepoint for HV and CKD patients (**OC**). This has to be clarified to substantiate the claim that status (HV,CKD) is not a significant covariate and consequently the obtained results are valid for both populations and might also be valid for the all-cause IDA population. Since no PK data are available for the all-cause IDA population and this population is very heterogeneous, the Applicant is asked to discuss potential differences in this population that might influence the PK and PD of ferumoxytol (**OC**).

Further, the Applicant claims that the presented model can account for effects of haemodialysis and consequently observed differences between HV and CKD patients are not actual differences between these populations but are an effect of haemodialysis. Simulated concentration-time profiles were generated to compare CKD patients with and without haemodialysis and CKD patients without haemodialysis vs. healthy volunteers, which were overall comparable and exposure simulations showed no greater change in exposure metrics (C_{max}, AUC_{inf} and AUC_{0-48h}) than 20% across all percentiles. It is acknowledged that haemodialysis likely has an influences on PK parameter especially on the estimated volume of distribution but the Applicant did not discuss that all CKD-patients in this dataset received haemodialysis and therefore those covariates/parameters are highly confounded. Consequently, the dataset is considered as not suitable to draw such conclusions. The Applicant is asked to further substantiate the claim, that the observed differences are only due to the effect of haemodialysis and no differences between populations are expected (**OC**).

Nevertheless, assuming that the discussed aspects can be further substantiated, the presented data from the separate studies, together with the simulation data and respective knowledge of the metabolism of ferumoxytol seem reassuring that no relevant differences are expected between HV and CKD patients.

The **applied analytical methods** raised some concerns already during the assessment of the original submission and are still valid. The bioanalytical methods and validation data were considered not to be in-line with the guidelines and recommendations effective at the time of the original submission (EMEA/CHMP/EWP/192217/2009). This also applies to the current version (EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2**). However, it was and is acknowledged that the validation was performed before the implementation of the respective guidelines. Upon request, missing aspects were sufficiently addressed retrospectively and are not requested again. It has to be noted that these aspects have not been discussed by the Applicant in the documentation for this MAA. Nevertheless, the applied methods are acceptable for this procedure.

Pharmacokinetics of Ferumoxytol

Ferumoxytol achieves 100% bioavailability since it is administered intravenously. Consequently, no influence of food is expected. A potential effect of concomitant oral iron treatment has however not been discussed. Respective co-medication is not recommended for other IV iron products. Respective amendments to the SmPC are requested.

A Cmax of approx. 200 µg/mL has been achieved for HV and CKD-patients. The volume of distribution is in line with plasma volume, which was also observed for other IV iron products.

The elimination of ferumoxytol from plasma is dose dependent. In healthy volunteers, over a dose-range from 1 - 4 mg/kg, Cmax increased proportionally with dose while half-lives decreased resulting in higher AUC. The intended dose was however not included in the respective study. While it has been applied in study -09, no comparative analysis was provided. The Applicant is asked to provide a discussion of dose proportionality including the intended dose of 2x510mg and the intended populations (**OC**).

The available results indicate a capacity-limited elimination. This is in-line with the release mechanism to free iron from ferumoxytol. Ferumoxytol is taken up by macrophages and iron is release in this context, consequently limiting the elimination of ferumoxytol. Subsequently, free iron is incorporated in the natural iron metabolism/storage system. Since IV iron products are not excreted via liver, kidney or gastrointestinal excretion, a potential risk of iron overload is apparent in patients receiving these products. This is further addressed in the efficacy and safety sections of this report.

Based on the population PK model the Applicant performed simulations of different dosing regimen administering both 510 doses at different intervals representative of the intended dosing intervals (2, 5 or 8 days). While all parameter are similar for dosing 5 and 8 days apart, Cmax, AUCinf and t1/2 were slightly higher when both doses were administered 2 days apart. The clinical relevance of these findings is not known. This could be relevant for patients at risk for iron overload. The Applicant is asked to discuss the implications for patients with higher ferritin at baseline and an increased potential for iron overload with a short administration interval. Potential recommendations for longer dosing intervals should be discussed for the SmPC (**OC**).

Inter-individual variability was estimated during the development of the final population PK model. While the variability for V1 is moderate with 16.6%, the variability for V2 is much higher with 53.3%. Further data from individual studies is requested together with a respective discussion (**OC**).

Special populations

No PK data is available for patients with impaired hepatic function. However, no difference is expected in these patients since the metabolism of ferumoxytol is not dependent on the liver and respective enzymes. Whether accumulation of iron in the liver is more likely in the patients has not been assessed. The Applicant provided a subgroup analysis from the pivotal study for 8 patients, which indicated slightly higher incidences of abnormal liver function serology. This is further discussed in the safety section. Gender and body weight were identified as significant covariates in the population PK analysis. The observed changes are regarded to be of low clinical relevance. However, no additional analyses of a potential effect was performed (e.g. the effect of body weight extremes on exposure) and no VPCs stratified by covariates were presented. The Applicant stated that potential dose adjustments are already implemented via different dose recommendations based on 50kg threshold as included in the SmPC. The clinical relevance of this 50kg threshold has however not been discussed. The Applicant is asked to substantiated this threshold and respective dose recommendations also including respective treatment data and acceptable safety from clinical studies in the intended population (**OC**).

No dedicated analysis for elderly subjects has been performed. Since this is an important part of both intended populations, the Applicant is asked to discuss the available PK and PD data in elderly subjects (**OC**). This should also be discussed in light of a potential increased risk in patients with cardiovascular risk factors (**OC**).

No PK data for the paediatric population is available. This is acceptable for this MAA, since an indication only including adult patients is pursued by the Applicant. Since body weight was identified as significant covariate on Vd, this is also expected for the paediatric population. In order to characterize this in the paediatric population and to determine whether other aspects/covariates could affect PK parameters in younger patients, the Applicant is strongly advised to collect also pharmacology data in future paediatric studies.

Interactions: Based on the metabolism of ferumoxytol no interactions with liver enzymes are expected. The Applicant did not perform dedicated drug-drug interaction studies, which is acceptable. In the clinical safety section, subgroup analyses based on concomitant medications are presented evaluating potential differences in AE incidences.

Pharmacodynamics

No clinical studies were provided to characterize the mechanism of action. This is however acceptable since the basic mechanism of action is well established and does not differ from other standard iron solutions for parenteral administration.

Ferumoxytol is an IV iron replacement therapy, which has been designed to provide bioactive iron for uptake by storage and transport proteins (ferritin and transferrin) and utilisation for Hgb production within erythroid precursors in patients with iron deficiency. The intended effect of iron repletion is to restore impaired erythropoiesis and to correct iron deficiency and increase Hgb. Consequently, measures of Hgb, serum iron, serum ferritin and transferrin saturation (TSAT) could be regarded as indicators for the pharmacological effect and therapeutic efficacy of ferumoxytol.

As expected iron parameters (serum iron, total iron binding capacity (TIBC), transferrin saturation (TSAT) and serum ferritin) increase after administration of ferumoxytol in all three studies, consistent with the intended PD effect. However, the laboratory test for serum iron could apparently not distinguish between ferumoxytol and transferrin-bound iron. Consequently, values of serum iron, TIBC and TSAT do not accurately reflect levels of bioavailable iron. Consequently, these parameter can only be regarded as supportive and do not directly substantiate the intended PD effect.

On the other hand, serum ferritin reflects increased iron metabolism and iron bioavailability and is consequently better suited to estimate the PD effect of ferumoxytol. In all studies, an increase in serum ferritin was observed after administration of ferumoxytol, consistent with the intended effect. This was also observed in the phase II and III clinical studies (see safety section of this report).

TQT study

The PD effect on cardiac electrophysiology (QT/QTc prolongation) subsequent to the administration of a supratherapeutic dosing regimen to healthy volunteers was investigated in study -9. Design, methods and conduct of the study are adequate and are in line with the requirement for a TQT study.

No effect of the 2 x 510 mg regimen on AV conduction and cardiac depolarization was observed (PR, QRS or QTc interval durations).

Some changes have however been observed:

- A slight decrease in QTcI (2 msec): The Applicant does not considered this clinically relevant, which cannot be fully agreed upon. This is further discussed below and in the safety section of this report.
- Although, the heart rate was not affected, T-wave changes in ECG waveform morphology were identified 3/57 subjects (5.3%) receiving Feraheme (opposed to none in the control groups). The clinical importance of this finding is unclear. This was not discussed by the Applicant.

The observed changes are considered to be not clinically relevant by the Applicant. This is supported by the fact that no other adverse events associated with cardiac dysfunction were noted. While this notion can be followed for healthy volunteers, the clinical relevance of these findings for patients with a history of cardiovascular disease, as often observed in IDA-CKD-patients, is currently unclear. Since cardiovascular events are common in the studies submitted for the characterisation of Feraheme's safety profile and constitute the majority of related (serious) AEs and fatal events, a more thorough discussion is required. Please refer to the safety section of this report (**safety OC**).

Interactions: No interaction studies were performed. Since ferumoxytol is not metabolized via liver enzymes etc., this is acceptable. The Applicant did however perform subgroup analysis of safety data based on concomitant medication. Please refer to the safety section of this report. In addition, a SmPC

amendment has been requested regarding the co-medication with oral iron, which is not recommended for other IV iron products.

Genetic differences: In general no differences in PD are expected based on genetic differences. The results of the TQT study however might be relevant for patients with cardiovascular disease and respective genetic risk factors. The Applicant is asked to discuss a potential increased risk in those patients (**OC**).

Relationship between plasma concentration and effect: The Applicant did not provide a dedicated discussion of the relationship between plasma concentration and effect. Nevertheless, the available data indicate increased serum ferritin levels with increasing dose, which is indicative of increase available iron and indirectly of the intended treatment effect. However, ferritin increases over 800 ng/mL might also be indicative for iron overload. For further discussion of this safety aspect, please refer to the safety section of this report.

3.2.3. Conclusions on clinical pharmacology

The presented data for clinical Pharmacology is overall rather limited, especially for the target populations 20 CKD patients on HD. No data for all-cause IDA is available and it has to be justified why the limited data could be extrapolated to this rather heterogenous population. Further, the data was derived from studies applying the old administration via rapid injection. Whether differences in PK or PD parameter might be expected with the new slower administration method, needs to be clarified. Some aspects including the increase in ferritin and findings of the TQT study are further disussed in the safety section.

Overall, no major objections have been raised but several other concerns have to sufficiently addressed including potential amendments of the SmPC.

3.2.4. Clinical efficacy

Table 1 Description of Clinical Efficacy Studies supporting CKD Indication

Protocol No.	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design / Duration	Study Objective	Route and Regimen	No. Subjects Enrolled/ Completed/	Demographics		Study Population	Primary Efficacy Endpoint Efficacy Parameters of Interest
							Sex M/F (%)	Age Median (Range)		
PIVOTAL EFFICACY STUDIES FOR THE REGISTRATIONAL PROGRAMME										
62,745-6	10 May 2004/ 25 Sep 2006	20 (USA)	**Randomised:** Phase III Open-label, multicentre, active controlled Pre-Screening Period of up to eight weeks, a 10-day Screening/Baseline Period, and a 5-week Randomised Study Period (SP)	Efficacy and Safety	2 x 510 mg ferumoxytol IV 200 mg/day oral iron for 21 days	304 randomised; ferumoxytol, N=228; oral iron, N=76 271 completed; ferumoxytol, N=208; oral iron, N=63	**Fer:** 58.8/ 41.2 **Oral iron:** 68.4/ 31.6	**Fer:** 66 (31-96) **Oral iron:** 64 (38-88)	CKD stages 1-5	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days predose and 21 and 35 days postdose
			Readmission Optional Phase III Open-label, multicentre, uncontrolled 5 weeks		2 x 510 mg ferumoxytol IV	62 entered Readmission 58 completed	61.3/ 38.7	64 (34-88)	CKD stages 1-5	Efficacy analysed separately Haematology and iron indices drawn at five days pre-dose in the Readmission Phase (or could use randomised Day 35 results if within 8 days of dosing), 21 and 35 days post-first dose in the Readmission Phase (Day 0R)

62,745-7	02 Jun 2004/ 20 Dec 2006	31 (USA)	**Randomised**: Phase III Open-label, multicentre, active controlled Pre-Screening Period of up to eight weeks, a 10-day Screening/Baseline Period, and a 5-week Randomised Study Period (SP)	Efficacy ad Safety	2 x 510 mg ferumoxytol IV 200 mg/day oral iron for 21 days	304 randomised [b]; ferumoxytol, N=227; oral iron, N=77 282 completed; ferumoxytol, N=215; oral iron, N=67	**Fer**: 58.0/ 42.0 **Oral iron**: 62.3/ 37.7	**Fer**: 67 (23-95) **Oral iron**: 68 (31-91)	CKD stages 1-5	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days predose and 21 and 35 days postdose
			Readmission *: Optional Phase III Open-label, multicentre, uncontrolled 5 weeks		2 x 510 mg ferumoxytol IV	51 entered Readmission 50 completed	62.7/ 37.3	68 (31-91)	CKD stages 1-5	Efficacy analysed separately Haematology and iron indices drawn at five days pre-dose in the Readmission Phase (or could use randomised Day 35 results if within 8 days of dosing), 21 and 35 days post-first dose in the Readmission Phase (Day 0R)

Protocol No.	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design /Duration	Study Objective	Route and Regimen	No. Subjects Enrolled/ Completed/	Demographics		Study Population	Primary Efficacy Endpoint Efficacy Parameters of Interest
							Sex M/F (%)	Age Median (Range)		
62,745-5 [c]	09 Aug 2004/ 24 Apr 2007	44 Postamendment (USA) 22 Preamendment (USA)	**Post-amendment (primary efficacy analysis population)**: Phase III Open-label, multicentre, randomised, active controlled Pre-Screening Period of up to eight weeks, a 10-day Screening/Baseline Period, and a 5-week Randomised Study Period (SP)	Efficacy and Safety	2 x 510 mg ferumoxytol IV 200 mg/day oral iron for 21 days Randomised 1:1	230 randomised; 2 x 510 ferumoxytol, N=114; oral iron, N=116 201 completed; 2 x 510 ferumoxytol, N=102; oral iron, N=99	**Fer**: **2x510**: 50/ 50 **Oral iron**: 36.2/ 62.9	**Fer**: **2x510**: 60 (27-87) **Oral iron**: 61 (24-87)	CKD stage 5D on haemodialysis	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days predose and 21 and 35 days postdose
			Pre-amendment: Phase III Open-label, multicentre, randomised, active controlled Pre-Screening Period of up to eight weeks, a 10-day Sreening/Baseline Period, and a 5-week Randomised Study Period (SP)	Efficacy and Safety	2 x 510 mg ferumoxytol IV 4 x 255 mg ferumoxytol IV 200 mg/day oral iron for 21 days Randomised 3:3:1	148 randomised; 2 x 510 ferumoxytol, N=64; 4 x 255 ferumoxytol, N=62; oral iron, N=22 125 completed; 2 x 510 ferumoxytol, N=54; 4 x 255 ferumoxytol, N=55; oral iron, N=16	**Fer**: **2x510**: 57.8/ 42.2 **4x255**: 56.5/ 43.5 **Oral iron**: 59.1/ 40.9	**Fer**: **2x510**: 57 (24-86) **4x255**: 58 (21-84) **Oral iron**: 61.5 (31-85)	CKD stage 5D on haemodialysis	Efficacy analysed separately Haematology and iron indices drawn at 10 and five days predose and 21 and 35 days postdose
			Readmission *: Optional Phase III Open-label, multicentre, uncontrolled CKD stage 5D on haemodialysis 5 weeks	Efficacy and Safety	2 x 510 mg ferumoxytol IV	75 entered Readmission (total from post- and pre- amendment populations) 73 completed	49.3/ 50.7	62 (24-83)	CKD stage 5D on haemodialysis	Efficacy analysed separately Haematology and iron indices drawn at five days pre-dose in the Readmission Phase (or could use randomised Day 35 results if within 8 days of dosing), 21 and 35 days post-first dose in the Readmission Phase (Day 0R)

Table 2 Post-Marketing Studies in CKD Indication

Protocol No.	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design /Duration	Study Objective	Route and Regimen	No. Subjects Enrolled/ Completed/	Demographics		Study Population	Primary Efficacy Endpoint Efficacy Parameters of Interest
							Sex M/F (%)	Age Median (Range)		
POST-MARKETING PROGRAMME										
FER-CKD-201	1 Mar 2010/ 19 Jul 2011	36 (USA, Poland, Germany, Canada, India, Belgium and United Kingdom)	Phase II, randomised, open-label, active controlled	Safety and Efficacy	2 x 510 mg ferumoxytol IV 5 x 200 mg [ND subjects] or 10 doses, each 100 mg [HD subjects] Iron Sucr IV	162 randomised; ferumoxytol, N=80; iron sucrose, N=82 148 completed; ferumoxytol, N=75; iron sucrose, N=73	**Fer**: 39/41 **Iron Sucr**: 43/39	**Fer**: 65 (30-89) **Iron Sucr**: 64 (29-88)	CKD stages 2-5 and 5D	Mean change in Hgb from Baseline to Week 5 Proportion of subjects with an increase in Hgb ≥1.0 g/dL during the period from Baseline to Week 5
AMAG-FER-CKD-401	19 Aug 2013/ 24 Feb 2016	35 (USA, Canada and United Kingdom)	Phase IV Open-label, multicentre, active controlled 2 Week Screening Period and 5 Week treatment period (TP)	Safety and Efficacy	2 x 510 mg ferumoxytol IV (original: IV injection), Amendment 1 allowed for IV infusion over 15 min Amendment 2: only IV infusion over 15 min 10 doses, each 100 mg Iron Sucr IV	293 randomised; ferumoxytol, N=196; iron sucrose, N=97 216 completed; ferumoxytol, N=142; iron sucrose, N=74	**Fer**: 114/82 **Iron Sucr**: 57/40	**Fer**: 59 (24-92) **Iron Sucr**: 57 (26-85)	Subjects with IDA and hemodialysis-dependent CKD	Mean haemoglobin change from Baseline to Week 5 for each TP Mean change in TSAT from TP Baseline to Week 5 for each TP

Abbreviations: Ctrs=centers; F=female; Fer=ferumoxytol; Gendr=gender; M=male; No.=number.

Table 7 Clinical Studies with Ferumoxytol supporting IDA Indication

Protocol No.	First Subject Entered/ Last Subject Completed	Total No. Ctrs	Study Design/ Population	Route and Regimen	No. Subjects Randomised/ Completed Study/ Withdrawn (ITT)	Demographics		
						Sex F/M (%)	Age Median (Range) in years	Race W/B/A/O (%) (c)
AMAG-FER-IDA-301 (a)	19 Jun 2010/ 27 Feb 2012	182	**Randomised**, placebo controlled, double-blind/subjects with IDA, and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.	**Ferumoxytol IV** (2 doses, each 510 mg) vs **Placebo IV** (2 doses, each 17 mL normal saline).	**Ferumoxytol:** 608/569/39 **Placebo:** 200/187/13	**Ferumoxytol:** 89.1/10.9 **Placebo:** 89.0/11.0	**Ferumoxytol:** 44.0 (18-88) **Placebo:** 44.0 (20-91)	**Ferumoxytol:** 55.9/25.0/16.1/2.3 **Placebo:** 55.5/25.0/16.0/2.5
AMAG-FER-IDA-302 (a)	10 Aug 2010/ 09 Nov 2011	96	**Randomised**, active controlled, open-label/subjects with IDA, and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used.	**Ferumoxytol IV** (2 doses, each 510 mg) vs **Iron sucrose IV** (5 doses, each 200 mg)	**Ferumoxytol:** 406/385/21 **Iron sucrose:** 199/191/8	**Ferumoxytol:** 84.2/15.8 **Iron sucrose:** 80.4/19.6	**Ferumoxytol:** 46.0 (18-89) **Iron sucrose:** 46.0 (19-85)	**Ferumoxytol:** 83.3/1.5/11.6/3.7 **Iron sucrose:** 86.4/1.0/8.5/4.0
AMAG-FER-IDA-303 (b)	27 Jul 2010/ 24 Sep 2012	140	**Open-label**, extension/IDA subjects who had a history of unsatisfactory oral iron therapy or in whom oral iron could not be used and completed **IDA-301.**	**Ferumoxytol IV** (2 doses, each 510 mg); 5-week TPs as needed over 6-month observation period.	**Ferumoxytol (d):** 337 (e)/262/73 **Untreated Subjects** 297/199/98	**Ferumoxytol:** 90.2/9.8 **Untreated Subjects** 90.6/9.4	**Ferumoxytol:** 44 (18.0-91.0) **Untreated Subjects** 43.0 (19.0-88.0)	**Ferumoxytol (f):** 55.5/28.2/12.2/4.2 **Untreated Subjects (f)** 62.0/20.5/16.5/1.0
AMAG-FER-IDA-304	29 Feb 2016 / 21 Jul 2017	129	**Randomised**, active controlled, open-label/subjects with IDA, and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used	**Ferumoxytol IV** (2 doses, each 510 mg) **Ferric carboxymaltose (FCM) IV** (2 doses, each 750 mg) Each IMP was administered as an infusion over at least 15 minutes diluted in 250cc normal saline	**Ferumoxytol:** 997 / 935 / 62 **FCM:** 1000 / 948 /52	**Ferumoxytol:** 254 / 743 **FCM:** 224 / 776	**Ferumoxytol:** 53 (19-95) **FCM:** 53 (18-96)	**Ferumoxytol** 71.3/23.8/3.2/0.8 **FCM:** 71.5/23.2/2.9/1.5

A=Asian, B=Black or African American, Ctrs=centres, F=female, Fer=ferumoxytol, Hgb=haemoglobin, ITT=intent-to-treat, M=male, O=Other/Multiracial, Plc=placebo, Sucr=sucrose, TP=treatment period, W=White or Caucasian.
(a) Subjects had Hgb <10.0 g/dL and TSAT <20%; plus history of unsatisfactory oral iron therapy or subject could not use oral iron.
(b) The Week 5 visit of **IDA-301** was completed within 14 days prior to enrolling; subjects found to have persistent or recurrent IDA (i.e., Hgb <11.0 g/dL and TSAT <20%), at any evaluation visit (with the exception of the Visit 7/Study Termination visit), began a 5-week TP (i.e., 2 doses of ferumoxytol IV 510 mg).
(c) Other/Multiracial category did not include the categories of "Native Hawaiian or Other Pacific Islander" and "American Indian or Alaska Native", which were tabulated separately; these additional categories by race included only 5 subjects (0.6%) in the American Indian or Alaska Native racial category and 1 subject (0.1%) in the Native Hawaiian or Other Pacific Islander racial category in the **IDA-301** study; for **IDA-302** and **IDA-303**, there were no subjects in either of these racial categories.
(d) These data are for the Safety Population and not ITT subjects.

(f) Other/Multiracial includes Native Hawaiian or Other Pacific Islander" and "American Indian or Alaska Native".
(g) Subjects assigned to the iron sucrose treatment group received treatment based on haemodialysis status. Subjects on haemodialysis received either slow IV injection or IV drip infusion of 100 mg of iron sucrose at Day 1 and at the following 9 consecutive haemodialysis sessions, for a total cumulative dose of 1.0 g. Subjects not on dialysis received either slow IV injection or IV drip infusion of iron sucrose 200 mg at Day 1 and at 4 subsequent visits on non-consecutive days over a 14-day period for a total cumulative dose of 1.0 g.

The proposed therapeutic indication for ferumoxytol is the intravenous treatment of iron deficiency anaemia (IDA):

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, or
- in adult patients with chronic kidney disease (CKD).

The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2).

Comment

Previously, ferumoxytol (Rienso) was indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease in the European Union.

Since the previous Rienso approval, three additional studies have been completed; Study CKD-201, CKD-401 and the Safety Study IDA-304.

Several uncertainties had remained based on the previous MAA.

There had been insufficient data on the long term use of Rienso, in particular for re-treatment with a fixed dosing regimen of 2x510 mg beyond a second treatment course or long term use above 6 months. This had been solved by including a statement on the lack of information into the SmPC and making reference to national treatment guidelines for re-assessment of indication of re-treatment after the initial dose. The new Study -401 evalautes ferumoxytol treatment over one year and will be important to address the remaining uncertainties on long term use of ferumoxytol.

In the initial Rienso MAA for the CKD IDA indication, the lack of a comparison compared to an IV comparator had been criticized, as the oral iron comparator in HD patients was not considered standard of care and the duration of oral treatment had overall been too short to allow an adequate comparison. A literature review on the efficacy and safety data of other IV iron products licensed in the EU and an ad hoc interim analysis of the ongoing study CKD-201 (with iron sucrose as comparator) had been conducted, and supported the data from the three pivotal studies. The Type II variation had provided further data on ferumoxytol treatment compared to iron sucose (and placebo).

Due to the major safety concern regarding the increased rate of hypersensitivity reactions and the resulting implementation of a slower administration of ferumoxytol via diluted infusion, the only study providing data on this new way of administration is study -304 (efficacy and safety).

For CKD, a first line indication had been approved on the basis that the Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure from 2004 had recommended IV iron treatment as acceptable first line treatment for the broad CKD population. As European treatment recommendations have changed since the conduct of the studies, a question is raised on the use of previous iron treatments by the study participants in order to be able to better describe the study population in the SmPC under section 5.1 (**OC**).

In addition, the indication wording should be amended (formal **MO).**

3.2.4.1. Dose-response studies

While no formal dose-ranging studies were performed in the ferumoxytol clinical program for CKD subjects, three dose regimens of ferumoxytol, 2 x 510 mg, 4 x 255 mg, and 8 x 128 mg, were studied during the clinical development program in Phase II and Phase III.

Table 7 provides an overview of the efficacy of each dose regimen in these studies. In general, response to the 2 x 510 mg dosing regimen was similar to the 4 x 255 mg regimen, and response to both of these regimens was better than the 8 x 128 mg dosing regimen in these studies.

No blood level-response studies were conducted in the ferumoxytol clinical program.

Table 7: Comparison of Efficacy with Ferumoxytol Dose Regimens in Randomized and Nonrandomized Subjects (Integrated Summary of Effectiveness)

Study Type	Ferumoxytol Dose Regimens					
	2 x 510 mg		4 x 255 mg		8 x 128 mg	
Endpoint	n	Value	n	Value	n	Value
Randomized/Pivotal (Integrated: Protocols 62,745-6, 62,745-7, and Pre- and Post-amendment 62,745-5)						
Hgb Change at Week 5 (g/dL)	605	1.03	60	0.89	NA [a]	NA
Hgb Responders at Week 5 (%)		46.8		48.3		NA
Ferritin Change at Week 3 (ng/mL)		461.93		454.36		NA
Randomized/Pivotal (Pre-amendment Protocol 62,745-5)						
Hgb Change at Week 5 (g/dL)	58	0.78	60	0.89	NA [a]	NA
Hgb Responders at Week 5 (%)		32.8		48.3		NA
Ferritin Change at Week 3 (ng/mL)		457.43		454.36		NA
Nonrandomized, Not Previously Exposed to Ferumoxytol (Integrated: Readmission Phases of Protocols 62,745-6, 62,745-7, and 62,745-5; Phase II Protocols 62,745-3 and 62,745-4)						
Hgb Change at Week 5 (g/dL)	139	0.81	10	0.78	15	0.38
Hgb Responders at Week 5 (%)		37.4		40.0		13.3
Ferritin Change at Week 3 (ng/mL)		440.89		539.40		295.05
Nonrandomized, Not Previously Exposed to Ferumoxytol (Protocol 62,745-3)						
Hgb Change at Week 5 (g/dL)	11	0.48	NA [a]	NA	15	0.38
Hgb Responders at Week 5 (%)		36.4		NA		13.3
Ferritin Change at Week 3 (ng/mL)		379.46		NA		295.05
Nonrandomized, Not Previously Exposed to Ferumoxytol (Protocol 62,745-4)						
Hgb Change at Week 5 (g/dL)	11	0.70	10	0.78	NA [a]	NA
Hgb Responders at Week 5 (%)		18.2		40.0		NA
Ferritin Change at Week 3 (ng/mL)		550.62		539.40		NA

a. Regimen was not used in the study.
Abbreviations: Hgb=hemoglobin; NA=not applicable.

3.2.4.2. Main studies

CKD: Study 62,745-6, Study 62,745-7, and Study 62,745-5

Study 62,745-6, Study 62,745-7: A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Chronic Kidney Disease Patients Not on Dialysis

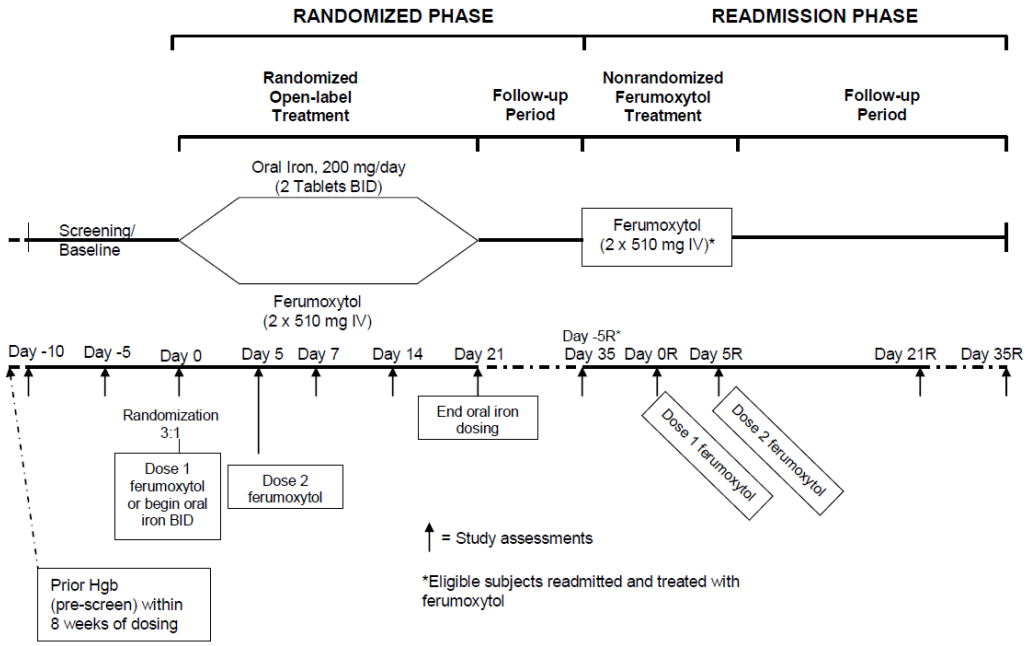
Study 62,745-5: A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Hemodialysis Patients who are Receiving Supplemental Erythropoietin Therapy

Methods

Studies 62,745-6 and 62,745-7

Both studies were phase 3, randomised, open-label, multicentre studies of the safety and efficacy of ferumoxytol (compared with oral iron) as an iron replacement therapy in subjects with CKD stages 1-5 (not on dialysis). Because of the identical design and methodology of these two studies, they are described together. The overall study design is displayed in Figure 8 below.

Figure 8: Study Protocol 62,745-6/7 Overall Design

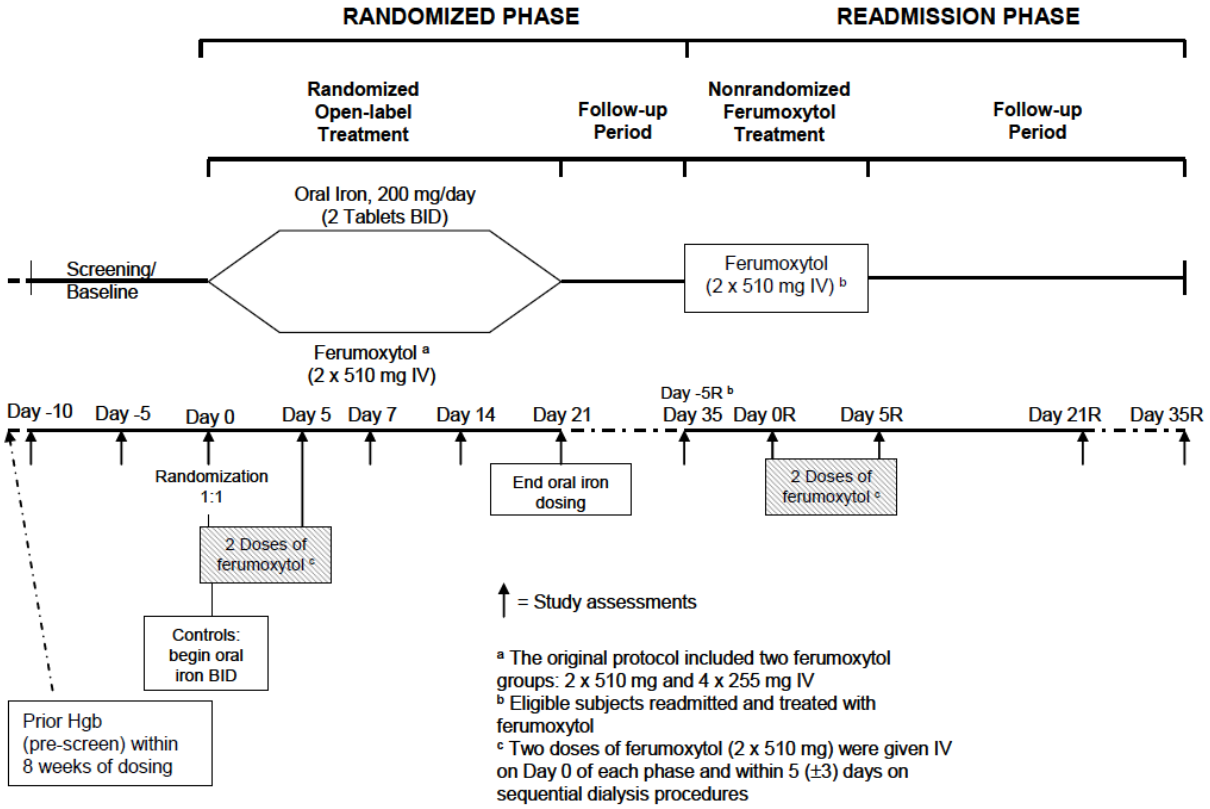


Study 62,745-5

62,745-5 was a phase 3, randomised, open-label, multicentre study investigating safety and efficacy of ferumoxytol (compared with oral iron) as an iron replacement therapy in subjects with CKD stage 5D who were on hemodialysis and received supplemental ESA therapy.

The overall study design is displayed in Figure 9.

Figure 9: Design of Protocol 62,745-5 (Post-amendment)



Study Participants

Inclusion criteria

Table 8: Inclusion Criteria for the phase 3 Efficacy Studies

Study Entry Criteria	**Protocol Number**		
	62,745-6 and 62,745-7	**62,745-5 Post-amendment**	**62,745-5 Pre-amendment**
Inclusion Criteria			
Male or female chronic kidney disease subjects ≥18 years	X	X	
Male or female subjects 18 years of age or older			X
Subject is able and willing to provide written informed consent and HIPAA Authorization to participate in the study	X	X	X
Have been undergoing **haemodialysis** for at least 90 days		X	X
Have chronic kidney disease per K/DOQI guidelines	X		
Patients on **EPO** must have received **stable** supplemental EPO therapy for at least 10 days (± 4 days) prior to dosing and be expected to remain on a stable dose for the duration of the study	X		

Study Entry Criteria	Protocol Number		
	62,745-6 and 62,745-7	**62,745-5 Post-amendment**	**62,745-5 Pre-amendment**
Have received stable supplemental **EPO** therapy for at least 10 (±4) days prior to dosing and be expected to remain on a stable dose for the duration of the study		X	
Have received stable supplemental EPO therapy (±25% of current dose) for at least 2 weeks			X
Have an **Hgb ≤ 11.0 g/dl** at Day -10 (±4 days) and Day -5 (±3 days)	X		
Have an **Hgb ≤ 11.5 g/dl** at Day -10 (±4 days) and Day -5 (±3 days)		X	
Have an **Hgb ≤12 g/dl** at three different time points within 4 weeks of dosing			X
Have a **TSAT ≤ 30%** at Day -5 (±3 days) prior to dosing	X	X	
Have a **ferritin of ≤ 600 ng/ml** at Day -5 (±3 days) prior to dosing	X	X	
Have an iron saturation (TSAT) ≤30% and a ferritin ≤600 ng/ml within 5±2 days before either ferumoxytol dosing or starting oral iron on study			X
Have a negative serum pregnancy test result prior to dosing, unless the subject is 2 years postmenopausal, or has a documented tubal ligation or total hysterectomy, confirmed by the Principal Investigator	X	X	

Table 9: Exclusion Criteria for the phase 3 Efficacy Studies

Study Entry Criteria	Protocol Number		
	62,745-6 and 62,745-7	**62,745-5 Post-amendment**	**62,745-5 Pre-amendment**
Exclusion Criteria			
Women who are pregnant, capable of becoming pregnant and not practicing an acceptable form of birth control, or who are breast feeding	X	X	X
Subjects currently participating in a clinical study with another investigational drug or device or who have received an investigational drug or device within 30 days of enrolment in this study	X	X	X
Subjects who have been on parenteral or oral iron therapy between the Day -10 (±4 days) visit and until completion of the study	X	X	
Subjects who have been on parenteral or oral iron therapy within 2 weeks prior to dosing			X
Subjects with active gastrointestinal bleeding or acute bleeding episodes within 4 weeks of enrolment	X	X	X

Study Entry Criteria	Protocol Number		
	62,745-6 and 62,745-7	**62,745-5 Post-amendment**	**62,745-5 Pre-amendment**
Subjects who have causes of anaemia other than iron deficiency (eg, systemic lupus erythematosus, myeloma, rheumatoid arthritis)	X	X	X
Subjects who have had major surgery within 1 month prior to enrolment in the study, or planned surgery (other than vascular access) while the subjects are on the study	X		
Subjects who have had major surgery within 1 month prior to enrolment in the study, or planned surgery while the subjects are on the study		X	
Subjects who have had major surgery within 1 month prior to enrolment in the study			X
Subjects who are refractory (not responding) to EPO or who are receiving in excess of **25,000 Units/week of EPO**		X	
Subjects who are refractory (not responding) or who are receiving in excess of **35,000 Units/week of EPO**	X		X
Subjects receiving in excess of 120 µg Aranesp per 2 weeks	X	X	
Subjects whose **EPO** status changes while on study	X		
Subjects with active infections requiring ongoing treatment	X	X	X
Subjects with uncontrolled hyperparathyroidism (known parathyroid hormone [PTH] ≥ 1,500 pg/ml and on medication to treat the disease)	X	X	
Subjects with uncontrolled hyperparathyroidism			X
Subjects who have had a malignancy (except for non melanoma cancer of the skin), unless the subject has received curative treatment and has been disease free for ≥2 years	X	X	
Subjects who have had a malignancy (except for non melanoma cancer of the skin), unless the subject has received curative treatment and has been disease free for >5 years			X
Subjects who the Investigator determines have a medical status that would preclude the subject's participation in this protocol	X	X	X
Subjects who receive blood transfusions within 2 weeks prior to enrolment and until completion of the study	X	X	
Subjects on haemodialysis / peritoneal dialysis	X		
Subjects with any allergies to iron products or multiple (two or more) drug allergies	X	X	

Abbreviations: HIPAA, Health Insurance Portability and Accountability Act.

Treatments

In the randomized phases of the three pivotal studies (study -5 post amendment), subjects were randomly assigned to one of two treatment groups and received open-label study medication as follows:

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

All patients who entered the optional non-randomised Readmission Phase received two separate doses of 510 mg Feraheme IV, the first given on Day 0 of the Readmission Phase (Day 0R) and the 2nd 5 (± 3) days later.

Administration:

Administration of ferumoxytol was performed by a physician or by a qualified individual under the direct supervision of a physician.

Two separate doses of 510 mg ferumoxytol were to be administered IV on Day 0 and Day 5 (±3 days).

Ferumoxytol was to be administered IV at a rate of 1 mL (30 mg Fe) per second (17 seconds).

Dose administrations that took longer than 1 minute (60 seconds) were considered protocol violations.

Objectives

Studies 62,745-6, 62,745-7
The objective of these studies was to evaluate the safety and efficacy of ferumoxytol versus oral iron for iron replacement therapy in subjects with CKD who were not on dialysis (stages 1-5).

62,745-5
The objective of this study was to evaluate the safety and efficacy of ferumoxytol compared with oral iron as an iron replacement therapy in subjects with chronic kidney disease (CKD) stage 5D on hemodialysis who were receiving supplemental erythropoiesis stimulating agent(s) (ESA) therapy.

Outcomes/endpoints

Primary and secondary endpoints as well as safety endpoints and additional efficacy measures were identical in the final protocol versions of studies 62,745-6 / 62,745-7 and of the post amendment part of study 62,745-5. The following endpoints were pre-defined for the randomized phase:

Primary efficacy endpoint:

- mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication

Secondary efficacy endpoints in the Randomized Phase of the study:

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

- Hemoglobin and Ferritin Responders defined as:
    - The proportion of subjects with an increase of at least 1.0 g/dL in Hgb at either post-initial dose timepoint (Day 21 or Day 35 visit) accompanied by an increase of at least 160 ng/mL in ferritin at either post-initial dose timepoint (Day 21 or Day 35 visit)
- The mean change from Baseline in ferritin at 3 weeks (Day 21 visit) post-initial dose of study medication

Exploratory endpoints:

- Mean change from Baseline in Hgb at Day 21 post-initial dose of study medication
- Mean change from Baseline in serum ferritin at Day 35 post-initial dose of study medication
- Mean change from Baseline in serum iron at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in percent hypochromic red cells at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in TIBC at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in reticulocyte count at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in TSAT at Day 21 and Day 35 post-initial dose of study medication
- Mean change from Baseline in reticulocyte Hgb content (CHr) at Day 21 and Day 35 post-initial dose of study medication

Sample size

Studies 62,745-6 and 62,745-7
Initially, no formal sample size calculation was performed. The sample size was changed twice during the conduct of the studies. In the second amendment, a sample size calculation was performed assuming a 0.6 g/dL difference between treatment groups in mean change from baseline in Hgb at the Day 35 visit and a common SD of 1.2 g/dL, the sample size would provide 90% power, with 57 subjects in the oral iron group and 171 subjects in the ferumoxytol group, to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (76 subjects) drop out rate due to potential exclusions from the ITT Population, a sufficient number of subjects were to be enrolled to result in 304 subjects randomized in a 3:1 ratio to ferumoxytol or oral iron.

No interim analyses were planned for this study and none were performed.

Study 62,745-5
Initially, no formal sample size calculation was performed. The sample size was changed twice during the conduct of the studies. In the second amendment, a sample size calculation was performed assuming a 0.6 g/dl difference between treatment groups in hemoglobin mean change from baseline and a common standard deviation of 1.2 g/dl. With 86 patients in the oral iron group and 86 patients in the ferumoxytol group, there is 90% power to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (58 subjects) drop out rate due to potential exclusions from the intent-to-treat population, a sufficient number of subjects were to be enrolled to result in 230 subjects randomized in a 1:1 ratio to oral iron or ferumoxytol.

No interim analyses were planned for this study and none were performed.

Randomisation and blinding (masking)

Studies 62745-6, 62745-7, and 62745-5 were open-label, randomized studies.

Statistical methods

Analysis sets:

The statistical methods in the final analysis plans were identical in the studies 62,745-6, 62,745-7 and the post amendment part of study 62,745-5.

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

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

To remove potential confounders of efficacy results, additional analyses were to be performed on the Efficacy Evaluable Population, which was pre-defined as all subjects who were randomized and:

- Did not violate any inclusion or exclusion criteria.
    - All inclusion and exclusion criteria were evaluated as collected on the CRF except for criteria that were designed to confirm lab test results or visit windows. Lab values were confirmed using the data collected via the central laboratory. Visit windows were assessed using broader boundaries than those required per protocol. Specifically, it was verified that both Baseline Hgb blood draws were taken within 15 days prior to dosing and that the Day 35 Hgb blood draw was taken within 45 days post-dosing
- Were compliant with study medication.
    - To enable a comparison of efficacy between subjects who received both doses of ferumoxytol and subjects who received a comparable dose of delivered oral iron, the Efficacy Evaluable Population was defined as subjects having taken at least 60% the prescribed amount. This corresponds to an administered dose of 2500 mg (50 pills of 50 mg each), which, factoring in the incomplete gastrointestinal absorption of oral iron (40%), represents a minimum delivered amount of 1000 mg iron.
    - Subjects in the ferumoxytol group were required to receive both injections of 510 mg (approximately 1.0 g of IV iron).
- Had non-missing Baseline and Day 35 Hgb values
- Had both Baseline Hgb blood draws within 15 days prior to dosing
- Had the Day 35 Hgb blood draw taken within 45 days post-dosing (taken within 40 days post-dosing for study 62745-5)
- Did not receive any other iron product after the Day -10 lab draw
- Did not start an ESA after the Day -10 lab draw
- Did not have an ESA dose change greater than 25% of Baseline ESA
- Did not receive a transfusion of packed RBCs after the Day -10 lab draw

The Efficacy Evaluable Population was used for confirmatory analysis of clinical efficacy.

Ad study 62745-5:

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

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

Primary analysis of efficacy

The pivotal studies evaluated a single primary efficacy endpoint. The full 5% Type I error (statistical significance considered to be reached at a p-value $\leq$0.05) was allocated to test the primary hypothesis.

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

The mean hemoglobin change from baseline will be compared across treatment groups using a two-sided, two-sample t-test with statistical significance considered to be reached at a p-value $\leq$ 0.05.

H0: Both ferumoxytol and oral iron provide an equivalent increase in hemoglobin at the Day 35 visit from baseline. The mean of patient-specific hemoglobin changes from baseline among ferumoxytol treated patients is equivalent to that of patients treated with oral iron.

HA: Ferumoxytol provides a greater increase in hemoglobin than does oral iron at the Day 35 visit from baseline. The mean of patient-specific hemoglobin changes from baseline among ferumoxytol treated patients is greater to that of patients treated with oral iron.

Additional Hb analyses

An additional analysis was performed using the Day 35 visit Hgb levels to evaluate the subject-specific mean changes from Baseline separately for each treatment group, using a two-sided, paired-sample t-test with a 1% Type I error (statistical significance considered to be reached at a p-value $\leq$0.01). The null hypothesis was that there is no change in Day 35 visit Hgb from Baseline.

<u>Adjustment for co-variates</u>

An analysis of covariance (ANCOVA) model was used to assess the impact of site on the Day 35 visit Hgb change from Baseline and included effects for categorical and continuous variables. An ANCOVA model also was used to compare the Day 35 visit Hgb change from Baseline between the two treatment groups when adjusted for Baseline Hgb (continuous), serum ferritin (continuous), and ESA use (dichotomous) in studies 62,745-6, 62,745-7, and alternatively ESA dose (continuous) in study 62,745-5.

A longitudinal model was used to quantify and test the average effect of treatment on the change from Baseline in Hgb over time and included a covariate for treatment (categorical), time (categorical), Baseline Hgb (continuous), and a treatment-by-time interaction. An additional longitudinal model was used post-hoc to quantify and test the average effect of treatment on actual Hgb values over time as the response and included a covariate for treatment (categorical), time (categorical), Baseline Hgb (continuous), and a treatment-by-time interaction.

All analyses involving modeling displayed two models; 1) Full Model, a model with all covariates, and 2) Reduced Model, a model with only statistically significant covariates (p-value <0.05). In the event of a significant site or treatment-by-site effect, these covariates were included in all modeling analyses. In

the event of a significant Baseline ferritin or ESA use effect, these covariates were included in the longitudinal modelling analysis.

In addition, the average Hgb value by visit was plotted over time for each treatment group.

Secondary analyses of efficacy

The following secondary efficacy endpoints were summarized:

- The difference in the proportions of subjects achieving at least a 1.0 g/dL increase from Baseline in Hgb at the Day 35 visit (Hgb responders) between the two treatment groups was analyzed using a two-sided chi-square test with statistical significance considered to be reached at a p-value ≤0.05. The null hypothesis was that the proportion of subjects achieving at least a 1.0 g/dL increase in Hgb from Baseline at the Day 35 visit is equivalent among subjects treated with ferumoxytol as compared with subjects treated with oral iron; ie, the difference in the proportion of hemoglobin responders in the ferumoxytol group compared to the oral iron group is zero.
- The difference in the proportions of subjects achieving at least a 1.0 g/dL increase from Baseline in Hgb accompanied by a 160 ng/mL increase from Baseline in ferritin at either the Day 21 or Day 35 visit (Hgb and ferritin responders) between the two treatment groups was analyzed using a two-sided chi-square test with statistical significance considered to be reached at a p-value ≤0.05. The null hypothesis was that the proportion of subjects achieving an increase of at least 1.0 g/dL in Hgb and an increase of at least 160 ng/mL in ferritin from Baseline at either the Day 21 or Day 35 visit is equivalent among subjects treated with ferumoxytol as compared with subjects treated with oral iron; ie, the difference in the proportion of Hgb and ferritin responders in the ferumoxytol group compared to the oral iron group is zero.

The following secondary efficacy endpoint was summarized:

- The mean change from Baseline in ferritin at 3 weeks (Day 21 visit) was compared across treatment groups using a two-sided, two-sample t-test with statistical significance considered to be reached at a p-value ≤0.05. The null hypothesis was that both ferumoxytol and oral iron provide an equivalent increase from Baseline in ferritin at the Day 21 visit; ie, the mean of subject-specific ferritin changes from Baseline among ferumoxytol treated subjects is equivalent to that of subjects treated with oral iron.

Handling of Missing Data

For the primary and secondary efficacy endpoints, in the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.

Note: The following was separately provided within the 'Integrated Summary of Effectiveness':

Subjects with a missing change from Baseline analysis value were conservatively assumed to have no change from Baseline (imputed change of zero). A sensitivity analysis examined the impact of three additional imputation methods on the primary efficacy analysis. The three imputation methods included last observation carry forward (LOCF), in group means, and worst case. The value for imputation was the change from Baseline. The LOCF method calculated the change from Baseline using the last non-missing value, the in group means method imputed the average treatment group change from Baseline mean, and the worst case method imputed the most unfavorable change from Baseline observed in the ferumoxytol treatment group for ferumoxytol-treated subjects with missing values and the most favorable change from Baseline observed in the oral iron group for oral iron-treated subjects with missing values.

For the results, see 'Ancillary analyses'.

Adjustment for multiple comparisons

The study evaluated a single primary efficacy endpoint and three secondary efficacy endpoints. No p-value adjustment was required.

Subgroup analyses

Studies 62,745-6 and 62,745-7
Subjects were permitted to be on an ESA during the study provided stable supplemental ESA therapy was received for at least 10 days (±4 days) prior to dosing and subjects remained on a stable dose for the duration of the study. A confirmatory subgroup analysis of subjects who were on ESA and who were not on ESA was performed using the ITT Population and repeated for the Evaluabale Population to evaluate the primary efficacy endpoint.

Study 62,745-5

Efficacy analyses were not stratified.

Note: The following was separately provided within the 'Integrated Summary of Effectiveness':

The Hgb endpoints (the mean change from Baseline in Hgb at Week 5 and Hgb Responders) have been analyzed in the subgroups defined in this section. Subgroups were chosen to illustrate a consistent treatment effect regardless of demographic subgroup and to examine potential confounders of the effect of treatment. Descriptive statistics (N, mean, SD, minimum, 25th percentile, median, 27th percentile, and maximum) are presented for each continuous endpoint, and frequency and percentage are presented for categorical endpoints. Statistical testing was not conducted for subgroup analyses. The following subgroup categories were defined.

Age (<50 years; 50 to <65 years; 65 to <75 years; ≥75 years); Gender (Male/female); Race (Caucasian; Black or African-American; Other); Geographic Region (Northeast; Midwest; South; West); Stage of CKD (Stage 1 and 2; Stage 3; Stage 4, Stage 5D, Stage 5D on PD, Stage 5D on HD), Kidney transplant (Native kidney function (stages 1-5); Functioning kidney transplant (stages 1-5); Dialysis (stage 5D)); Baseline Hb (<9.0 g/dL; 9.0 to <10.0 g/dL; 10.0 to <11.0 g/dL; 11.0 to <12.0 g/dL; ≥12.0 g/dL); Baselien Ferritin (<150 ng/mL; 150 to <300 ng/mL; 300 to <450 ng/mL; ≥450 ng/mL); Erythropoiesis Stimulating Agent Therapy (Not receiving ESA therapy; Receiving stable ESA therapy (dose within 25% of Baseline); Started ESA therapy or unstable ESA dose (increase or decrease of dose >25% of Baseline)); Other concomitant medications: ACE Inhibitors/ARB and Anticoagulants (ACE inhibitors/ARB; Anticoagulants; ACE inhibitors/ARB and anticoagulants; Neither ACE inhibitors/ARB nor anticoagulants); Calcium-containing compounds (yes/no).

For the results, see 'Ancillary analyses'.

Results

Participant flow

Table 10: Subject Disposition (Study 62,745-6)

Subject Disposition	Ferumoxytol 2 x 510 mg N=228 n (%)	Oral Iron 200 mg/day N=76 n (%)
Randomized	228 (100)	76 (100)
Withdrawn prior to initial dose	11 (4.8)	1 (1.3)
Completed Randomized Phase	208 (91.2)	63 (82.9)
Withdrawn post-initial dose	9 (3.9)	12 (15.8)
Protocol violation	2 (0.9)	1 (1.3)
Adverse event	4 (1.8)	9 (11.8)
Lost to follow-up	2 (0.9)	1 (1.3)
Withdrew consent	1 (0.4)	0
Other/administrative	0	1 (1.3)
Subjects Entering Readmission Phase	22 (9.6)	40 (52.6)

Note: All percentages based on number of subjects enrolled in the study.
Data Source: Table 14.1.1.1.1 and Table 14.1.2.1.

Table 11: Subject Disposition (Study 62,745-7)

Subject Disposition	Ferumoxytol 2 x 510 mg N=227 n (%)	Oral Iron 200 mg/day N=77 n (%)
Subjects Randomized [a]	227 (100)	77 (100)
Withdrawn prior to initial dose	7 (3.1) [a]	3 (3.9)
Completed Randomized Phase	215 (94.7)	67 (87.0)
Withdrawn post-initial dose	5 (2.2)	7 (9.1)
Protocol violation	0	0
Lack of compliance	1 (0.4)	0
Adverse event	1 (0.4)	7 (9.1)
Lost to follow-up	0	0
Withdrew consent	1 (0.4)	0
Death	2 (0.9)	0
Other/administrative	0	0
Subjects Entering Readmission Phase	21 (9.3)	30 (39.0)

Table 12: Subject Disposition (Study 62,745-5, post-amendment)

Subject Disposition	2 x 510 mg Ferumoxytol N=114 n (%)	Oral Iron 200 mg/day N=116 n (%)
Randomized	114 (100)	116 (100)
Withdrawn prior to initial dose	4 (3.5)	2 (1.8)
Completed Randomized Phase	102 (89.5)	99 (85.3)
Withdrawn post-initial dose	8 (7.0)	15 (12.9)
Protocol violation	3 (2.6)	4 (3.4)
Adverse event	4 (3.5)	9 (7.8)
Death	1 (0.9)	1 (0.9)
Withdrew consent	0	1 (0.9)
Subjects Entering Readmission Phase	7 (6.1)	39 (33.6)

Note: All percentages based on number of subjects randomized in the study.
Data Source: Table 14.1.1.1.1, Table 14.1.3.1, and Listing 16.2.5.1.

Table 13: Subject Disposition (Study 62,745-5, pre-amendment)

Subject Disposition	2 x 510 mg Ferumoxytol N=64 n (%)	4 x 255 mg Ferumoxytol N=62 n (%)	Oral Iron 200 mg/day N=22 n (%)
Randomized	64 (100.0)	62 (100.0)	22 (100.0)
Withdrawn prior to initial dose	6 (9.4)	2 (3.2)	5 (22.7)
Completed Randomized Phase	54 (84.4)	55 (88.7)	16 (72.7)
Withdrawn post-initial dose	4 (6.3)	5 (8.1)	1 (4.5)
Protocol violation	1 (1.6)	2 (3.2)	0
Adverse event	0	3 (4.8)	1 (4.5)
Lost to follow-up	1 (1.6)	0	0
Death	1 (1.6)	0	0
Withdrew consent	1 (1.6)	0	0
Subjects Entering Readmission Phase	7 (10.9)	12 (19.4)	10 (45.5)

Note: All percentages based on number of subjects randomized in the study.
Data Source: Table 14.1.2.1.1 and Listing 16.2.5.1

Recruitment

Studies 62745-6 and 62,745-7

Both studies were multicentre studies conducted at sites in the United States (62,745-6: 20 sites, 62,745-7: 31 sites)

In study 62,745-6, the first subject was randomized on 10 May 2004. The last subject's final visit occurred on 25 September 2006.

In study 62,745-7, the first subject was randomized on 02 June 2004. The last subject's final visit occurred on 20 December 2006.

62,745-5

The first subject was randomized on 09 August 2004. The last subject’s final visit occurred on 24 April 2007.

Conduct of the study

The original study protocols were subject to extensive amendments while the open label studies were ongoing. Two major amendments were implemented to the study protocols of each pivotal study including alterations of the sample size, the primary endpoint hypothesis and statistical methods for primary endpoint analysis (see table below). These amendments were made in response to changing standards of care or as a result of regulatory discussions with FDA.

Study 62-745-5 originally was planned as a 3-arm study to compare two different dosage schemes of Rienso (i.e. 2 x 510 mg IV and 4 x 255 mg IV) controlled by oral iron. After randomisation of 148 patients (about half the planned study-population) the sponsor decided to abandon the study protocol and changed the study design. Apart from the changes described above, the Hgb entry criterium was lowered, the 4 x 255mg Rienso treatment arm was dropped since the primary goal of the ferumoxytol development program was to safely deliver the full 1 g target treatment course of iron in as few doses as possible; therefore the randomisation pattern was changed from 3 : 3 : 1 to a 1 : 1 randomisation.

In the dossier the 'post-amendment part' is presented as the pivotal study to confirm efficacy in HD patients and the 'pre-amendment part' as descriptive data only.

Table 14 Major Amendments to Protocols of the pivotal studies

Studies 62-745-6 and -7		**Study 62-745-5**	
Original protocol: 01-16-2004		**Original protocol: 03-25-2004**	
1. Sample size	200 150 IV: 50 oral	1. Sample size	350 150 : 150 (4 x IV): 50 oral
2.Randomisation	3 : 1	2. Randomisation	3 : 3: 1
3. Inclusion criterion	Hgb ≤ 11 g/dl	3. Inclusion criterion	Hgb ≤ 12 g/dl
4. Primary endpoint	Hgb-change at Day 35 each patient as his own control	4. Primary endpoint	Hgb-change at Day 35 each patient as his own control
5. Test method	no information	5. Test method	no information
Amendment 1: 10-26-2005		**Amendment 2: 10-26-2005**	
1. Sample size 2. Randomisation	'up to' 400 300 IV : 100 oral 3 : 1	1. Sample size 2. Randomisation 3. Therapy groups 4. Inclusion criterion 5. Introduction of ESA changing rules	290 (145 : 145) 1 : 1 4 x 255mg IV group removed Hgb ≤ 11,5 g/dl ESA dose may be changed if drop in Hgb >0.5 g/dl and Hgb <11.0g/dl
Amendment 2: 06-08-2006		**Amendment 3: 06-08-2006**	
1. Sample size	304 (228 IV : 76 oral)	1. Sample size	230 (115 IV : 115 oral)
2.Randomisation	3 : 1	2. Randomisation	1 : 1
3. Primary endpoint	Mean Hgb-change at Day 35 across treatment groups	3. primary endpoint	Mean Hgb-change at Day 35 across treatment groups
4. Test method	t-test	4. test method	t-test

Notes: Study 62-745-5 Amendment 1 dated 12-06-2004: ESA dosing to be adjusted ± 25% at the discretion of the Investigator and other minor changes only.
Statistical analysis plans for all 3 pivotal studies dated 06-22-2006. Study periods: Date of first subject randomized to date of last subject completed. Study 62-745-5: 09 August 2004 - 24 April 2007; study 62-745-6: 05-10-2004 – 09-26-2006; study 62-745-7: 06-02-2004 – 12-20-2006. Reviewers table

Baseline data

Demographic characteristics

Table 15: Demographics, All Randomize Subjects (Modified ITT Population) (Integrated Summary of Effectiveness)

	N	Age (Years) Mean±SD	Gender (%) Male/Female	Race (%) C/B/O [a]
Protocol 62,745-6				
Ferumoxytol 2 x 510 mg	217	64.99±14.34	41.0/59.0	58.1/33.2/8.8
Oral Iron 200 mg/day	75	63.43±10.85	32.0/68.0	60.0/37.3/2.7
Protocol 62,745-7				
Ferumoxytol 2 x 510 mg	220	65.58±14.14	41.4/58.6	66.8/31.8/1.4
Oral Iron 200 mg/day	74	67.57±13.19	37.8/62.2	62.2/33.8/4.1
Post-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	110	59.19±14.30	49.1/50.9	32.7/60.0/7.3
Oral Iron 200 mg/day	113	60.75±13.04	62.8/37.2	35.4/57.5/7.1
Pre-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	58	57.10±14.15	41.4/58.6	39.7/51.7/8.6
Ferumoxytol 4 x 255 mg	60	58.55±14.86	43.3/56.7	35.0/53.3/11.7
Oral Iron 200 mg/day	17	60.18±11.51	41.2/58.8	41.2/58.8/0.0
All Protocols				
Ferumoxytol 2 x 510 mg	605	63.39±14.55	42.6/57.4	54.9/39.3/5.8
Ferumoxytol 4 x 255 mg	60	58.55±14.86	43.3/56.7	35.0/53.3/11.7
Oral Iron 200 mg/day	279	63.24±12.70	46.6/53.4	49.5/45.9/4.7
All Subjects	944	63.04±14.08	43.9/56.1	52.0/42.2/5.8

a. Race: C=Caucasian; B=Black or African-American; O=Other (Asian, Pacific Islander, Native Hawaiian, American Indian, and Alaska Native).
Abbreviation: SD=Standard deviation.
Data Source: Statistical Table 2.1, Statistical Table 4.1, and Statistical Table 5.1

Body weight

Study 62745-6

Demographic	Ferumoxytol 2 x 510 mg N=228	Oral Iron 200 mg/day N=76	p-value [a]
Weight (kg)			0.0369*
n	226	76	
Mean ± SD	86.65±22.79	93.24±26.33	
Median (range)	82.41 (41.77-166.62)	88.76 (51.76-175.50)	

Study 62745-7

Demographic	Ferumoxytol 2 x 510 mg N=226	Oral Iron 200 mg/day N=77	p-value [a]
Weight (kg)			0.1635
N	224	76	
Mean ± SD	89.72±23.56	85.34±23.72	
Median (range)	85.63 (44.49-180.69)	82.41 (45.40-161.62)	

Study 62745-5 (post amendment)

Demographic	2 x 510 mg Ferumoxytol N=114	Oral Iron 200 mg/day N=116	p-value [a]
Weight (kg)			0.8326
n	114	115	
Mean±SD	87.08±24.91	86.33±28.49	
Median (range)	80.75 (48.70-176.40)	81.20 (40.70-277.50)	

[a] Pearson's chi-square test and two sample t-test for evaluating a treatment difference in categorical and continuous variables, respectively. A p-value <0.05 is considered statistically significant.

Efficacy Variables collected at baseline

Table 16: Efficacy Variables Collected at Baseline (ITT Population, Study 62,745-6) (CSR)

Variable at Baseline [a]	Ferumoxytol 2 x 510 mg N=228	Oral Iron 200 mg/day N=76
Hgb (g/dL), n	228	76
Mean±SD	9.96±0.69	9.95±0.78
Ferritin (ng/mL), n	228	76
Mean±SD	146.10±173.55	143.53±144.87
Serum Iron (µg/dL), n	228	75
Mean±SD	44.99±18.24	43.83±18.58
TIBC (µg/dL), n	228	76
Mean±SD	441.01±124.57	458.25±117.92
TSAT (%), n	228	76
Mean±SD	11.28±6.10	10.14±5.47
Hypochromic Red Cells (%), n	228	76
Mean±SD	21.18±17.05	23.75±18.78
CHr (pg), n	228	76
Mean ± SD	29.90±2.58	29.24±3.07
Reticulocyte count (%), n	228	76
Mean±SD	1.77±0.67	1.76±0.79

a. Baseline was the average of Day -10 and Day -5 measures.
Abbreviations: CHr=reticulocyte hemoglobin content; Hgb=hemoglobin; SD=standard deviation; TIBC=total iron binding capacity; TSAT=transferrin saturation.
Data Source: Table 14.2.1.1.1, Table 14.2.1.6.1, and Table 14.2.1.7.1.

Table 17: Efficacy Variables Collected at Baseline (ITT Population, Study 62,745-7) (CSR)

Variable at Baseline [a]	Ferumoxytol 2 x 510 mg N=226	Oral Iron 200 mg/day N=77
Hgb (g/dL), n	225	77
Mean ± SD	9.85±0.77	9.94±0.73
Ferritin (ng/mL), n	225	77
Mean ± SD	123.74±125.36	146.18±136.34
Serum Iron (µg/dL), n	224	77
Mean ± SD	41.57±18.19	42.68±16.70
TIBC (µg/dL), n	225	77
Mean ± SD	463.62±129.58	446.99±134.53
TSAT (%), n	225	77
Mean ± SD	9.79±5.42	10.37±5.22
Hypochromic red cells (%), n	224	77
Mean ± SD	24.98±19.49	22.86±16.37
CHr (pg), n	224	77
Mean ± SD	29.26±2.89	29.94±2.58
Reticulocyte count (%), n	224	77
Mean ± SD	1.77±0.76	1.91±0.88

a. Baseline was the average of Day -10 and Day -5 measures.
Abbreviations: CHr=reticulocyte hemoglobin content; Hgb=hemoglobin; SD=standard deviation; TIBC=total iron binding capacity; TSAT=transferrin saturation.
Data Source: Table 14.2.1.1.1, Table 14.2.1.6.1, and Table 14.2.1.7.1.

Table 18: Efficacy Measures Collected at Baseline (Post-amendment ITT Population, Study 62,745-5) (CSR)

Variable at Baseline [a]	2 x 510 mg Ferumoxytol N=114	Oral Iron 200 mg/day N=116
Hgb (g/dL), n	114	115
Mean±SD	10.59±0.67	10.69±0.57
Ferritin (ng/mL), n	114	115
Mean±SD	340.52±159.07	357.56±171.65
Serum Iron (µg/dL), n	112	115
Mean±SD	49.49±20.20	48.23±18.73
TIBC (µg/dL), n	114	115
Mean±SD	322.36±76.78	313.89±65.84
TSAT (%), n	114	115
Mean±SD	15.71±7.21	15.91±6.29
Hypochromic red cells (%), n	114	115
Mean±SD	11.05±13.77	9.09±10.77
CHr (pg), n	114	115
Mean±SD	31.12±2.62	31.57±2.48
Reticulocyte count (%), n	114	115
Mean±SD	1.93±0.80	1.93±0.79

a. Baseline was the average of Day -10 and Day -5 measures.
Abbreviations: CHr=reticulocyte hemoglobin content; Hgb=hemoglobin; ITT=Intent-to-treat; SD=standard deviation; TIBC=total iron binding capacity; TSAT=transferrin saturation.
Data Source: Table 14.2.1.1.1, Table 14.2.1.6.1, and Table 14.2.1.7.1.

Medical History and Disease Characteristics

62745-6

In study 62,745-6 more patients in the oral group had Diabetes as primary reason for CKD compared to the IV group (49.6% (113/228) IV vs. 68.4% (52/76) oral) and more patients in the Feraheme group had Hypertension as primary reason for CKD compared to the oral group (35% (81/228) IV vs. 17.1% (13/76) oral). The distribution of causes of CKD was statistically significantly different between treatment groups (p=0.0321). Most subjects entered the study with CKD stage 3 (ferumoxytol, 36.0%; and oral iron, 39.5%) or stage 4 (ferumoxytol, 46.9%; and oral iron, 47.4%).

Medical history was comparable between treatment groups and no statistically significant differences were observed. As expected for this target population, >90% of subjects in either treatment group had abnormalities in the cardiovascular, genitourinary, and endocrine body systems.

62745-7

Disease characteristics were comparable across treatment groups. The primary reasons for CKD in the majority of subjects were diabetes (ferumoxytol, 39.4%; and oral iron, 42.9%) and hypertension (ferumoxytol, 33.6%; and oral iron, 33.8%). Most subjects entered the study with CKD stage 3 (ferumoxytol, 37.6%; and oral iron, 39.0%) or stage 4 (ferumoxytol, 47.3%; and oral iron, 53.2%). No statistically significant differences were observed.

Medical history was comparable between treatment groups and no statistically significant differences were observed. As expected for this target population, >90% of subjects in either treatment group had abnormalities in the cardiovascular, genitourinary, and endocrine body systems.

62745-5

Disease characteristics were comparable across treatment groups. The primary reasons for CKD in the majority of subjects were diabetes (2 x 510 mg ferumoxytol, 43.0%; and oral iron, 42.2%) and hypertension (2 x 510 mg ferumoxytol, 34.2%; and oral iron, 34.5%); the distribution of causes of CKD was not statistically different between treatment groups.

Medical history was comparable between treatment groups and no statistically significant differences were observed. As expected for this target population, >80% of subjects in either treatment group had abnormalities in the cardiovascular, genitourinary, and endocrine body systems.

CKD Stages

Table 19: Stage of CKD at Baseline in the pivotal studies (integrated summary of effectiveness)

	Stage of CKD at Baseline using eGFR [a] ($mL/min/1.73m^2$) n (%)					
	N	Stage 1 or 2	Stage 3	Stage 4	Stage 5	Stage 5D on HD
Protocol 62,745-6 [b]						
Ferumoxytol 2 x 510 mg	217	4 (1.8)	78 (35.9)	101 (46.5)	30 (13.8)	0
Oral Iron 200 mg/day	75	2 (2.7)	29 (38.7)	36 (48.0)	8 (10.7)	0
Protocol 62,745-7 [c]						
Ferumoxytol 2 x 510 mg	220	3 (1.4)	84 (38.2)	103 (46.8)	25 (11.4)	0
Oral Iron 200 mg/day	74	1 (1.4)	29 (39.2)	39 (52.7)	4 (5.4)	0
Post-amendment Protocol 62,745-5						
Ferumoxytol 2 x 510 mg	110	0	0	0	0	110 (100.0)
Oral Iron 200 mg/day	113	0	0	0	0	113 (100.0)
Pre-amendment Protocol 62,745-5						
Ferumoxytol 2 x 510 mg	58	0	0	0	0	58 (100.0)
Ferumoxytol 4 x 255 mg	60	0	0	0	0	60 (100.0)
Oral Iron 200 mg/day	17	0	0	0	0	17 (100.0)
All Protocols						
Ferumoxytol 2 x 510 mg	605	7 (1.2)	162 (26.8)	204 (33.7)	55 (9.1)	168 (27.8)
Ferumoxytol 4 x 255 mg	60	0	0	0	0	60 (100.0)
Oral Iron 200 mg/day	279	3 (1.1)	58 (20.8)	75 (26.9)	12 (4.3)	130 (46.6)
All Subjects	944	10 (1.1)	220 (23.3)	279 (29.6)	67 (7.1)	358 (37.9)

a. eGFR=186 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.21 if African-American) (57).
Stage 1 or 2: eGFR≥60; Stage 3: eGFR=30-59; Stage 4: eGFR=15-29; Stage 5: eGFR<15.
b. In Protocol 62,745-6, the CKD stage was not obtained for four subjects in the ferumoxytol treatment group.
c. In Protocol 62,745-7, the CKD stage was not obtained for five subjects in the ferumoxytol treatment group and one subject in the oral iron treatment group.
Note: There were no randomised subjects with CKD stage 5D on peritoneal dialysis.
Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; HD=hemodialysis; ITT=intent-to-treat.
Data Source: Statistical Table 7.1

Kidney Transplant Status at Baseline

In Protocols 62,745-6 and 62,745-7 at Baseline, the distribution of subjects in the kidney transplant status subgroups was similar between treatment groups, with most subjects having native kidney function, and 5.3% of subjects having a functioning kidney transplant. No subject was on dialysis (stage 5D), as defined by the inclusion and exclusion criteria of the protocol.

In study 62745-6, 5.5% (12/217) of subjects in the ferumoxytol treatment arm, and 6.7% (5/75) in the oral iron control group had a kidney transplant. In study 62745-7, 5.0% (11/220) of subjects in the ferumoxytol treatment arm, and 4.1% (3/74) in the oral iron control group had a kidney transplant.

All subjects in the post- and pre-amendment protocols of study *62,745-5* were on dialysis (stage 5D) at baseline.

Use of Erythropoiesis Stimulating Agents (Integrated Summary of Effectiveness)

Table 20: Use of Erythropoiesis Stimulating Agents in the pivotal studies (Integrated summary of effectiveness)

	Use of ESA Therapy			
	N	Not Receiving ESA Therapy n (%)	Received Stable ESA Therapy n (%)	Started ESA Therapy or Dose Change >25% [a] n (%)
Protocol 62,745-6				
Ferumoxytol 2 x 510 mg	217	138 (63.6)	68 (31.3)	11 (5.1)
Oral Iron 200 mg/day	75	43 (57.3)	27 (36.0)	5 (6.7)
Protocol 62,745-7				
Ferumoxytol 2 x 510 mg	220	129 (58.6)	84 (38.2)	7 (3.2)
Oral Iron 200 mg/day	74	41 (55.4)	30 (40.5)	3 (4.1)
Post-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	110	0	86 (78.2)	24 (21.8)
Oral Iron 200 mg/day	113	0	88 (77.9)	25 (22.1)
Pre-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	58	0	29 (50.0)	29 (50.0)
Ferumoxytol 4 x 255 mg	60	0	34 (56.7)	26 (43.3)
Oral Iron 200 mg/day	17	0	12 (70.6)	5 (29.4)
All Protocols				
Ferumoxytol 2 x 510 mg	605	267 (44.1)	267 (44.1)	71 (11.7)
Ferumoxytol 4 x 255 mg	60	0	34 (56.7)	26 (43.3)
Oral Iron 200 mg/day	279	84 (30.1)	157 (56.3)	38 (13.6)
All Subjects	944	351 (37.2)	458 (48.5)	135 (14.3)

a. The ESA therapy dose change could be an increase or decrease >25% at any time between Day -10 and Day 35.
Abbreviations: ESA= Erythropoiesis stimulating agent(s); ITT=intent-to-treat.
Data Source: Statistical Table 9.1

Concomitant medications with potential impact on the results (Integrated Summary of Effectiveness)

Use of ACE Inhibitors/ARB and Anticoagulants, All Randomized Subjects

Angiotensin antagonism (ACE inhibitors or ARB) is well described to inhibit erythropoiesis, and the use of anticoagulants (including aspirin, warfarin, heparin and other agents such as clopidogrel) may enhance bleeding. The possible effect of these agents may be to blunt the mean change from Baseline in Hgb at five weeks, relative to subjects who are not on these agents.

Table 19: Use of ACE Inhibitors/ARB and Anticoagulants, All Randomized Subjects (Modified ITT)

	Use of ACE Inhibitors/ARB and Anticoagulants				
	N	ACE Inhibitors/ARB n (%)	Anticoagulants n (%)	ACE Inhibitors/ARB and Anticoagulants n (%)	Neither ACE Inhibitors/ARB nor Anticoagulants n (%)
Protocol 62,745-6					
Ferumoxytol 2 x 510 mg	217	85 (39.2)	26 (12.0)	84 (38.7)	22 (10.1)
Oral Iron 200 mg/day	75	21 (28.0)	12 (16.0)	34 (45.3)	8 (10.7)
Protocol 62,745-7					
Ferumoxytol 2 x 510 mg	220	67 (30.5)	39 (17.7)	85 (38.6)	29 (13.2)
Oral Iron 200 mg/day	74	18 (24.3)	12 (16.2)	32 (43.2)	12 (16.2)
Post-amendment Protocol 62,745-5					
Ferumoxytol 2 x 510 mg	110	18 (16.4)	27 (24.5)	40 (36.4)	25 (22.7)
Oral Iron 200 mg/day	113	18 (15.9)	40 (35.4)	28 (24.8)	27 (23.9)
Pre-amendment Protocol 62,745-5					
Ferumoxytol 2 x 510 mg	58	12 (20.7)	19 (32.8)	11 (19.0)	16 (27.6)
Ferumoxytol 4 x 255 mg	60	7 (11.7)	23 (38.3)	18 (30.0)	12 (20.0)
Oral Iron 200 mg/day	17	2 (11.8)	5 (29.4)	7 (41.2)	3 (17.6)
All Protocols					
Ferumoxytol 2 x 510 mg	605	182 (30.1)	111 (18.3)	220 (36.4)	92 (15.2)
Ferumoxytol 4 x 255 mg	60	7 (11.7)	23 (38.3)	18 (30.0)	12 (20.0)
Oral Iron 200 mg/day	279	59 (21.1)	69 (24.7)	101 (36.2)	50 (17.9)
All Subjects	944	248 (26.3)	203 (21.5)	339 (35.9)	154 (16.3)

Abbreviations: ACE=Angiotensin converting enzyme; ARB= angiotensin receptor blocker; ITT=intent-to-treat.

Use of Calcium-Containing Compounds

The effect of concurrent therapy with oral calcium-containing products, which are commonly used for lowering phosphorus in patients with CKD, may be to impair oral iron absorption.

Table 22: Use of Calcium-Containing Compounds, All Randomized Subjects (Modified ITT)

	Use of Calcium-Containing Compounds		
	N	No Calcium-containing Compounds n (%)	Calcium-containing Compounds n (%)
Protocol 62,745-6			
Ferumoxytol 2 x 510 mg	217	173 (79.7)	44 (20.3)
Oral Iron 200 mg/day	75	53 (70.7)	22 (29.3)
Protocol 62,745-7			
Ferumoxytol 2 x 510 mg	220	175 (79.5)	45 (20.5)
Oral Iron 200 mg/day	74	56 (75.7)	18 (24.3)
Post-amendment Protocol 62,745-5			
Ferumoxytol 2 x 510 mg	110	54 (49.1)	56 (50.9)
Oral Iron 200 mg/day	113	47 (41.6)	66 (58.4)
Pre-amendment Protocol 62,745-5			
Ferumoxytol 2 x 510 mg	58	34 (58.6)	24 (41.4)
Ferumoxytol 4 x 255 mg	60	29 (48.3)	31 (51.7)
Oral Iron 200 mg/day	17	6 (35.3)	11 (64.7)
All Protocols			
Ferumoxytol 2 x 510 mg	605	436 (72.1)	169 (27.9)
Ferumoxytol 4 x 255 mg	60	29 (48.3)	31 (51.7)
Oral Iron 200 mg/day	279	162 (58.1)	117 (41.9)
All Subjects	944	627 (66.4)	317 (33.6)

Abbreviations: ITT=intent-to-treat.
Data Source: Statistical Table 13.1

Compliance

62745-6

In the oral iron treatment group, 92.0% of subjects were assumed to have received at least 2500 mg cumulative dose of oral iron, and 86.7% of subjects were at least 80% compliant with the oral iron dosing regimen (ie, received at least 3360 mg cumulative dose of iron). The median cumulative dose for all 75 subjects was 4100 mg (range: 300 to 8200 mg).

Treatment compliance with ferumoxytol was 97.2%; ie, 211 subjects received two complete doses (Table 18). The mean dose administration time for completed doses was 31.01 seconds. Five (2.3%) subjects received just one complete dose, and 1 (0.5%) subject did not receive any complete doses. Three subjects received at least one incomplete dose ranging in volume from 6 to 9 mL (180 to 270 mg).

62745-7

In the oral iron treatment group, 93.2% of subjects were assumed to have received at least 2500 mg cumulative dose of oral iron, and 89.2% of subjects were at least 80% compliant with the oral iron dosing regimen (ie, received at least 3360 mg cumulative dose of iron). The median cumulative dose for all 74 subjects was 4100 mg (range: 100-5000 mg).

Treatment compliance with ferumoxytol was 95.5%; ie, 210 subjects received two complete doses (Table 18). The mean dose administration time for completed doses was 40.84 seconds. Eight subjects (3.6%) received just one complete dose, and 2 subjects (0.9%) did not receive any complete doses. Eight subjects (3.6%) received at least one incomplete dose ranging in volume from 6 to 12 mL (180 to 360 mg).

62745-5

In the oral iron treatment group, 77.9% of subjects were at least 80% compliant with the oral iron dosing regimen as defined by the protocol (ie, received at least 3360 mg cumulative dose of iron) (Table 26). Furthermore, 90.3% of subjects received at least 2500 mg cumulative dose of oral iron based on pill counts, which, assuming a 40% absorption rate, corresponds to approximately 1.0 g of absorbed iron. The median cumulative dose for all 113 subjects was 4000 mg (range: 100 to 7800 mg).

Treatment compliance with ferumoxytol 2 x 510 mg was 94.5%; ie, 104 subjects received two complete doses (Table 25). Each complete dose of ferumoxytol (510 mg in 17 mL) was scheduled by the protocol to be administered over 17 seconds but no greater than 60 seconds; dose administrations taking longer than 60 seconds were considered protocol violations. The mean dose administration time for completed doses was 31.65 seconds. Six subjects received just one complete dose. One subject received one complete dose and one incomplete dose of 15 mL.

Numbers analysed

Table 21: Study 62,745-6: Subject Evaluability (CSR)

Subject Population	Ferumoxytol 2 x 510 mg N=228 n (%)	Oral Iron 200 mg/day N=76 n (%)
Randomized	228 (100)	76 (100)
ITT	228 (100)	76 (100)
Safety (evaluable)	217 (95.2)	75 (98.7)
Not evaluable (no test agent received), n	11	1
Efficacy Evaluable [a]	181 (79.4)	55 (72.4)
No test agent received	11	1
Violated inclusion/exclusion criteria [b]	3	2
Not compliant with study medication [c]	6	6
Missing Baseline or Day 35 Hgb value	11	12
Baseline Hgb draws out of window [d]	2	1
Day 35 Hgb draw out of window [e]	11	7
Started ESA after Day -10 lab drawn	6	6
Change in ESA dose >25% of Baseline ESA	8	3
Received any other iron product after Day -10 lab drawn	4	0
Received transfusion of packed RBCs after Day -10 lab drawn	0	1
Subjects Entering Readmission Phase	22 (9.6)	40 (52.6)

a. Subjects can be included in more than one category.
b. Violated inclusion/exclusion criteria with regard to laboratory values. Laboratory values (Hgb, TSAT, and serum ferritin) were confirmed using the data collected via the central laboratory.
c. Oral iron compliance for the Efficacy Evaluable Population was defined as taking at least 50 pills (50x50 mg=2500 mg) and ferumoxytol compliance as receipt of two complete IV doses (2x510 mg=1020 mg).
d. Baseline Hgb not within 15 days prior to dosing.
e. Day 35 Hgb not within 45 days post first dose.

Abbreviations: Hgb=hemoglobin; ITT=intent-to-treat; ESA=erythropoiesis stimulating agent(s); RBCs=red blood cells
Note: All percentages based on number of subjects enrolled in the study.
Data Source: Table 14.1.1.2.1 and Table 14.1.2.1.

Table 22: Study 62,745-7: Subject Evaluability (CSR)

Subject Population	Ferumoxytol 2 x 510 mg N=227 n (%)	Oral Iron 200 mg/day N=77 n (%)
Randomized	227 (100)	77 (100)
ITT	226 (99.6)	77 (100)
Randomized twice [a]	1 (0.4)	0
Safety (Evaluable)	220 (96.9)	74 (96.1)
Not Evaluable (did not receive study medication)	6 (2.6)	3 (3.9)
Efficacy Evaluable [b]	183 (80.6)	54 (70.1)
Violated inclusion/exclusion criteria [c]	11	6
Not compliant with study medication [d]	10	5
Missing Baseline or Day 35 Hgb value	5	6
Baseline Hgb draws out of window [e]	2	1
Day 35 Hgb draw out of window [f]	9	3
Started an ESA after Day -10 lab drawn	7	5
Change in an ESA dose >25% of Baseline ESA	4	2
Received any other iron product after Day -10 lab drawn	3	2
Received transfusion of packed RBCs after Day -10 lab drawn	0	0
Subjects Entering Readmission Phase	21 (9.3)	30 (39.0)

b. Subjects can be included in more than one category.
c. Violated inclusion/exclusion criteria with regard to laboratory values. Laboratory values (Hgb, TSAT, and serum ferritin) were confirmed using the data collected via the central laboratory.
d. Oral iron compliance for the Efficacy Evaluable Population was defined as taking at least 50 pills (50x50 mg=2500 mg) and ferumoxytol compliance as receipt of two complete IV doses (2x510 mg=1020 mg).
e. Baseline Hgb not within 15 days prior to dosing.
f. Day 35 Hgb not within 45 days post first dose.

Abbreviations: Hgb=hemoglobin; ITT=intent-to-treat; ESA=erythropoiesis stimulating agent(s); RBCs=red blood cells
Note: All percentages based on number of subjects enrolled in the study.
Data Source: Table 14.1.1.1.1, Table 14.1.1.2.1., and Table 14.1.2.1.

62,745-5

The Post-amendment ITT Population was defined as all subjects who were randomized and was the primary population used in the analysis of efficacy.

The Efficacy Evaluable Population included subjects in the Post-amendment ITT Population who did not have confounding factors that could potentially impact the mean change from Baseline in Hgb at Day 35. The specific reasons for subjects being excluded from the Efficacy Evaluable Population are presented in the table below. The Efficacy Evaluable Population was used for confirmatory analysis.

Table 23: Study 62,745-5: Subject Evaluability (CSR)

Subject Population	2 x 510 mg Ferumoxytol N=114 n (%)	Oral Iron 200 mg/day N=116 n (%)
Randomized	114 (100)	116 (100)
ITT	114 (100)	116 (100)
Safety (evaluable)	110 (96.5)	113 (97.4)
Not evaluable (no test agent received), n	4	3
Efficacy Evaluable [a]	65 (57.0)	64 (55.2)
No test agent received	4	3
Violated inclusion/exclusion criteria [b]	2	2
Not compliant with study medication [c]	10	14
Missing Baseline or Day 35 Hgb value	12	15
Baseline Hgb draws out of window [d]	4	3
Day 35 Hgb draw out of window [e]	7	7
Started ESA after Day -10 lab drawn	19	20
Change in ESA dose >25% of Baseline ESA	21	20
Received any other iron product after Day -10 lab drawn	7	1
Subjects Entering Readmission Phase	7 (6.1)	39 (33.6)

a. Subjects can be included in more than one category.
b. Violated inclusion/exclusion criteria with regard to laboratory values. Laboratory values (Hgb, TSAT, and serum ferritin) were confirmed using the data collected via the central laboratory.
c. Oral iron compliance for the Efficacy Evaluable Population was defined as taking at least 50 pills of the total 84 pills expected (50x50 mg=2500 mg) and ferumoxytol compliance as receipt of two complete IV doses (2x510 mg=1020 mg).
d. Baseline Hgb not within 15 days prior to dosing.
e. Day 35 Hgb not within 45 days post first dose.

Abbreviations: Hgb=hemoglobin; ITT=intent-to-treat; ESA=erythropoietin stimulating agent; RBCs=red blood cells.
Note: All percentages based on number of subjects randomized in the study.
Data Source: Table 14.1.1.2.1.

Outcomes and estimation

In the final versions of the study protocols, the primary endpoint for all three studies was the mean change from baseline in hemoglobin at Day 35. Secondary endpoints were the percentage of subjects who were hemoglobin responders (defined as an increase in hemoglobin from baseline of ≥1 g/dL) at Day 35, the percentage of subjects who were hemoglobin and ferritin responders (the latter defined as an increase in ferritin from baseline of ≥160 ng/mL), and the mean change from baseline in serum ferritin at Day 21. There was a statistically significant achievement of all the primary and secondary endpoints across all three studies, with greater increases in hemoglobin and ferritin and higher responder rates following ferumoxytol treatment relative to oral iron treatment

Analyses of primary and main secondary Efficacy Endpoints

62745-6

Table 24: Primary Efficacy Endpoint: Mean Change from Baseline in Hemoglobin at Day 35 (ITT and Efficacy Evaluable Populations, Study 62,745-6)

	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day	
Primary Efficacy Endpoint	**n**	**Mean±SD**	**n**	**Mean±SD**
Hgb (g/dL): ITT Population	**N=228**		**N=76**	
Baseline [a]	228	9.96±0.69	76	9.95±0.78
Day 35	206	10.88±1.27	63	10.15±1.07
Mean change from Baseline at Day 35 [b]	228	0.82±1.24	76	0.16±1.02
p-value for treatment difference [c]	<0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.1871	
Hgb (g/dL): EE Population	**N=181**		**N=55**	
Baseline [a]	181	9.99±0.67	55	10.05±0.72
Day 35	181	10.84±1.27	55	10.11±1.07
Mean change from Baseline at Day 35 [b]	181	0.86±1.23	55	0.06±1.09
p-value for treatment difference [c]	<0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.6849	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and change from Baseline in Hgb was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: EE=Efficacy Evaluable; Hgb=hemoglobin; ITT=Intent-to-treat; SD=standard deviation.
Data Source: Table 14.2.1.1.1 and Table 14.2.1.1.2.

Table 25: Study 62,745-6 Summary of Secondary Efficacy (ITT Population,)

Efficacy Endpoint (ITT Population)	**Ferumoxytol N=228**	**Oral Iron N=76**	**p-value [a]**
Change from Baseline in Hgb at Day 35, mean±SD g/dl	**0.82±1.24**	**0.16±1.02**	**<0.0001**
Secondary:			
Proportion of Hgb responders, n (%)	89 (39.0%)	14 (18.4%)	0.0010
Proportion of Hgb and ferritin responders, n (%)	98 (43.0%)	0 (0.0%)	<0.0001
Ferritin Baseline values	*146.10±173.55*	*143.53±144.87*	
Mean change from Baseline in ferritin at Day 21, mean±SD ng/ml	518.08±331.86	6.47±47.16	<0.0001
Mean change from Baseline in serum ferritin at Day 35 post-initial dose of study medication, mean±SD ng/ml	381.72±278.61	6.94±60.11	<0.0001

[a] Two sample t-test for evaluating a treatment difference. Statistically significant at a p value <0.05.
Abbreviations: Hgb=Haemoglobin; ITT=intent-to-treat; SD=standard deviation.
Reviewer's table

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Table 26: Primary Efficacy Endpoint: Mean Change from Baseline in Hemoglobin at Day 35 (ITT and Efficacy Evaluable Populations, Study 62,745-7)

Primary Efficacy Endpoint	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day	
	n	Mean±SD	n	Mean±SD
Hgb (g/dL): ITT Population	**N=226**		**N=77**	
Baseline [a]	225	9.85±0.77	77	9.94±0.73
Day 35	214	11.15±1.33	68	10.55±1.14
Mean change from Baseline at Day 35 [b]	226	1.22±1.25	77	0.52±0.98
p-value for treatment difference [c]	<0.0001*			
p-value for change from Baseline [d]	<0.0001**		<0.0001**	
Hgb (g/dL): EE Population	**N=183**		**N=54**	
Baseline [a]	183	9.90±0.71	54	9.94±0.79
Day 35	183	11.25±1.29	54	10.65±1.14
Mean change from Baseline at Day 35 [b]	183	1.35±1.25	54	0.71±1.01
p-value for treatment difference [c]	0.0007*			
p-value for change from Baseline [d]	<0.0001**		<0.0001**	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and the mean change from Baseline in Hgb was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: EE=Efficacy Evaluable; Hgb=hemoglobin; ITT=Intent-to-treat; SD=standard deviation.
Data Source: Table 14.2.1.1.1 and Table 14.2.1.1.2.

Table 27: Study 62,745-7 Summary of Secondary Efficacy (ITT Population)

Efficacy Endpoint (ITT Population)	Ferumoxytol N=226	Oral Iron N=77	p-value [a]
Change from Baseline in Hgb at Day 35, mean±SD g/dl	**1.22±1.25**	**0.52±0.98**	**<0.0001**
Secondary:			
Proportion of Hgb responders, n (%)	117 (51.8)	15 (19.5)	<0.0001
Proportion of Hgb and ferritin responders, n (%)	115 (50.9)	0	<0.0001
Ferritin Baseline values	*123.74±125.36*	*146.18±136.34*	
Mean change from Baseline in ferritin at Day 21, mean±SD ng/ml	412.58±247.95	4.26±48.22	<0.0001
Mean change from Baseline in serum ferritin at Day 35 post-initial dose of study medication, mean±SD ng/ml	300.66±214.90	0.33±82.03	<0.0001

a. Two sample t-test for evaluating a treatment difference. Statistically significant at a p value <0.05.
Abbreviations: Hgb=Haemoglobin; ITT=intent-to-treat; SD=standard deviation.
Reviewer's table

62745-5 (Post-amendment)

Table 28: Primary Efficacy Endpoint: Mean Change from Baseline in Hemoglobin at Day 35 (ITT and Efficacy Evaluable Populations, Study 62,745-5)

Primary Efficacy Endpoint	Ferumoxytol 2 x 510 mg		Oral Iron 200 mg/day	
	n	Mean±SD	n	Mean±SD
Hgb (g/dL): ITT Population	**N=114**		**N=116**	
Baseline [a]	114	10.59±0.67	115	10.69±0.57
Day 35	102	11.72±1.20	101	11.22±1.22
Mean change from Baseline at Day 35 [b]	114	1.02±1.13	116	0.46±1.06
p-value for treatment difference [c]	0.0002*			
p-value for change from Baseline [d]	<0.0001**		0.0001**	
Hgb (g/dL): EE Population	**N=65**		**N=64**	
Baseline [a]	65	10.66±0.59	64	10.70±0.62
Day 35	65	11.79±1.07	64	11.16±1.02
Mean change from Baseline at Day 35	65	1.13±1.01	64	0.46±0.86
p-value for treatment difference [c]	0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.0001**	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both the pre-dose measures were missing, then Baseline was set to missing and the mean change from Baseline in Hgb was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: EE=Efficacy Evaluable; Hgb=hemoglobin; ITT=Intent-to-treat.
Data Source: Table 14.2.1.1.1 and Table 14.2.1.1.2.

Table 29: Study 62,745-5 Summary of Secondary Efficacy (Post-amendment ITT Population)

Efficacy Endpoint (ITT Population)	Ferumoxytol N=114	Oral Iron N=116	p-value [a]
Proportion of Hgb responders, n (%)	56 (49.1)	29 (25.0)	0.0002
Proportion of Hgb and ferritin responders, n (%)	53 (46.5)	1 (0.9)	<0.0001
Ferritin Baseline values	*340.52±159.07*	*357.56±171.65*	
Mean change from Baseline in ferritin at Day 21, mean ± SD ng/ml	356.66±247.12	-37.56±106.98	<0.0001
Mean change from Baseline in serum ferritin at Day 35 post-initial dose of study medication, mean±SD ng/ml	233.93±206.95	-59.23±106.22	<0.0001

[a] Two sample t-test for evaluating a treatment difference. Statistically significant at a p value <0.05.
Abbreviations: Hgb=Haemoglobin; ITT=intent-to-treat; SD=standard deviation. Reviewer's table

62745-5 (Pre-amendment)

Table 30: Study 62,745-5 Summary of secondary efficacy (Pre-amendment Randomized Population)

	Ferumoxytol 2 x 510 mg N=64	**Ferumoxytol 4 x 255 mg N=62**	**Oral Iron 200 mg/day N=22**	
Primary				**p-value**
Baseline Hgb (g/dL)	*11.08±0.72*	*11.11±0.58*	*11.19±0.63*	
Had Day 35 evaluable data	**n=54**	**n=55**	**n=16**	
Change from Baseline at Day 35 mean ± SD g/dl	**0.71±1.00**	**0.87±1.14**	**0.31±0.82**	
Secondary				
Hgb Responders [b] , n (%)	19 (29.7)	29 (46.8)	5 (22.7)	0.0517[a]
Hgb and Ferritin Responders [c], n (%)	23 (35.9)	32 (51.6)	0	0.0001[a]*
Ferritin Baseline (ng/mL)	*307.22±159.01*	*314.54±166.12*	*316.76±155.61*	
Had Day 35 evaluable data	**n=56**	**n=55**	**n=15**	
Mean change from Baseline at Day 21	414.55±296.47	439.70±270.20	-20.98±43.86	*<0.0001[d]**

[a] Two-sided chi-square test for evaluating a treatment difference across all three groups. *Statistically significant at a p-value <0.05. [b] Hemoglobin responders are defined as subjects who achieved at least a 1.0 g/dL increase in Hgb from Baseline at the Day 35 visit. [c] Hemoglobin and ferritin responders are defined as subjects who achieved at least a 1.0 g/dL increase in Hgb from Baseline at either post-initial dose assessment accompanied by at least a 160 ng/mL increase in serum ferritin from Baseline at either post-initial dose assessment. [d] Single factor ANOVA for evaluating a treatment difference. *Statistically significant at a p-value <0.05. Reviewers table

Note: Additional Sensitivity analyses were conducted post hoc for the primary efficacy endpoint. These are discussed under ''Ancillary Analyses'.

Additional analyses adjusted for covariates

The Applicant provided also additional Analyses adjusted for certain co-variates involving modeling displayed two models: 1) Full Model, a model with all covariates, and 2) Reduced Model, a model with only statistically significant covariates (p-value <0.05). ANCOVA adjusted for study site (included covariates: treatment, baseline haemoglobin, site and treatment*site interaction), adjusted for baseline heamoglibin, ferritin and ESA use/dose (included covariates: treatment, baseline haemoglobin, baseline ferritin, EPO), and longitudinal Analyses including different time points (included additional coavariates time that includes values of four or three vistis and time*treatment interaction) were calculated. The covariate ESA was included as ESA use (dichotomous) in studies 62,745-6, 62,745-7, and alternatively ESA dose (continuous) in study 62,745-5.

Subgroup analyses by ESAuse (Yes/No) (Studies 62,745-6/-7 only)

Table 31: Mean Change from Baseline in Hemoglobin at Day 35 by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-6) (CSR)

ESA Status at Baseline	ESA(+) N=116				ESA(-) N=188			
	Ferumoxytol 2 x 510 mg N=83		Oral Iron 200 mg/day N=33		Ferumoxytol 2 x 510 mg N=145		Oral Iron 200 mg/day N=43	
Subgroup Analysis	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Hgb (g/dL)								
Baseline [a]	83	9.93±0.64	33	9.89±0.83	145	9.98±0.71	43	10.00±0.74
Day 35	76	11.20±1.49	26	10.21±1.20	130	10.69±1.08	37	10.11±0.97
Mean change from Baseline at Day 35 [b]	83	1.16±1.49	33	0.19±1.14	145	0.62±1.02	43	0.13±0.93
p-value for treatment difference [c]	0.0010*				0.0052*			
p-value for change from Baseline [d]	<0.0001**		0.3415		<0.0001**		0.3714	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and change from Baseline was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: ESA=erythropoiesis stimulating agents; Hgb=hemoglobin; SD=standard deviation.
Data Source: Table 14.2.1.8.1.

Table 32: Analysis of Hemoglobin Responders and Hemoglobin and Ferritin Responders by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-6)

ESA Status at Baseline	ESA(+) N=116			ESA(-) N=188		
	Ferumoxytol 2 x 510 mg N=83	Oral Iron 200 mg/day N=33		Ferumoxytol 2 x 510 mg N=145	Oral Iron 200 mg/day N=43	
Subgroup Analysis	n (%)	n (%)	p-value [a]	n (%)	n (%)	p-value [a]
Hgb Responders [b]	46 (55.4)	8 (24.2)	0.0024*	43 (29.7)	6 (14.0)	0.0394*
Hgb and Ferritin Responders [c]	48 (57.8)	0	<0.0001*	50 (34.5)	0	<0.0001*
Day 21 Visit						
Hgb increase ≥1 g/dL	39 (47.0)	7 (21.2)	-	35 (24.1)	5 (11.6)	-
Ferritin increase ≥160 ng/mL	71 (85.5)	1 (3.0)	-	127 (87.6)	0	-
Day 35 Visit						
Hgb increase ≥1 g/dL	46 (55.4)	8 (24.2)	-	43 (29.7)	6 (14.0)	-
Ferritin increase ≥160 ng/mL	61 (73.5)	3 (9.1)	-	117 (80.7)	0	-

a. Two-sided chi-square test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
b. Hemoglobin responders are defined as subjects who achieve at least a 1.0 g/dL increase in Hgb from Baseline at the Day 35 visit.
c. Hemoglobin and ferritin responders are defined as subjects who achieve at least a 1.0 g/dL increase in Hgb from Baseline at either post-initial dose assessment accompanied by at least a 160 ng/mL increase in ferritin from Baseline at either post-initial dose assessment.
Abbreviations: ESA=erythropoiesis stimulating agents; Hgb=hemoglobin; SD=standard deviation.
Data Source: Table 14.2.1.9.1.

Table 33: Mean Change from Baseline in Ferritin at Day 21 by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-6)

ESA Status at Baseline	ESA(+) N=116				ESA(-) N=188			
	Ferumoxytol 2 x 510 mg N=83		Oral Iron 200 mg/day N=33		Ferumoxytol 2 x 510 mg N=145		Oral Iron 200 mg/day N=43	
Subgroup Analysis	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Serum Ferritin (ng/mL)								
Baseline [a]	83	154.08±125.77	33	144.90±134.09	145	141.53±195.99	43	142.48±154.19
Day 21	76	666.78±346.27	26	182.72±161.51	132	723.99±360.45	37	140.02±149.07
Mean change from Baseline at Day 21 [b]	83	473.48±319.31	33	9.93±58.77	145	543.61±337.27	43	3.81±36.39
p-value for treatment difference [c]	<0.0001*				<0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.3390		<0.0001**		0.4966	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and change from Baseline was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for both safety and efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: ESA=erythropoiesis stimulating agents; SD=standard deviation.
Data Source: Table 14.2.1.10.1.

Table 34: Mean Change from Baseline in Hemoglobin at Day 35 by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-7) (CSR)

ESA Status at Baseline	ESA(+) N=129				ESA(-) N=174			
	Ferumoxytol 2 x 510 mg N=95		Oral Iron 200 mg/day N=34		Ferumoxytol 2 x 510 mg N=131		Oral Iron 200 mg/day N=43	
Subgroup Analysis	N	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Hgb (g/dL)								
Baseline [a]	95	9.84±0.81	34	9.77±0.80	130	9.87±0.74	43	10.07±0.65
Day 35	88	11.61±1.50	30	10.76±1.38	126	10.84±1.10	38	10.38±0.89
Mean change from Baseline at Day 35 [b]	95	1.64±1.39	34	0.86±1.26	131	0.91±1.05	43	0.25±0.56
p-value for treatment difference [c]	0.0052*				<0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.0004**		<0.0001**		0.0056**	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and change from Baseline was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for the efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: ESA=erythropoiesis stimulating agent(s); Hgb=hemoglobin; SD=standard deviation.
Data Source: Table 14.2.1.8.1.

Table 35: Analysis of Hemoglobin Responders and Hemoglobin and Ferritin Responders by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-7)

ESA Status at Baseline	ESA(+) N=129			ESA(-) N=174		
	Ferumoxytol 2 x 510 mg N=95	Oral Iron 200 mg/day N=34		Ferumoxytol 2 x 510 mg N=131	Oral Iron 200 mg/day N=43	
Subgroup Analysis	n (%)	n (%)	p-value [a]	n (%)	n (%)	p-value [a]
Hgb Responders [b]	62 (65.3)	13 (38.2)	0.0061*	55 (42.0)	2 (4.7)	<0.0001*
Hgb and Ferritin Responders [c]	60 (63.2)	0	<0.0001*	55 (42.0)	0	<0.0001*
Day 21 Visit						
Hgb increase ≥1 g/dL	57 (60.0)	8 (23.5)	-	40 (30.5)	4 (9.3)	-
Ferritin increase ≥160 ng/mL	78 (82.1)	0	-	116 (88.5)	0	-
Day 35 Visit						
Hgb increase ≥1 g/dL	62 (65.3)	13 (38.2)	-	55 (42.0)	2 (4.7)	-
Ferritin increase ≥160 ng/mL	63 (66.3)	1 (2.9)	-	98 (74.8)	0	-

a. Two-sided chi-square test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
b. Hemoglobin responders are defined as subjects who achieve at least a 1.0 g/dL increase in Hgb from Baseline at the Day 35 visit.
c. Hemoglobin and ferritin responders are defined as subjects who achieve at least a 1.0 g/dL increase in Hgb from Baseline at either post-initial dose assessment accompanied by at least a 160 ng/mL increase in ferritin from Baseline at either post-initial dose assessment.
Abbreviations: ESA=erythropoiesis stimulating agent(s); Hgb=hemoglobin.
Data Source: Table 14.2.1.9.1.

Table 36: Mean Change from Baseline in Ferritin at Day 21 by Use of Erythropoiesis Stimulating Agents at Baseline (ITT Population, Study 62,745-7)

ESA Status at Baseline	ESA(+) N=129				ESA(-) N=174			
	Ferumoxytol 2 x 510 mg N=95		Oral Iron 200 mg/day N=34		Ferumoxytol 2 x 510 mg N=131		Oral Iron 200 mg/day N=43	
Subgroup Analysis	N	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Serum Ferritin (ng/mL)								
Baseline [a]	95	132.15±143.81	34	144.52±122.91	130	117.60±110.13	43	147.50±147.51
Day 21	89	551.83±313.83	30	118.50±96.89	124	569.90±289.22	37	178.82±152.77
Mean change from Baseline at Day 21 [b]	95	388.34±249.20	34	-12.21±44.11	131	430.15±246.50	43	17.29±47.80
p-value for treatment difference [c]	<0.0001*				<0.0001*			
p-value for change from Baseline [d]	<0.0001**		0.1161		<0.0001**		0.0224	

a. Baseline was the average of Day -10 and Day -5 measures. If one of the pre-dose measures was missing, the nonmissing Day -10 or Day -5 measure was used to impute Baseline. If both pre-dose measures were missing, then Baseline was set to missing and change from Baseline was set to zero.
b. If laboratory samples were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was used for the efficacy analyses. In the event that either post-dose (Day 21 or Day 35 visit) efficacy parameter was missing, the analysis assumed no change from Baseline for that efficacy parameter and a value of zero was imputed for change from Baseline at that timepoint.
c. Two sample t-test for evaluating a treatment difference. *Statistically significant at a p-value <0.05.
d. Paired t-test for evaluating a change from Baseline. **Statistically significant at a p-value <0.01.
Abbreviations: ESA=erythropoiesis stimulating agent(s); SD=standard deviation.
Data Source: Table 14.2.1.10.1.

Ancillary analyses

An integrated Summary of Effectiveness was provided, where analyses were presented comparatively for all studies and across all protocols (pooled). The latter are described under section 3.7 Analysis performed across trials. In the following, the sensitivity analyses conducted on the primary efficacy endpoint are presented. Please see 'Statistical methods' for details on the method.

Sensitivity analyses with different imputation methods

Three additional imputation methods (LOCF analyses, in group means analysis, and worst case analysis) were examined for the mean change from Baseline at Week 5 for nonrandomized, subjects not previously exposed to ferumoxytol in the Modified ITT Population.

Results from these analyses were largely consistent with the imputation presented for the primary analysis where subjects with a missing change from Baseline analysis value were assumed to have no change from Baseline, with the exception for study 62745-6 and the Worst case imputation (Table 37).

Table 37: Hemoglobin (g/dL) – Week 5 change from Baseline – Worst case analysis

Modified Intent-to-Treat- All Randomized Subjects

	N	Mean	SD	Min	25th Percentile	Median	75th Percentile	Max	p-value*
Post-amendment 62745-5									0.0210
Ferumoxytol 2x510 mg	110	1.02	1.21	-1.50	0.30	1.00	1.80	5.05	
Oral Iron 200 mg/day	113	0.64	1.26	-2.75	-0.05	0.40	1.20	4.05	
Pre-amendment 62745-5									0.9383
Ferumoxytol 2x510 mg	58	0.70	1.13	-1.50	0.05	0.63	1.35	3.80	
Ferumoxytol 4x255 mg	60	0.75	1.36	-2.05	-0.03	0.88	1.65	3.55	
Oral Iron 200 mg/day	17	0.64	1.26	-1.20	-0.25	0.50	1.20	4.05	
62745-6									0.4376
Ferumoxytol 2x510 mg	217	0.71	1.52	-3.25	0.05	0.70	1.35	6.20	
Oral Iron 200 mg/day	75	0.55	1.46	-2.95	-0.25	0.35	1.15	3.70	
62745-7									0.0069
Ferumoxytol 2x510 mg	220	1.22	1.31	-1.45	0.33	1.10	2.03	5.25	
Oral Iron 200 mg/day	74	0.74	1.26	-2.05	0.00	0.50	0.95	4.00	
All Protocols									0.0065
Ferumoxytol 2x510 mg	605	0.95	1.37	-3.25	0.15	0.90	1.75	6.20	
Ferumoxytol 4x255 mg	60	0.75	1.36	-2.05	-0.03	0.88	1.65	3.55	
Oral Iron 200 mg/day	279	0.64	1.31	-2.95	-0.15	0.45	1.15	4.05	

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* Two sample t-test for protocols with two treatment groups for evaluating a treatment difference. A single factor ANOVA for protocols with more than two treatment groups for evaluating a treatment difference. A p-value < 0.05 is considered statistically significant.
Note: Subjects with a missing change from baseline calculation have been imputed using the least favorable change from baseline observed in the ferumoxytol group for ferumoxytol subjects and the most favorable change from baseline observed in the oral iron group for oral iron subjects.
Note: In pre-amendment protocol of 62745-5, no pairwise comparisons were significant at alpha 0.05 level. In integrated protocols, pairwise comparison by Bonferroni method between 2x510 Ferumoxytol and Oral Iron indicates a p-value 0.0080, no other pairwise comparisons were significant at alpha 0.05 level.

REF: Listing 5

Study FER-CKD-201

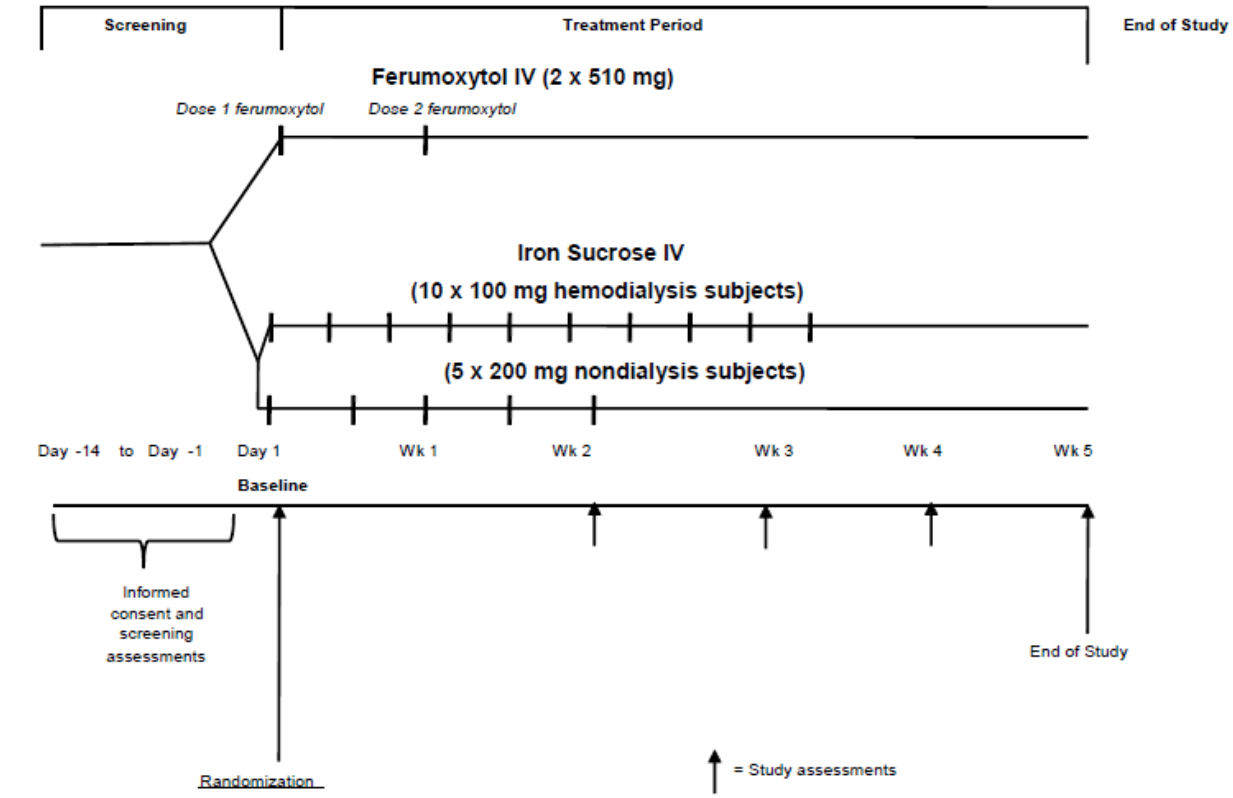
A Randomized, Multicenter Trial of Ferumoxytol Compared to Iron Sucrose for the Treatment of Iron Deficiency Anemia in Adult Subjects with Chronic Kidney Disease

(EUDRACT No. 2009-015630-30)

Methods

This was a Phase II, randomized (1:1), open-label, active-controlled, multicenter clinical trial to evaluate the safety and efficacy of ferumoxytol compared with IV iron sucrose for the treatment of IDA in subjects with CKD.

Figure 1: Study design



Study Participants

Main inclusion criteria (excerpt)

1. Males and females ≥18 years of age
2. An estimated glomerular filtration rate (eGFR) <60 mL/min or a diagnosis of underlying CKD (e.g., nephropathy, nephritis)
3. Hemoglobin <11.0 g/dL
4. TSAT <30%
5. Hemodialysis subjects on maintenance dialysis for at least three months prior to screening and receiving dialysis three times per week

Main exclusion criteria

1. History of allergy to IV iron
2. Allergy to 2 or more classes of drugs
3. Female subjects who were pregnant or intended to become pregnant, breastfeeding, within 3 months postpartum, or had a positive serum or urine pregnancy test
4. Hemoglobin value ≤7.0 g/dL
5. Parenteral iron therapy within 4 weeks prior to screening or oral iron therapy within 2 weeks prior to screening
6. Red blood cell (RBC) or whole blood transfusion within 2 weeks prior to screening or planned during the study
7. ESA therapy initiated, stopped, or dose changed by >20% within 4 weeks prior to screening, or an anticipated ESA dose change of >20% during the study
8. Receiving peritoneal dialysis (PD)

9. Subjects was not on dialysis for whom initiation of dialysis was considered imminent
10. Recent (within 4 weeks of screening) blood loss from causes other than dialysis (e.g., gastrointestinal bleeding, recent major surgery, etc)
11. Received another investigational agent within 4 weeks prior to screening, or planned receipt of an investigational agent not specified by this protocol during the study period
12. Known causes of anemia other than iron deficiency (e.g., hemolysis, vitamin B12 or folate deficiency, etc)
13. Active malignancy (except non-melanoma skin cancer or carcinoma in situ that has been excised)
14. Acute serious medical illness that required intervention or therapy within 2 weeks prior to screening (e.g., acute liver disease, coronary event)
15. Any other clinically significant medical disease or condition (e.g., uncontrolled hypertension), or label specific contraindication(s), or responsibility that, in the Investigator's opinion, could have interfered with a subject's ability to adhere to the protocol, interfere with assessment of the investigational product, or serve as a contraindication to the subject's participation in the study

Prior and prohibited therapy
Subjects were prohibited from concomitant use of any of the following medications or therapies during the 5-week Treatment Period:

• Any parenteral iron therapy other than study drug

• Any oral iron therapy, including multivitamins containing iron

• Immunosuppressive treatments including systemic steroids, unless on a stable dose prior to enrolling in the study

• Any interventions or medications to reduce bleeding or to treat anemia, unless on a stable dose prior to enrolling in the study

When medically necessary, investigators could use standard rescue therapies, including red blood cell or whole blood transfusions, or other rescue therapies, including any of the otherwise prohibited concomitant treatments listed above.

Treatments

Both hemodialysis and nondialysis subjects assigned to the ferumoxytol treatment group received two IV injections of ferumoxytol 510 mg (17 mL), the first on Day 1 and the second 5±3 days later, for a total cumulative dose of 1.02 g.

Subjects assigned to the iron sucrose treatment group received iron sucrose as a slow IV injection or IV infusion per the following treatment schedule based on dialysis status.

• Hemodialysis subjects received 100 mg iron sucrose on Day 1 and at the following 9 consecutive hemodialysis sessions over approximately 3 weeks for a total cumulative dose of 1.0 g.

• Nondialysis subjects received 200 mg iron sucrose at Day 1 and at 4 other nonconsecutive visits over a 14-day (±2 days) period for a total cumulative dose of 1.0 g.

Administration:

Intravenous ferumoxytol was administered as a rapid IV injection into a new or existing venous access site (e.g., catheter or portacath). For hemodialysis subjects, dosing began no earlier than 60 minutes following start of dialysis and when blood pressure was stable.

Intravenous iron sucrose was administered by slow injection or infusion, per the product prescribing information.

Hemodialysis Subjects: Iron Sucrose was administered undiluted as a 100 mg slow intravenous injection over 2 to 5 minutes or as an infusion of 100 mg, diluted in 100 mL of 0.9% NaCl over a period of at least 15 minutes per consecutive hemodialysis session for a total cumulative dose of 1000 mg.

Nondialysis Subjects: Iron Sucrose was administered as either a 200 mg slow IV injection undiluted over 2 to 5 minutes or as an infusion of 200 mg diluted in 100 mL of 0.9% NaCl over a period of at least 30 minutes on 5 different occasions within a 14±2 day period for a total cumulative dose of 1000 mg.

Objectives

The purpose of the study was to evaluate the safety and efficacy of IV ferumoxytol compared to IV iron sucrose for the treatment of IDA in subjects with CKD.

Primary Objective

To evaluate the safety of a 1.02 g course of IV ferumoxytol compared to 1.0 g IV iron sucrose

Additional Objective

To evaluate the efficacy of ferumoxytol as compared to iron sucrose by assessing changes in hemoglobin from Baseline to Week 5

Outcomes/endpoints

Primary efficacy endpoint:

· Mean change in hemoglobin from Baseline to Week 5

Additional endpoint:

· Proportion of subjects with an increase in hemoglobin ≥1.0 g/dL during the period from Baseline to Week 5.

Exploratory endpoints:

· Health care utilization, including hospitalizations, procedures, and outpatient visits.

· Proportion of subjects achieving a hemoglobin level ≥12.0 g/dL from Baseline to Week 5

· Mean change in TSAT from Baseline to Week 5

· Time to hemoglobin increase of ≥1.0 g/dL or to a hemoglobin level of ≥12.0 g/dL from Baseline

· Proportion of subjects requiring blood transfusion during the study

· Proportion of subjects requiring an increase in dose by >20% or initiation of ESA therapy

· Mean change in markers of iron stores (e.g., serum ferritin, serum iron) from Baseline to Week 5

Baseline blood samples were collected during the Screening Period (Day -14 to -1), on Day 1 (Baseline) Pre-Dose, Week 2 (Day 14±2), Week 3 (Day 21±2), Week 4 (Day 28±2), and Week 5 (Day 35±2) or Early Termination. Additional blood draws from hemodialysis subjects in the iron sucrose treatment arm were obtained at Week 2 and Week 3 pre-dose.

The baseline values used for the efficacy analysis will be the results collected at Day 1 (Baseline Visit). If the result is missing, the latest value available prior to initial dosing will be used.

Predose value is defined as the last measure taken during a study visit prior to dosing of study medication.

Examination of subgroups

Subgroup analyses of efficacy (Change in hemoglobin from Baseline to Week 5 and proportion of subjects with an increase in hemoglobin ≥1.0 g/dL during the period from Baseline to Week 5 parameters) were to be performed on the primary efficacy endpoints on baseline Hb level (>7.0 to ≤9.0 g/dL; >9.0 to <11.0 g/dL); hemodialyis status; age; race, sex, Baseline CKD status (Stage 1-3 and Stage 4-5) and Baseline ESA status, Prohibited medications or therapy status (received or did not receive prohibited therapies or interventions (e.g., transfusions, non-study iron therapy, interventions to stop bleeding).

Note: During the study, only 3 subjects were administered prohibited medication, thus, not permitting analysis on this subgroup.

Sample size

Approximately one hundred fifty (150) subjects (100 nondialysis and 50 hemodialysis subjects) were planned to be randomized in a 1:1 ratio to receive either ferumoxytol or iron sucrose.

The 75 subjects per treatment group gives 81% power for a non-inferiority test at alpha level of 0.05, assuming a non-inferiority margin of 0.5 (g/dL) and a common standard deviation of 1.2 for the mean hemoglobin change from Baseline at Week 5.

From a safety perspective, a sample size of 75 subjects exposed to ferumoxytol enables the detection of at least one subject with an AE with probabilities of 53%, 78%, and 90% assuming AE rates of 1%, 2%, and 3%, respectively.

No interim analyses were formally planned or conducted. However, a preliminary cut of data among 107 subjects was performed specifically to respond to inquiries from the European Medicines Agency (EMA) (18 October 2010). Because a formal interim analysis was not planned for this study, the review of these preliminary data was restricted to a limited number of AMAG staff, none of whom were directly associated with the design or conduct of the study, for the sole purpose of compiling the response; these data were not used to modify the study design or study conduct in any way. At the time of the analysis, 107 subjects had completed the Week 5 follow-up visit and had data available for analysis. Please refer to sub-point 'Ancillary analyses'.

Randomisation and blinding (masking)

This was an open-label study. Study drug was not blinded. Subjects were randomized 1:1 (ferumoxytol: iron sucrose).

Randomization into treatment groups was stratified by dialysis dependence at Baseline and Baseline haemoglobin level (>7.0 to ≤9.0 g/dL; >9.0 to <11.0 g/dL) so that equal numbers were randomized to iron sucrose and ferumoxytol.

Statistical methods

Analysis sets:

Intent-to-Treat (ITT) Population: Any randomized subject who had any exposure to study drug (IV ferumoxytol or IV iron sucrose); the efficacy analysis will be based upon randomized treatment assignment.

Evaluable Population: Any randomized subject who received either 2 doses of IV ferumoxytol or all doses

of iron sucrose (10 for hemodialysis subjects, 5 for nondialysis subjects) and had evaluable data for hemoglobin at Baseline and Week 5; the efficacy analysis will be based on actual treatment received.

The primary efficacy analyses (of efficacy and exploratory endpoints) will be performed on the ITT Population. Efficacy analyses on selected parameters will be repeated for the Evaluable Population. All safety analyses will be performed on the Safety Population.

Efficacy analyses

Efficacy analyses in the study will be carried out on both the intent-to-treat (ITT) population and efficacy evaluable (EE) population. The EE population will be used as a confirmatory analysis of the efficacy endpoints. The primary analyses of efficacy endpoints will use LOCF imputation methods for missing values for the ITT population.

Hemoglobin Change from Baseline

The change in hemoglobin from Baseline to Week 5 will be calculated for each subject as:

Hemoglobin Change = Hemoglobin (Week 5) – Hemoglobin (Baseline).

Descriptive statistics for hemoglobin change from baseline by visit will be presented by treatment group along with treatment difference. P-value and a two-sided 95% confidence interval for the treatment difference in mean change in hemoglobin from Baseline at Week 5, based on an analysis of variance (ANOVA) model adjusted for baseline hemoglobin level, and hemodialysis status. Non-inferiority will be concluded if the lower bound of the 95% confidence interval is ≥ minus 0.5 g/dL and superiority if the lower bound is ≥0 g/dL.

Baseline hemoglobin for each subject will be the Day 1 hemoglobin (prior to injection of the study drug); the screening hemoglobin value will be used for any subjects with missing Day 1 hemoglobin.

The mean hemoglobin value and the mean changes from baseline by visit will be plotted over time by treatment group.

Proportion of subjects with an increase in hemoglobin ≥1.0 g/dL

For the binary efficacy endpoint of change in hemoglobin of ≥1 g/dL during the period from Baseline to Week 5, the frequency and percentage of responding subjects will be tabulated by treatment group, along with a point estimate of the treatment difference. The p-value for the treatment difference to Week 5 from Cochran-Mantel-Haenszel test will be presented. Baseline hemoglobin level and hemodialysis status at Baseline will be the covariates for the CMH test. 95% confidence interval around treatment differences will also be presented.

The proportion of subjects with increase in hemoglobin ≥1.0 g/dL by visit will be plotted over time by treatment group.

Exploratory endpoints will be analyzed with the intent-to-treat population. Results will be summarized as observed.

Proportion of subjects achieving a hemoglobin level ≥12.0 g/dL

For the binary endpoint of subjects achieving a hemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5, the frequency and percentage of responding subjects will be tabulated by visit and by treatment, along with a point estimate of the treatment difference in percentages.

Analysis of time to hemoglobin increase

For the analysis of time to hemoglobin increase of ≥1.0 g/dL from Baseline or to a hemoglobin level achieving ≥12.0 g/dL, all the hemoglobin values obtained at post-baseline study visits will be used to determine time to hemoglobin increase of ≥1.0 g/dL or to a hemoglobin level ≥12.0 g/dL. The actual study day of collection, rather than the scheduled visit day, will be the basis for analysis. Subjects who never achieve ≥1.0 g/dL increase in haemoglobin or a ≥12.0 g/dL by the time of the last assessment will be censored. The date of censoring will be the date study completion at Week 5 or date of study

discontinuation for those who terminated study early. The time (days) to this response will be calculated for each treatment arm using a Kaplan-Meier curve, and a treatment comparison will be performed using a log-rank statistic. Cox proportional hazard model will be used to adjust for baseline hemoglobin level and hemodialysis status.

Time to hemoglobin increase of ≥1.0 g/dL from Baseline or to a haemoglobin level achieving ≥12.0 g/dL will be presented by treatment group in a figure.

For the analysis of binary endpoints of *proportion of subjects requiring blood transfusion* and *proportion of subjects requiring an increase in dose by >20% or initiation of ESA therapy*, the frequency and percentage of responding subjects will be tabulated by treatment group, along with a point estimate of the treatment difference in response percentages.

Mean change of parameters of iron stores

For the mean change from Baseline in serum ferritin, TSAT, serum iron, and reticulocyte hemoglobin content, descriptive statistics for the summary and changes from Baseline by study visit will be presented by treatment group along with the treatment difference.

Handling of Missing Data: For analysis on ITT population, missing post-Baseline values for efficacy parameters will be imputed using Last Observation Carried Forward (LOCF) method. Sensitivity analyses for the efficacy parameters will assess the impact of imputation of missing data with no imputation and using Markov chain Monte Carlo (MCMC) method (Schafer, 1977). Subjects lost to follow-up prior to Week 5 without any recorded response will be treated as non-responders. For the intervention binary endpoints (transfusion and/or ESA use), subjects who discontinue study prior to Week 5 without an observed intervention will be treated as having no intervention. In the event that all post-dose efficacy parameters are missing, the analysis will assume no change from baseline for that efficacy parameter and a value of zero imputed for change from baseline.

Adjustment for multiple comparisons: Only mean change in hemoglobin from Baseline to Week 5 is formally tested at alpha level of 0.05. No p-value adjustment is needed.

Adjustment for Covariates

For the binary efficacy endpoint of change in hemoglobin of ≥1 g/dL during the period from Baseline to Week 5, the frequency and percentage of responding subjects was tabulated by treatment group, along with a point estimate of the treatment difference. The p-value for the treatment difference to Week 5 from Cochran-Mantel-Haenszel test was presented. Baseline hemoglobin level and hemodialysis status at Baseline were the covariates for the CMH test. 95% confidence interval around estimated treatment differences are presented.

Results

Participant flow

Table 38: Subject Disposition (ITT Population) (CSR)

Parameter	Ferumoxytol (n=80) n (%)	Iron Sucrose (n=82) n (%)	Total (N=162) n(%)
Intent-to-Treat Population	80 (100.0)	82 (100.0)	162 (100.0)
Subjects Completed Study Drug	77 (96.3)	74 (90.2)	151 (93.2)
Early Discontinuation from Study Drug	3 (3.8)	8 (9.8)	11 (6.8)
Reasons for Early Discontinuation from Study Drug			
AE	1	4	5
Investigator Discretion	0	1	1
Missing	2	3	5
Subjects Completed Study	75 (93.8)	73 (89.0)	148 (91.4)
Early Withdrawal from Study	5 (6.3)	9 (11.0)	14 (8.6)
Reasons for Early Withdrawn from Study			
AE	1	4	5
Withdrawal of Consent	1	2	3
Other	3	3	6

Note: Source table presents the percentages for reasons for discontinuation based on denominator of only those subjects who discontinued.

Data Source: Table 14.1.2.1

"Other" reasons for study withdrawal involved the Week 5 visit being missed in 2 subjects and taking a prohibited medication (Venofer) in 1 subject. In the iron sucrose group, "Other" reasons for study withdrawal involved organ transplantation in 2 subjects and administration of oral iron in 1 subject.

Protocol deviations

A total of 17 (10.5%) subjects had a total of 18 protocol deviations. Fifteen (9.3%) subjects failed to meet the inclusion/exclusion criteria for the study (5 [6.3%] ferumoxytol vs. 10 [12.2%] iron sucrose). Protocol deviations primarily involved timing of iron therapy washout (exclusion criterion 5) and ESA changes relative to study drug administration (exclusion criterion 7). For 1 subject, recorded history of recent hemodialysis indicated a 1-month difference from requirements under Inclusion Criterion 3, although this subject had a long-term history of hemodialysis prior to the gap month.

Three (1.9%) subjects received prohibited medication during the study. In the ferumoxytol group (n=80), 2 (2.5%) subjects each initiated Venofer (100 mg IV three times/week) for low iron saturation approximately 2 days after their second administration of ferumoxytol. For each of these subjects, Venofer was inadvertently continued by the Investigator for approximately 7 days. In the iron sucrose group (n=82), 1 (1.2%) subject initiated ferrous sulfate (1 tablet twice/day) for iron deficiency anemia on an unknown date in April 2011 and continuing to an unknown date in May 2011; the subject had received the first treatment with iron sucrose on 11 April 2011.

Recruitment

This study was performed at 36 sites: United States (14 sites), Poland (6), Germany (6), Canada (4), India (3), Belgium (2), and the United Kingdom (1). No analyses were performed to determine center effect.

The first subject was randomized on 01 March 2010. The last subject's final visit occurred on 19 July 2011.
This multicenter study was conducted at 36 sites: United States (14 sites), Poland (6), Germany (6), Canada (4), India (3), Belgium (2), and the United Kingdom (1). One site in Germany and 3 sites in India did not randomize subjects.

Conduct of the study

Protocol amendments: The protocol was amended twice to include administrative and editorial changes and changes in data analyses or study requirements.
Protocol Amendment 1 (26 January 2010) implemented the following changes to the study:
• To ensure subject safety with regard to the potential occurrence of hypersensitivity reactions
• Bicarbonate and magnesium were added to the list of serum chemistry analytes for completeness.

Protocol Amendment 2 (01 November 2010) implemented the following changes to the study:
• To examine the effects of ferumoxytol and iron sucrose on biomarkers of oxidative stress and tubular damage, an optional substudy was added. This substudy required participating subjects to give additional blood samples (between 5 and 7 draws) of 8mL each, before and after study drug administration. The addition of this substudy required no change to the inclusion/exclusion criteria or to the conduct of the main study and, therefore, did not alter the integrity of FER-CKD-201. Subjects who chose to enroll in the substudy signed an additional consent form.
• The protocol was updated to provide clarification regarding the timing of vital signs (measured from initiation of dosing) and the timing around the collection of AEs (60 minutes from completion of dosing).
Changes to the Planned Analyses
The following changes were made (before unblinding the data) in the statistical analysis plan from the study protocol.

• *Oxidative stress substudy*: Statistical analyses were not prospectively defined in the analysis plan. For each dose and for pooled doses, descriptive statistics were provided for biomarker data collected pre- and post-dose and the difference from pre-dose. All available data were listed by subject.

• *Exploratory Endpoints*: the following exploratory endpoints were added to the analysis to confirm the efficacy of ferumoxytol in this study.
– Proportion of subjects achieving a hemoglobin level ≥12.0 g/dL from Baseline to Week 5
– Mean change in TSAT from Baseline to Week 5
– Time to hemoglobin increase of ≥1.0 g/dL or to a hemoglobin level of ≥12.0 g/dL from Baseline
– Proportion of subjects requiring blood transfusion during the study
– Proportion of subjects requiring an increase in dose by >20% or initiation of ESA therapy
– Mean change in other markers of iron stores (e.g., serum ferritin, serum iron, reticulocyte hemoglobin content) from Baseline to Week 5.

• *Safety Endpoint*: the following safety endpoint was added to the safety analysis:
– Cardiovascular AEs (nonfatal myocardial infarction, heart failure (HF), moderate-to-severe hypertension, and hospitalization due to any cardiovascular cause)

• *Method of statistical testing*
– To be consistent with statistical analysis method used for the ferumoxytol Phase III clinical development programs in CKD subjects, the method and statistical testing for the continuous efficacy endpoint was changed from analysis of covariance (ANCOVA) to ANOVA.

After database lock, the following changes were made to the planned descriptive analyses:
• Efficacy parameters summarized at Week 5 by race were categorized into 2 groups (White and Other) as a result of the small numbers of races other than White.
• Efficacy parameters summarized at Week 5 by Baseline CKD status were categorized into CKD stages 1-3 and 4-5 because too few subjects were enrolled with Baseline CKD Stage 1 or 2 to analyze them separately.
• Efficacy parameters were not summarized at Week 5 by usage of prohibited medication or therapy because only 3 subjects received prohibited medication.

The Protocol amendments are not considered to have an impact on the study integrity.

Study Drug Compliance

The majority of Non Dialaysis patients completed their assigned total dose of 1020 and 1000 mg (95.7% and 87.0% for ferumoxytol and IS, respectively). Likewise, the majority of Dialysis patients completed their assigned entire dose (97.1% and 88.9% for ferumoxytol and IS, respectively.

Table 14.1.6
Study Drug Complinace
Intent-to-Treat Population

	Ferumoxytol			Iron Sucrose		
	Dialysis (n=34)	Non-Dialysis (n=46)	Total (n=80)	Dialysis (n=36)	Non-Dialysis (n=46)	Total (n=82)
Dose Administration [n (%)]						
0 Complete Dose	0	0	0	0	1 (2. 2%)	1 (1. 2%)
1 Complete Dose	1 (2. 9%)	2 (4. 3%)	3 (3. 8%)	0	2 (4. 3%)	2 (2. 4%)
2 Complete Dose	33 (97.1%)	44 (95.7%)	77 (96.3%)	1 (2. 8%)	0	1 (1. 2%)
3 Complete Dose	0	0	0	0	1 (2. 2%)	1 (1. 2%)
4 Complete Dose	0	0	0	1 (2. 8%)	2 (4. 3%)	3 (3. 7%)
5 Complete Dose	0	0	0	1 (2. 8%)	40 (87.0%)	41 (50.0%)
9 Complete Dose	0	0	0	1 (2. 8%)	0	1 (1. 2%)
10 Complete Dose	0	0	0	32 (88.9%)	0	32 (39.0%)

For the analysis of efficacy parameters, 3 ferumoxytol subjects (all non-dialysis) and 5 iron sucrose subjects (3 on dialysis and 2 non-dialysis) did not have Week 5 efficacy values. Missing data were handled as described in Section 'Statistical Methods' above.

Baseline data

Overall, differences in Demographics and Baseline Characteristics between the ferumoxytol group and iron sucrose group were small and not clinically meaningful. Overall (N=162), male (82 subjects, 50.6%) and female (80 subjects, 49.4%) subjects were predominantly White (70.4%) and from the United States (59.9%). Black or African American subjects comprised 21.6% (35 subjects) of the total study population. Subjects from European countries comprised 27% (44 subjects) of the total study population. The mean (SD) age and weight were 62.6 (15.05) years and 85.6 (22.15) kg, respectively, at Baseline, with subjects in the iron sucrose group being, on average, slightly heavier than the subjects in the ferumoxytol group (88.26 vs 82.85 kg, respectively). This could have slightly favoured the investigational treatment arm. The majority of subjects (122/162; 75.3%) had CKD Stage 4 or 5 and 70/162 (43.2%) subjects were on hemodialysis; no subjects had CKD Stage 1. A history of renal transplant was reported in 14 (8.6%) subjects.

The majority of subjects (87%, 141 subjects) enrolled with hemoglobin levels between 9.0 - 11.0 g/dL (vs. >7.0 to ≤9.0 g/dL; 13%, 21 subjects). Since it is known that higher effect sizes can be anticipated in patients with lower Hb levels, this could have accounted for the rather small observed mean Hb changes from baseline in the present study. Of note, while for the IS treatment group, both subgroups showed consistent results in terms of mean Hb change from baseline (0.63 and 0.58g/dL for Hb level >7.0 to ≤9.0 g/dL and 9.0 - 11.0 g/dL, respectively, for the ferumoxytol treatment group, the mean Hb change from baseline for subjects with lower Hb levels were much higher (1.39 g/dL) compared to the subgroup with higher Hb levels (0.59g/dL). The small group size for patients with lower Hb levels (10 and 11 subjects for ferumoxytol and IS, respectively) do not allow any firm conclusions.

No clinically meaningful differences were observed between the ITT Population, Safety Population, or Evaluable Population in term of Baseline characteristics.

Prior and concomitant Medications:

Overall (N=162), prior and concomitant medications with the incidences of use in >50% of the total ITT Population included the following classes:

• Alimentary tract and metabolism: 92% (150/162 subjects) as prior medication and 92% (149/162 subjects) as concomitant medication. Common therapies in this class were vitamins and drugs for acid reflux and diabetes.

• Blood and blood forming organs: 82.7% (134/162 subjects) as prior medication and 82.7% (134/162 subjects) as concomitant medication. Common therapies in this class were anti-anemic and anti-thrombotic drugs.

• Cardiovascular system (e.g., cardiac rhythm control): 96.3% (156/162 subjects) as prior medication and 97.5% (158/162 subjects) as concomitant medication. Common therapies in this class were beta-blocking agents and lipid-modifying agents.

• Nervous system (e.g., analgesics): 48.8% (79/162 subjects) as prior medication and 53.1% (86/162 subjects) as concomitant medication. Common therapies in this class were analgesics and psycholeptics.

Differences between the ferumoxytol group and iron sucrose group in the incidence of use were within 10% of subjects for all concomitant medication classes.

Numbers analysed

Table 39: Subject Evaluability (All Enrolled Subjects) (CSR)

Subject Population	Ferumoxytol (n=80) n (%)	Iron Sucrose (n=82) n (%)
Randomized	80 (100)	82 (100)
ITT Population	80 (100)	82 (100)
Safety Population	80 (100)	82 (100)
Evaluable Population	73 (91)	72 (89)
Missing Baseline or Week 5 Hgb value	4 (5)	0 (0)
Not compliant* with study medication	3 (4)	10 (12)

* Did not receive all scheduled doses

Data Source: Table 14.1.1, Table 14.1.2.3, Table 14.1.6, Listing 16.2.1, Listing 16.2.5

Outcomes and estimation

Primary efficacy endpoint: Hemoglobin Change from Baseline to Week 5

Table 40: Summary of Hemoglobin Change from Baseline to Week 5 (ITT Population and Evaluable Population) (CSR)

	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Difference			
			Difference	95% CI	P-value	Non-inferiority[3]
Intent-to-Treat Population						
Hgb Change from Baseline to Week 5						
N	80	82				
Mean (SD)	0.71 (1.03)	0.61 (0.97)				
LS mean (StdErr)	0.84 (0.14)	0.74 (0.14)	0.10	(-0.21, 0.41)	0.515 [1]	Yes
Median	0.5	0.5				
Q1, Q3	0.0, 1.4	0.1, 1.3				
Min, Max	-1.3, 4.0	-3.9, 2.6				
% of Subjects Postdose to Week 5 with Hgb Increase ≥1.0 g/dL	40 (50.0%)	34 (41.5%)	8.5%	(-6.8%, 23.8%)	0.287 [2]	
Evaluable Population						
Hgb Change from Baseline to Week 5						
N	73	72				
Mean (SD)	0.76 (1.04)	0.65 (0.97)				
LS mean (StdErr)	0.95 (0.15)	0.86 (0.16)	0.09	(-0.23, 0.42)	0.574 [1]	Yes
Median	0.6	0.7				
Q1, Q3	0.1, 1.4	0.1, 1.3				
Min, Max	-1.1, 4.0	-3.9, 2.3				
% of Subjects Postdose to Week 5 with Hgb Increase ≥1.0 g/dL	38 (52.1%)	33 (45.8%)	6.2 %	(-10.0%, 22.5%)	0.580 [2]	

1 p-value and 95% CI for Hgb change from Baseline are from ANOVA adjusted for baseline hemoglobin level and hemodialysis status.
2 p-value for percent with ≥1 g/dL increase in Hgb is from Cochran-Mantel-Haenszel test adjusted for Baseline hemoglobin level and hemodialysis status. 95% CI is unadjusted.
3 Lower bound of 95% CI was ≥ -0.5 g/dL (pre-defined non- inferiority margin).
StdErr = standard error
Source Data: Table 14.2.1.1 and 14.2.1.3

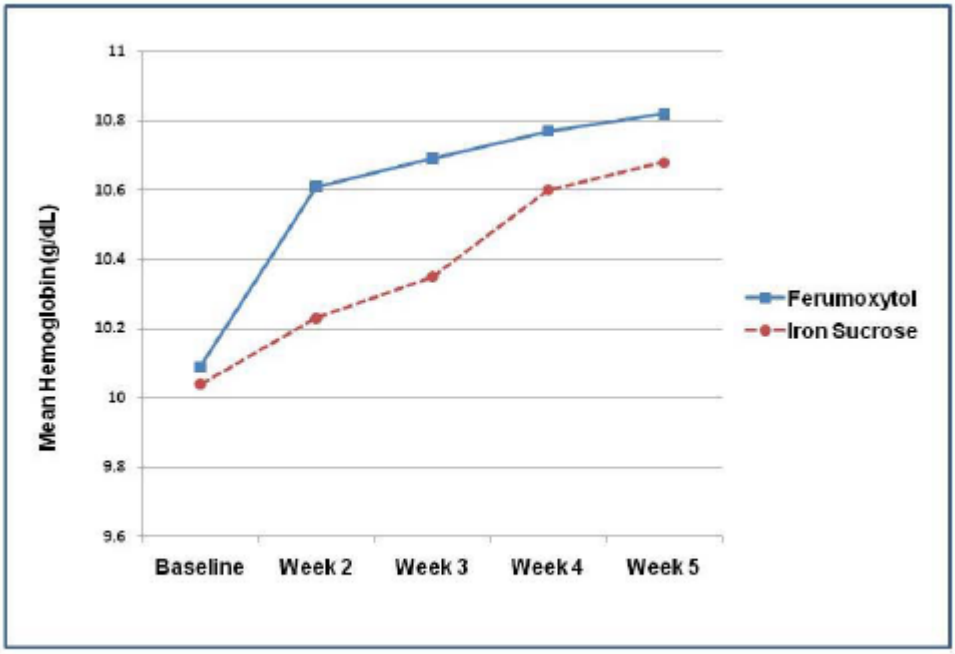
Table 41: Summary of Hemoglobin Change from Baseline to Week 5: Sensitivity Analyses (ITT Population) (CSR)

	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Difference			
			Difference	95% CI	P-value	Non-inferiority[3]
Method: No Imputation for Missing Values						
Hgb Change from Baseline to Week 5						
N	75	77				
Mean (SD)	0.73 (1.05)	0.64 (0.99)				
LSmean (StdErr)	0.89 (0.15)	0.80 (0.15)	0.09	(-0.23, 0.41)	0.587 [1]	Yes
Median	0.6	0.6				
Q1, Q3	0.0, 1.4	0.1, 1.3				
Min, Max	-1.3, 4.0	-3.9, 2.6				
% of Subjects Postdose to Week 5 with Hgb Increase ≥1.0 g/dL	40 (50.0%)	34 (41.5%)	8.5%	(-6.8%, 23.8%)	0.287 [2]	
Missing Values Imputed by Multiple Imputation (MCMC)						
Hgb Change from Baseline to Week 5						
N	80	82				
Mean (SD)	0.72 (1.07)	0.64 (0.88)				
LSmean (StdErr)	0.85 (0.14)	0.76 (0.14)	0.09	(-0.22, 0.40)	0.588 [1]	Yes
Median	0.6	0.5				
Q1, Q3	0.0, 1.3	0.1, 1.3				
Min, Max	-4.1, 3.1	-1.3, 3.1				

1 p-value and 95% CI for Hgb change from baseline are from ANOVA adjusted for baseline hemoglobin level, and hemodialysis status.
2 p-value for percent with ≥1 g/dL increase in Hgb is from Cochran-Mantel-Haenszel test adjusted for baseline hemoglobin level, and hemodialysis status. 95% CI is unadjusted.
3 Lower bound of 95% CI was ≥ -0.5 g/dL (pre-defined non- inferiority margin)
Source Data: Table 14.2.1.2 and 14.2.1.4

Hemoglobin Changes Over Time

Figure 10: Serum Hemoglobin (g/dL) Over Time by Treatment Group (ITT Population) (CSR)



Source: Figure 14.2.1.1

Baseline mean ± SD hemoglobin levels were similar between the ferumoxytol and iron sucrose treatment groups at 10.09±0.92 g/dL vs. 10.04±0.98 g/dL, respectively.

The number of subjects with hemoglobin increases ≥1.0 g/dL at any time from Baseline to Week 5 by study visit is summarized by treatment group and total study population in the following Table.

Table 42: Subjects with Hemoglobin Increases ≥1.0 g/dL by Study Visit (ITT Population) (CSR)

Visit	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Total (n=162)
Week 2 Hemoglobin Increase ≥1.0 g/dL, n (%)	20 (25.0)	11 (13.4)	31 (19.1)
Week 3 Hemoglobin Increase ≥1.0 g/dL, n (%)	32 (40.0)	20 (24.4)	52 (32.1)
Week 4 Hemoglobin Increase ≥1.0 g/dL, n (%)	37 (46.3)	31 (37.8)	68 (42.0)
Week 5 Hemoglobin Increase ≥1.0 g/dL, n (%)	40 (50.0)	34 (41.5)	74 (45.7)

Data Source: Table 14.2.3.1

Exploratory Analyses

Proportion of subjects with Hb≥12 g/dL

Table 43: Subjects with Hemoglobin ≥12.0 g/dL by Study Visit (ITT Population) (CSR)

Visit	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Total (n=162)
Week 2 Hemoglobin ≥12.0 g/dL, n (%)	6 (7.5)	1 (1.2)	7 (4.3)
Week 3 Hemoglobin ≥12.0 g/dL, n (%)	11 (13.8)	3 (3.7)	14 (8.6)
Week 4 Hemoglobin ≥12.0 g/dL, n (%)	14 (17.5)	5 (6.1)	19 (11.7)
Week 5 Hemoglobin ≥12.0 g/dL, n (%)	18 (22.5)	9 (11.0)	27 (16.7)

Data Source: Table 14.2.3.3

The median time to a hemoglobin increase ≥1.0 g/dL or an achieved hemoglobin level ≥12.0 g/dL was similar between the ferumoxytol group (36 days; N=41)) and iron sucrose group (38 days; n=34) (p=0.208, Logrank Test) (data not shown). The mean (StdErr) time to a hemoglobin increase ≥1.0 g/dL or a hemoglobin level ≥12.0 g/dL was 28.8 (1.15) days in the ferumoxytol group and 33.4 (1.24) days in the iron sucrose group (data not shown).

Markers of Iron Stores

Table 44: Summary of Changes in Iron Stores Parameters Over Time (ITT Population)(CSR)

	Ferumoxytol (n=80)		Iron Sucrose (n=82)		Total (n=162)	
Time Point	n	Mean±SD	n	Mean±SD	n	Mean±SD
TSAT (%)						
Baseline	80	21.46 (18.053)	82	18.93 (11.839)	162	20.18 (15.233)
Week 2	77	32.98 (13.050)	74	26.03 (17.240)	151	29.57 (15.591)
Week 3	73	30.32 (11.474)	74	23.53 (7.422)	147	26.90 (10.201)
Week 4	75	30.03 (11.611)	74	25.99 (11.022)	149	28.02 (11.464)
Week 5	76	27.52 (8.030)	77	25.50 (12.646)	153	26.50 (10.621)
Ferritin (ng/mL)						
Baseline	80	278.9 (293.25)	82	256.4 (259.42)	162	267.5 (276.01)
Week 2	73	886.7 (421.11)	73	559.4 (312.67)	146	723.0 (404.45)
Week 3	74	846.5 (521.43)	72	598.7 (313.35)	146	724.3 (447.67)
Week 4	74	725.6 (422.54)	72	563.9 (347.86)	146	645.8 (394.61)
Week 5	75	660.4 (373.01)	76	505.3 (325.53)	151	582.3 (357.32)
Serum Iron (µg/dL)						
Baseline	80	57.7 (45.96)	82	52.5 (31.67)	162	55.1 (39.34)
Week 2	77	80.0 (32.71)	74	66.8 (42.63)	151	73.6 (38.35)
Week 3	73	72.0 (28.17)	74	60.1 (20.65)	147	66.0 (25.30)
Week 4	75	70.4 (32.15)	74	66.3 (25.85)	149	68.3 (29.17)
Week 5	76	64.2 (20.82)	77	64.2 (26.91)	153	64.2 (24.00)
Reticulocyte Hemoglobin Count (%)						
Baseline	80	1.98 (0.788)	82	1.96 (0.727)	162	1.97 (0.755)
Week 2	77	2.39 (1.301)	72	2.42 (1.376)	149	2.40 (1.333)
Week 3	73	2.01 (0.970)	73	2.08 (0.808)	146	2.05 (0.891)
Week 4	75	1.94 (0.918)	74	2.08 (0.966)	149	2.01 (0.941)
Week 5	75	2.07 (1.292)	77	1.87 (0.773)	152	1.97 (1.062)

Data Source: Table 14.2.4.1, 14.2.4.2, 14.2.4.3, 14.2.4.4

ESA Usage and Blood transfusions

Table 45: Summary of ESA Usage (ITT Population) (CSR)

Parameter	Ferumoxytol (n=80) n (%)	Iron Sucrose (n=82) n (%)	Total (n=162) n (%)
On ESA	44 (55.0)	40 (48.8)	84 (51.9)
Initiation of ESA	1 (1.3)	1 (1.2)	2 (1.2)
ESA Dosing Increased ≥20%	0	2 (2.4)	2 (1.2)
ESA Dosing Decreased ≥20%	1 (1.3)	1 (1.2)	2 (1.2)
Cessation of ESA/Dose Held	2 (2.5)	2 (2.4)	4 (2.5)
No change >20 % in ESA	40 (50.0)	35 (42.7)	75 (46.3)

Data Source: Table 14.1.10

One subject (1.3%) in the ferumoxytol group received a blood transfusion of packed red blood cells after initiating treatment with study drug (data not shown).

Examination of subgroups

Table 46: Summary of Hemoglobin Change from Baseline to Week 5: Subgroup Analyses (ITT Population) (CSR)

Subgroup	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Difference		
			Difference	95% CI	P-value
Hgb Level >7.0 to ≤9.0 g/dL, n	10	11			
LSmean (StdErr)	1.39 (0.309)	0.63 (0.293)	0.76	(-0.14, 1.66)	0.093
Hgb Level >9.0 to <11.0 g/dL, n	70	71			
LSmean (StdErr)	0.59 (0.119)	0.58 (0.119)	0.01	(-0.32, 0.35)	0.931
Hemodialysis Subjects, n	34	36			
LSmean (StdErr)	1.02 (0.239)	0.54 (0.224)	0.47	(-0.05, 1.00)	0.078
Non-Dialysis Subjects, n	46	46			
LSmean (StdErr)	0.74 (0.167)	0.91 (0.171)	-0.17	(-0.53, 0.20)	0.365
Age: <50 years, n	17	19			
LSmean (StdErr)	0.55 (0.208)	0.94 (0.201)	-0.39	(-0.93, 0.14)	0.146
Age: 50 to <65, n	22	24			
LSmean (StdErr)	0.67 (0.294)	0.39 (0.305)	0.28	(-0.36, 0.92)	0.381
Age: 65 to <75, n	20	15			
LSmean (StdErr)	1.73 (0.388)	1.76 (0.474)	-0.03	(-0.77, 0.71)	0.942
Age: ≥75, n	21	24			
LSmean (StdErr)	0.72 (0.296)	0.57 (0.237)	0.15	(-0.46, 0.76)	0.618
Race: White, n	52	62			
LSmean (StdErr)	0.96 (0.172)	0.72 (0.159)	0.23	(-0.16, 0.63)	0.245
Race: Other, n	28	20			
LSmean (StdErr)	0.70 (0.325)	0.82 (0.368)	-0.13	(-0.64, 0.38)	0.614
Female, n	41	39			
LSmean (StdErr)	0.57 (0.184)	0.66 (0.196)	-0.1	(-0.49, 0.30)	0.626
Male, n	39	43			
LSmean (StdErr)	1.07 (0.228)	0.75 (0.201)	0.32	(-0.17, 0.81)	0.200
CKD Status Stage 1-3, n	20	19			
LSmean (StdErr)	0.65 (0.421)	1.20 (0.423)	-0.55	(-1.24, 0.14)	0.113
CKD Status Stage 4-5, n	60	62			
LSmean (StdErr)	0.89 (0.148)	0.59 (0.147)	0.31	(-0.03, 0.64)	0.076
ESA Use (Yes), n	44	40			
LSmean (StdErr)	0.89 (0.180)	0.64 (0.192)	0.26	(-0.19, 0.71)	0.258
ESA Use (No), n	36	42			
LSmean (StdErr)	1.04 (0.279)	1.15 (0.273)	-0.11	(-0.54, 0.33)	0.634

P-value and 95% CI for Hgb change from baseline are from ANOVA adjusted for baseline hemoglobin level, and hemodialysis status.

Source Data: Table 14.2.1.5, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9, 14.2.1.10, 14.2.1.11

Table 47: Summary of Percent of Subjects Post-dose to Week 5 with Hemoglobin Increase ≥ 1.0 g/dL (ITT Population) (CSR)

Subgroup	Ferumoxytol (n=80)	Iron Sucrose (n=82)	Difference		
			Difference	95% CI	P-value
Baseline Hgb Level >7.0 to ≤9.0 g/dL, n	10	11			
≥1.0 g/dL, n (%)	7 (70.0%)	5 (45.5%)	24.5%	(-16.4%, 65.4%)	0.311
Baseline Hgb Level >9.0 to <11.0 g/dL, n	70	71			
≥1.0 g/dL, n (%)	33 (47.1%)	29 (40.8%)	6.3%	(-10.1%, 22.7%)	0.456
Hemodialysis Subjects, n	34	36			
≥1.0 g/dL, n (%)	19 (55.9%)	14 (38.9%)	17.0%	(-6.1%, 40.1%)	0.156
Non-Dialysis Subjects, n	46	46			
≥1.0 g/dL, n (%)	21 (45.7%)	20 (43.5%)	2.2%	(-18.1%, 22.5%)	0.870
Age: <50 years, n	17	19			
≥1.0 g/dL, n (%)	6 (35.3%)	10 (52.6%)	-17.3%	(-49.3%, 14.6%)	0.302
Age: 50 to <65, n	22	24			
≥1.0 g/dL, n (%)	10 (45.5%)	7 (29.2%)	16.3%	(-11.3%, 43.9%)	0.273
Age: 65 to <75, n	20	15			
≥1.0 g/dL, n (%)	12 (60.0%)	6 (40.0%)	20.0%	(-12.8%, 52.8%)	0.320
Age: ≥75, n	21	24			
≥1.0 g/dL, n (%)	12 (57.1%)	11 (45.8%)	11.3%	(-17.8%, 40.4%)	0.475
Race: White, n	52	62			
≥1.0 g/dL, n (%)	28 (53.8%)	27 (43.5%)	10.3%	(-8.0%, 28.6%)	0.287
Race: Other, n	28	20			
≥1.0 g/dL, n (%)	12 (42.9%)	7 (35.0%)	7.9%	(-19.9%, 35.7%)	0.611
Female, n	41	39			
≥1.0 g/dL, n (%)	23 (56.1%)	17 (43.6%)	12.5%	(-9.2%, 34.3%)	0.358
Male, n	39	43			
≥1.0 g/dL, n (%)	17 (43.6%)	17 (39.5%)	4.1%	(-17.3%, 25.4%)	0.727
CKD Status Stage 1-3, n	20	19			
≥1.0 g/dL, n (%)	8 (40.0%)	12 (63.2%)	-23.2%	(-53.7%, 7.4%)	0.164
CKD Status Stage 4-5, n	60	62			
≥1.0 g/dL, n (%)	32 (53.3%)	21 (33.9%)	19.5%	(2.2%, 36.7%)	0.037
ESA Use (Yes), n	44	40			
≥1.0 g/dL, n (%)	26 (59.1%)	17 (42.5%)	16.6%	(-4.5%, 37.7%)	0.180
ESA Use (No), n	36	42			
≥1.0 g/dL, n (%)	14 (38.9%)	17 (40.5%)	-1.6%	(-23.4%, 20.2%)	0.878

P-value for percent with ≥1 g/dL increase in Hgb is from Cochran-Mantel-Haenszel test adjusted for baseline hemoglobin level, and hemodialysis status. 95% CI is unadjusted.
Source Data: Table 14.2.1.5, 14.2.1.6, 14.2.1.7, 14.2.1.8, 14.2.1.9, 14.2.1.10, 14.2.1.11

Among all subpopulations, except subjects <50 years old, with CKD Stage 1-3, or those not using ESA, a higher proportion of subjects in the ferumoxytol group compared to iron sucrose had a change in hemoglobin ≥1.0 g/dL during the period from Baseline to Week 5; again these analyses are limited by the relatively small number of subjects in some subgroups.

Ancillary analyses

An unplanned preliminary analysis of data from the CKD trial was performed to support the results of the pivotal studies.

Study AMAG–FER–CKD-401

Ferumoxytol for Anemia of CKD Trial (FACT): A Phase IV, Open-Label, Multicenter Trial, with MRI Substudy, of Repeated Doses of Ferumoxytol Compared with Iron Sucrose for the Treatment of Iron Deficiency Anemia (IDA) in Chronic Kidney Disease (CKD) Patients on Hemodialysis

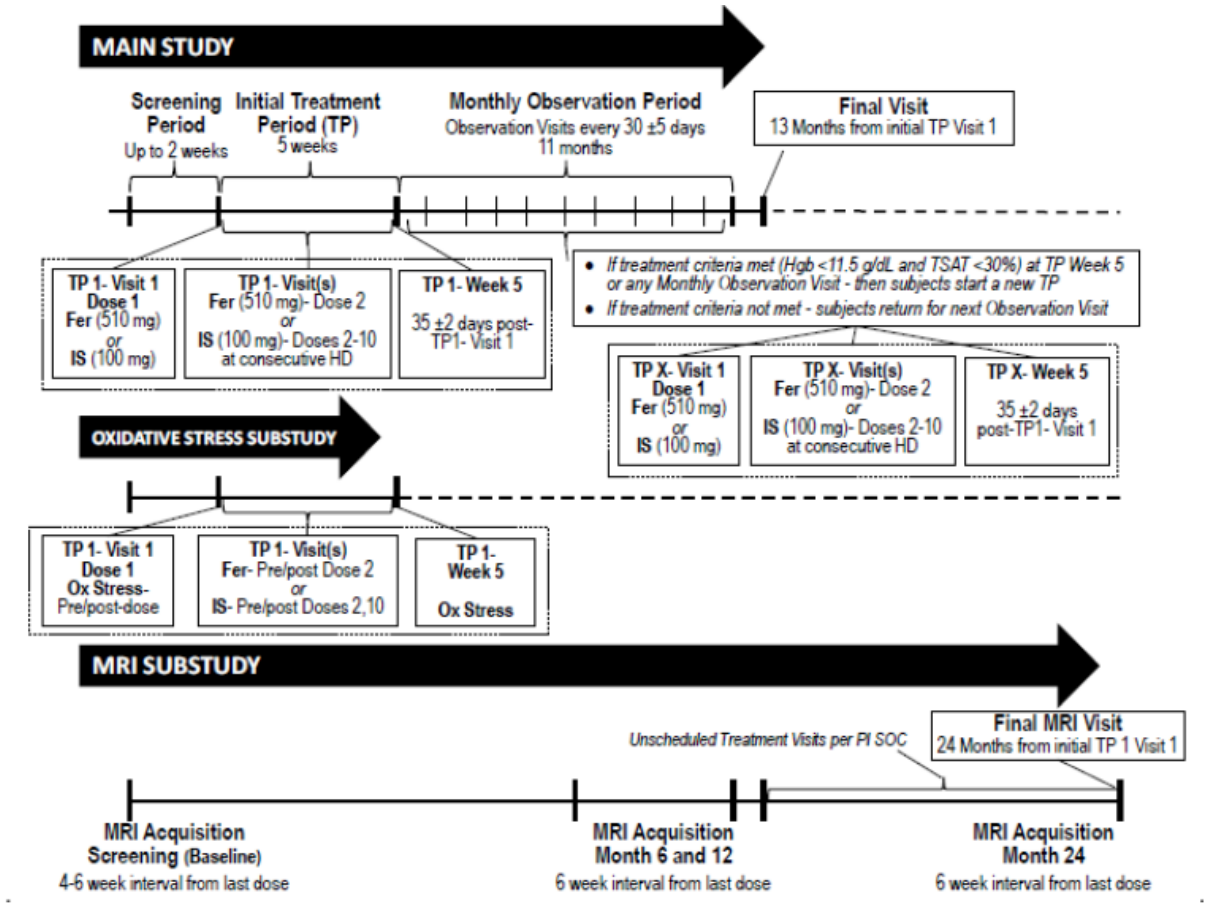
EUDRACT NO. 2010-022133-28

Methods

This was a Phase IV, randomised, Open-label, multicentre (35 study sites in the United States, Canada and United Kingdom), active controlled clinical trial designed to evaluate the safety, efficacy, and frequency of use of ferumoxytol compared to iron sucrose for the episodic treatment of IDA in hemodialysis subjects with CKD over a 1-year period.

An overview of the study design is provided in Figure 11.

Figure 11: Overview of CKD-401 Study Design



Evaluation of IDA Status: Following the initial 5-week TP, subjects entered the 11-month Monthly Observation Period during which they were serially evaluated for IDA (monthly observation visits). Subjects who had *persistent or recurrent IDA, defined as a hemoglobin <11.5 g/dL and TSAT <30% at any Monthly Observation Visit or final visit (Week 5) of any TP*, entered another TP and were treated again with an additional course of their randomized treatment.
As part of this Main Study, an Oxidative Stress Substudy and an MRI Substudy were conducted. These are discussed under 3.8 'supportive studies'.

Study Participants

Main inclusion criteria

1. Males and females ≥18 years of age
2. Subjects with IDA defined as:

a) hemoglobin <11.5 g/dL; and

b) transferrin saturation (TSAT) <30%

3. Serum ferritin <800 ng/mL

4. Subjects must have been **on hemodialysis** for at least 3 months prior to Screening
5. Female subjects of childbearing potential who were sexually active must have been on an effective method of birth control for at least 1 month prior to Screening and agree to remain on birth control until completion of the study
6. Subject capable of understanding and complying with the protocol requirements and available for the duration of the study
7. Subject had been informed of the investigational nature of this study and had given voluntary written informed consent and, if applicable, Health Insurance Portability and Accountability Act (HIPAA) authorization in accordance with institutional, local, and national personal health data protection guidelines

Main Exclusion criteria

1. History of allergy to either oral or IV iron
2. Female subjects who were pregnant or intended to become pregnant, breastfeeding, within 3 months postpartum, or had a positive serum or urine pregnancy test
3. Parenteral iron therapy within 30 days prior to Screening or red blood cell (RBC)/whole blood transfusion within 14 days prior to Screening or planned during the study
4. Untreated vitamin B12 or folate deficiency
5. Erythropoiesis-stimulating agent (ESA) therapy initiated, stopped, or dose changed by >20% within 30 days prior to Screening, or an anticipated ESA dose change of >20% during the initial TP
6. Received an investigational agent within 30 days prior to Screening, or planned receipt of an investigational agent not specified by this protocol during the study period
7. Any other clinically significant medical disease or psychiatric disease or condition (e.g., active malignancy, uncontrolled hypertension, acute medical illness/infection, psychosis) or subject responsibility that, in the Investigator's opinion, might have interfered with the subject's ability to give informed consent or adhere to the protocol, interfered with assessment of the study agent, or served as a contraindication to the subject's participation in the study

Concomitant ESA Therapy

For subjects in the Main Study who were receiving ESA therapy, the ESA dose was not modified during any 5-week TP following the administration of ferumoxytol or iron sucrose unless required for subject safety.

Treatments

Original Protocol:

IV injection of ferumoxytol 510 mg (17 mL) on Day 1 with a second dose 5 ± 3 days after Dose 1, each administered as an IV injection of 17 mL at a rate not to exceed 1 mL/sec, for a total cumulative dose of 1.02 g

Amendment 1:

Either undiluted IV injection administered over approximately 1 minute, but at a rate not to exceed 1 mL/sec, or diluted IV infusion over a period of at least 15 minutes of ferumoxytol 510 mg (17 mL) on Day 1 with a second dose 5 ± 3 days after Dose 1, for a total cumulative dose of 1.02 g

Amendment 2:

Diluted IV infusion over a period of at least 15 minutes of ferumoxytol 510 mg (17 mL) on Day 1 with a second dose 5 ± 3 days after Dose 1, for a total cumulative dose of 1.02 g

Iron Sucrose

Either slow IV injection or IV infusion of iron sucrose 100 mg on Day 1 and at the following 9 consecutive hemodialysis sessions for a total cumulative dose of 1.0 g

During the Observation Period of the Main Study, subjects found to have persistent or recurrent IDA, defined as hemoglobin <11.5 g/dL and TSAT <30%, were to receive additional treatment with ferumoxytol or iron sucrose, according to their treatment assignment. Subjects found to have IDA at the Main Study Final Visit would not receive ferumoxytol or iron sucrose as part of this study, but would be managed according to the physician's standard of care.

Objectives

Primary Objective: To demonstrate that 1.02 g courses of ferumoxytol (delivered as either an undiluted IV injection or diluted IV infusion of 510 mg each) are noninferior to 1.0 g courses of iron sucrose (delivered either as slow IV undiluted injections or IV diluted infusions of 100 mg each) in raising haemoglobin after each treatment period in hemodialysis-dependent CKD subjects with IDA over a 1-year period.

Secondary Objective: To evaluate the safety of repeat doses of ferumoxytol compared to iron sucrose for the treatment of IDA over a 1-year period in subjects with hemodialysis-dependent CKD.

Outcomes/endpoints

Primary efficacy endpoint:

Mean hemoglobin change from Baseline to Week 5 for each TP

Secondary efficacy endpoints:

- Mean change in TSAT from TP Baseline to Week 5 for each TP
- Proportion of subjects with an increase in hemoglobin of ≥1.0 g/dL at any time from TP Baseline to Week 5 for each TP

Exploratory Efficacy Endpoints:

- Time to subsequent treatment courses of ferumoxytol or iron sucrose
- Cumulative IV iron exposure per subject over the course of the study
- Proportion of subjects requiring blood transfusion
- Proportion of subjects who had a change in ESA dose over the course of the study

Sample size

This study was planned to enroll approximately 300 subjects with hemodialysis-dependent CKD in a 2:1 ratio (ferumoxytol: iron sucrose). The retreatment rate for the current study with a 12 month observation period was estimated to be approximately 80% (240) for subjects on hemodialysis. A sample size of 240 subjects provides approximately 90% power for testing non-inferiority of ferumoxytol to iron sucrose, assuming a non-inferiority margin of 0.5 g/dL, a one-sided alpha of 0.025, and a SD of 1.13 g/dL for the primary endpoint change from Baseline in hemoglobin based in data from the AMAG CKD studies.

No interim analysis was planned.

Randomisation and blinding (masking)

This was an open label study. The randomization will be centralized for the Main Study and will follow a blocked randomization scheme designed to ensure that subjects are allocated in a 2:1 ratio (ferumoxytol: iron sucrose) in the Main Study.

Statistical methods

Analysis sets:

Intent-to-treat Population

The Intent-to-Treat (ITT) Population for efficacy analyses will include all subjects who had any exposure to study drug (ferumoxytol or iron sucrose).

Evaluable population

All subjects who met all inclusion and did not violate any exclusion criteria, received two doses of ferumoxytol (1.02 g) or all 10 doses of iron sucrose at the initial TP, and had evaluable data for hemoglobin (primary endpoint) at the TP Baseline and Week 5.

Note: Major deviations/violations, including subjects who entered the study but did not satisfy the entry criteria, received the wrong treatment or incorrect dose, and received an excluded concomitant treatment, will be tabulated. Subjects identified with major protocol deviations/violations that impact the study integrity prior to database lock will also be excluded from evaluable populations.

General considerations

In general, analyses will pool data for injection and infusion for both treatment arms. Analyses performed separately for Ferumoxytol injection and infusion will be specified. For continuous endpoints, the number of available observations (n), mean, standard deviation (SD), median, 25th and 75th percentiles, minimum and maximum values will be provided. For categorical endpoints, the frequency and percentage of subjects in each category will be displayed. All tables will be presented by treatment groups. Listings will be presented for all the data used in the summary tables.

The terms 'Treatment Period (TP)' and 'Treatment Course' are considered to be identical in definition and are defined as from date of first dose of study drug to the date of the Week 5 visit in a 5-week treatment period.

A windowing algorithm will be applied only if the value from the scheduled visit could not be obtained or missing. Within each TP, post-TP Baseline visits will be determined by a windowing algorithm (-7, +6 days) based on study visit date relative to date of Dose 1. In the case of multiple values collected before or at Week 5, the non-missing value closest to the date of scheduled visit will be used for the week 5 visit. *Post-Study Baseline monthly visits, which could also happen at TP week 5 visits*, will be determined by a windowing algorithm based on study visit date relative to the date of initial dose of study drug. *In the case of multiple values collected in a given month, the average value will be used for the monthly visit*.

Post Study Baseline monthly visit value is defined using 15-day window started from day 35 with 30-day increments thereafter as the following:

>>> Month 1 – number of days from initial dosing date to date of value collected falls into the interval 20 to <50

>>> Month 2 – number of days from initial dosing date to date of value collected falls into the interval 50 to <80

>>> Month k+1 – number of days from initial dosing date to date of value collected falls into the interval 35+30k -15 to < 35+30k+15 for k=0,1,2,…12

Statistical test will be performed on the primary efficacy endpoint only. Two sided test will be used at

alpha level of 0.05. Descriptive summary statistics will be present for all efficacy endpoints.

All statistical analyses for efficacy endpoints will be performed on the ITT population. Analyses of the primary efficacy endpoint will also be performed on the Evaluable Population.

Definition of baseline measurement

A Treatment Period (TP) Baseline value is defined as the last non-missing value collected prior to the first dosing of study drug in that TP.

A Study Baseline value is defined as the last non-missing value collected prior to the initial dosing of study drug (equivalent to initial TP baseline).

Efficacy Endpoints Analysis

Primary Endpoint Analyses: The primary efficacy endpoint for this study is the mean change in hemoglobin from TP Baseline to TP Week 5 following each of the courses of ferumoxytol or iron sucrose treatment, and will be calculated for each subject as:

Hemoglobin Change = Hemoglobin (TP Week 5) – Hemoglobin (TP Baseline).

The statistical test on the first two TP data on the primary endpoint will be performed in a sequential manner with a fixed sequence ordered by TP number. If non-inferiority is demonstrated for the first and second TP, i.e., if lower bound of 95% confidence interval (CI) for ferumoxytol minus iron sucrose in hemoglobin change is ≥ - 0.5 in the first two TP, they will then be tested for superiority of ferumoxytol to iron sucrose in the same sequential manner. Superiority of ferumoxytol to iron sucrose is achieved if lower bound of 95% CI for ferumoxytol minus iron sucrose in hemoglobin change is > 0 in the first two TP.

The point estimate and 95% CI and p-value for the treatment difference in haemoglobin change will be calculated, using an ANCOVA model, adjusting for baseline haemoglobin level.

Summary statistics will also be presented for hemoglobin monthly visit.

In addition, descriptive summary statistics of the primary endpoint will also be presented for ferumoxytol treated subjects, separately for injection and infusion, on ITT population.

Secondary Efficacy Endpoint Analyses

Summary statistics will be presented for mean change in TSAT from TP Baseline to TP Week 5 following each course of treatment.

Frequencies and percentages of subjects with an increase in hemoglobin of ≥1 g/dL at any time from TP baseline to Week 5 will be presented by treatment group for each TP. For this endpoint analysis, all valid hemoglobin values collected post dose 1 and before or at Week 5 in the same TP will be used.

In addition, descriptive statistics of the secondary endpoints will be presented on ferumoxytol treatment subjects, separately for injection and infusion, on ITT population.

Exploratory Efficacy Endpoints Analyses

Summary statistics will be presented for the mean time to subsequent treatment courses of study drug treatment. Summary statistics will be presented for the cumulative IV iron exposure per subject over the course of study. Frequencies and percentages of subjects requiring blood transfusion will be presented. Frequencies and percentages of subjects who had a change in ESA dose equal to or more than 20% increase or decrease from Study Baseline or initiation/cessation of ESA therapy over the course of study will be presented. Monthly ESA use will be summarized.

Study completion

A subject completed the study if one had exposure to study drug during the study and had Week 5 visit data.

Handling of missing data

For primary and secondary efficacy endpoints, change from TP baseline will be imputed to be zero for missing post-TP Baseline parameter values. No data imputation for missing data will be used for analysis of exploratory efficacy endpoints.

Adjustment for Multiple Comparisons

No adjustment for multiple comparisons is needed for the primary endpoint, the mean change in hemoglobin from TP Baseline to TP Week 5 following each of the courses of ferumoxytol, will be tested in a sequential manner ordered by TP number to control the type I error rate at 2-sided 0.05 level.

Study subgroups

No subgroup analysis is planned for the study.

Results

Participant flow

Table 48: Subject Population (All Enrolled Subjects) (CSR)

Subject Population	Treatment Group		Total N=296
	Ferumoxytol N=197	Iron Sucrose N=99	
	n (%)	n (%)	n (%)
Randomized	197 (100.0)	99 (100.0)	296 (100.0)
Withdrawn prior to study drug dosing	1 (0.5)	2 (2.0)	3 (1.0)
Safety Population	196 (99.5)	97 (98.0)	293 (99.0)
ITT Population	196 (99.5)	97 (98.0)	293 (99.0)
Early discontinuation from study drug	10 (5.1)	1 (1.0)	11 (3.8)
Reason for discontinuation from study drug			
Adverse event	8 (4.1)	0	8 (2.7)
Investigator discretion	1 (0.5)	1 (1.0)	2 (0.7)
Subject's request	1 (0.5)	0	1 (0.3)
Completed study	142 (72.4)	74 (76.3)	216 (73.7)
Early withdrawal from study	54 (27.6)	23 (23.7)	77 (26.3)
Reasons for withdrawal:			
Adverse event	8 (4.1)	2 (2.1)	10 (3.4)
Death	13 (6.6)	5 (5.2)	18 (6.1)
Withdrawal of consent	10 (5.1)	7 (7.2)	17 (5.8)
Lost to follow-up	3 (1.5)	1 (1.0)	4 (1.4)
Other	20 (10.2)	8 (8.2)	28 (9.6)
Main Study Evaluable Population	181 (91.9)	83 (83.8)	264 (89.2)
Early discontinuation from study drug	8 (4.1)	1 (1.0)	9 (3.0)
Reason for discontinuation from study drug			
Adverse event	6 (3.3)	0	6 (2.3)
Investigator discretion	1 (0.6)	1 (1.2)	2 (0.8)
Subject's request	1 (0.6)	0	1 (0.4)
Completed study	135 (68.5)	64 (64.6)	199 (67.2)
Early withdrawal from study	46 (23.4)	19 (19.2)	65 (22.0)
Reasons for Withdrawal:			
Other	19 (9.6)	6 (6.1)	25 (8.4)
Death	11 (5.6)	5 (5.1)	16 (5.4)
Withdrawal of consent	8 (4.1)	6 (6.1)	14 (4.7)
Adverse event	6 (3.0)	1 (1.0)	7 (2.4)
Lost to follow-up	2 (1.0)	1 (1.0)	3 (1.0)

Source: Tables 14.1.1, 14.1.2.1 and 14.1.2.3.
Note: All percentages were based on the number of subjects randomized in the study.

Recruitment

First subject enrolled: 19 Aug 2013
Last subject completed: 24 Feb 2016
Release Date of Report: 17 Feb 2017

Conduct of the study

Protocol amendments

The Original Protocol was dated 07 December 2012. Two protocol amendments were dated 15 August 2014 and 09 April 2015. Amendment 1 allowed physicians to choose between delivering ferumoxytol as either an IV injection over 1 minute or an IV infusion over a minimum of 15 minutes. Amendment 1 also updated the AE reporting rates with current postmarketing information and changed the collection of prior prescription medications at Screening to the collection of all prior medications at Screening. Amendment 2 required all subjects to receive ferumoxytol as a 15-minute infusion and updated safety information with warnings regarding serious hypersensitivity/anaphylaxis reactions and a new contraindication regarding history of allergy to any IV iron product. The changes were instituted to align the protocol with changes in the Prescribing Information (PI) for ferumoxytol.

The MRI substudy in dialysis patients was terminated prior to the 24 month evaluation due to marked attrition of participants willing to have follow up MRIs beyond the 12-month period.

Changes to the Planned Analysis of the Study

1. There was an insufficient number of subjects in the infusion group. A total of 27 subjects received 54 treatment courses by infusion but 23 received both ferumoxytol injection and infusion courses. Therefore, all analyses, including efficacy and safety, were not performed separately for the injection/infusion groups and only pooled data were presented.

2. Since many visits occurred outside of scheduled visit windows, the following criteria were applied for efficacy endpoints and laboratory data analyses by treatment period. The allowances are larger than those defined in the Statistical Analysis Plan (SAP) (35-7, 35+6).

• Baseline value must be within 14 days (inclusive) prior to the first dose of the corresponding treatment period.

• The window to collect Week 5 data was expanded to 35 (±10) days (inclusive) after the first dose of the corresponding treatment period. The process was to first select the record in the window that was labeled as "Week 5." If no such record was found, then the record (monthly observation or unscheduled visit) closest to Day 35 and in the same window was selected. If 2 records were equally close to Day 35, the record collected at an earlier time was selected ie, if data were collected on Day 35-k and 35+k (k=1, 2,3…,10), then the record from Day 35-k was chosen.

3. Since it was determined, by discussion with investigators, that during the course of this long-term evaluation various random extraneous events unrelated to clinical course affected the ESA dose received (eg, changes in insurance company formularies), ESA data were presented only as a monthly summary table and the analysis of a 20% change was deemed no longer meaningful.

Measurements of Treatment Compliance

Table 49: Treatment Compliance by Treatment Period (ITT Population) (CSR)

Treatment Compliance	Treatment Group		Total N=293
	Ferumoxytol N=196	Iron Sucrose N=97	
Treatment Period 1			
Number of Subjects	196	97	293
Mean ± SD	99.3 ± 6.01	98.0 ± 6.87	98.9 ± 6.32
Median (range)	100 (50, 100)	100 (50, 141)	100 (50, 141)
Treatment Period 2			
Number of Subjects	173	88	261
Mean ± SD	99.7 ± 3.80	94.8 ± 17.02	98.0 ± 10.58
Median (range)	100 (50, 100)	100 (10, 100)	100 (10, 100)
Treatment Period 3			
Number of Subjects	133	65	198
Mean ± SD	99.6 ± 4.34	93.4 ± 20.71	97.6 ± 12.67
Median (range)	100 (50, 100)	100 (10, 100)	100 (10, 100)
Treatment Period 4			
Number of Subjects	85	33	118
Mean ± SD	100 ± 0	97.3 ± 10.98	99.2 ± 5.87
Median (range)	100 (100, 100)	100 (40, 100)	100 (40, 100)
Treatment Period 5			
Number of Subjects	49	18	67
Mean ± SD	100 ± 0	90.0 ± 21.69	97.3 ± 11.88
Median (range)	100 (100, 100)	100 (20, 100)	100 (20, 100)
Treatment Period 6			
Number of Subjects	22	8	30
Mean ± SD	97.7 ± 10.66	82.5 ± 32.4	93.7 ± 19.56
Median (range)	100 (50, 100)	100 (10, 100)	100 (10, 100)

Source: Table 14.1.6.1

Baseline data

Baseline characteristics

A summary of the demographic characteristics of the ITT Population at Baseline, which served as the primary dataset for analysis, is presented by treatment group and overall subjects in the following Table.

Table 50: Subject Population (ITT Population) (CSR)

Baseline Characteristics	Treatment Group		Total N=293
	Ferumoxytol N=196	Iron Sucrose N=97	
Age (years)			
Mean ± SD	59.3 ± 14.13	57.6 ± 13.62	58.8 ± 13.96
Median (range)	59 (24, 92)	58 (26, 85)	58 (24, 92)
Gender, n (%)			
Male	114 (58.2)	57 (58.8)	171 (58.4)
Female	82 (41.8)	40 (41.2)	122 (41.6)
Race, n (%)			
White	101 (51.5)	47 (48.5)	148 (50.5)
Black or African American	62 (31.6)	26 (26.8)	88 (30.0)
Asian	15 (7.7)	13 (13.4)	28 (9.6)
American Indian or Alaska Native	10 (5.1)	4 (4.1)	14 (4.8)
Other/Multiracial	6 (3.1)	4 (4.1)	10 (3.4)
Native Hawaiian or Other Pacific Islander	2 (1.0)	3 (3.1)	5 (1.7)
Ethnicity, n (%)			
Hispanic and/or Latino	68 (34.7)	40 (41.2)	108 (36.9)
Not Hispanic or Latino	128 (65.3)	57 (58.8)	185 (63.1)
Height (cm)			
Mean ± SD	168.3 ± 10.49	167.2 ± 10.39	167.9 ± 10.45
Median (range)	168 (142, 196)	168 (144, 196)	168 (142, 196)
Weight (kg)			
Mean ± SD	86.8 ± 23.40	83.2 ± 20.95	85.6 ± 22.65
Median (range)	84 (40, 186)	81 (43, 149)	83 (40, 186)
Country, n (%)			
United States	185 (94.4)	90 (92.8)	275 (93.9)
Canada	5 (2.6)	2 (2.1)	7 (2.4)
United Kingdom	6 (3.1)	5 (5.2)	11 (3.8)

Source: Table 14.1.3.1

Medical History and Comorbid Diseases

All subjects reported a medical history. Subjects had numerous reported medical history and comorbid conditions. Overall Blood and lymphatic system disorders (82.1% ferumoxytol vs. 79.4% iron sucrose), Cardiac Disorders (64.3% vs. 57.7%), Endocrine disorders (79.1% vs. 80.4%), Gastointestinal Disorders (68.4% vs. 69.1%), Metabolism and Nutrition Disorders (98.5% vs. 95.9%), Musculoskeletal and connective tissue disorders (54.6% vs. 61.9%), Nervous system disorders (52.2%), Renal and urinary disorders (61.2% vs 67.0%), Surgical and medical procedures (62.8% vs. 57.7%) and vascular disorders (99.0% vs. 99.0) were reported in more than 50% of subjects (data not shown).

Previous anemia was reported in around 60% off subjects, anemia of chronic disease in around 17% and IDA in around 12% of subjects, with no meaningful differences between treatment groups.

Prior and Concomitant Medications

Prior medication use was comparable across treatment groups and was consistent with the underlying conditions reported for the population. The most commonly used class of medications was: Drugs for treatment of hyperkalemia and hyperphosphatemia (ferumoxytol, 57.1%; and iron sucrose, 49.5%; data not shown). Other prior medications used in more than 25% of subjects in either treatment group by class included other anti-parathyroid agents, calcium, dihydropyridine derivatives, hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitors, alpha and beta-blocking agents and beta-blocking agents (selective), natural opium alkaloids, platelet aggregation inhibitors excluding heparin, proton pump inhibitors, sulfonamides, plain, vitamin B-complex with vitamin C, and vitamin D and analogues (data not shown).

Concomitant medication use was also comparable across treatment arms.

'Other antianemic preparations' were reported in 12.2 and 5.2% of ferumoxytol- and IS-treated subjects, respectively.

Numbers analysed

ITT Population and Safety Population (n=293); Evaluable Population (n=264)

Table 14.1.2.4.1
Subject Exclusion from Main Study Evaluable Population
Intent-to-Treat Population

	Ferumoxytol (N=196) n (%)	Iron Sucrose (N=97) n (%)	Total (N= 293) n (%)
Intent-to-Treat Populaton	196 (100.0)	97 (100.0)	293 (100.0)
Evaluable Population	181 (92.3)	83 (85.6)	264 (90.1)
Excluded from Evaluable Population	15 (7.7)	14 (14.4)	29 (9.9)
Reasons for Exclusion:			
Study drug compliance in first TP	2 (1.0)	11 (11.3)	13 (4.4)
Inclusion/Exclusion Violation	9 (4.6)	1 (1.0)	10 (3.4)
No Baseline/Week 5 Hgb data	4 (2.0)	2 (2.1)	6 (2.0)
No Drug Received	0	0	0

Other protocol deviations/violations in the study included: received prohibited medication or therapy (overall: n=17, 5.8%; ferumoxytol n=14, 7.1%; iron sucrose: n=3, 3.1%), did not receive study drug as randomized (iron sucrose: n=1, 1.0%) and hemoglobin collection visit outside of scheduled windows in first and/or second Treatment Period (overall: n=51, 26.%; ferumoxytol: n=51, 26.0%; iron sucrose: n=24, 24.7%) (Table 51).

Table 51: Protocol Deviations and Violations

Intent-to-treat Population

	Ferumoxytol (N=196) n (%)	Iron Sucrose (N=97) n (%)	Total (N= 293) n (%)
Failed to Meet Inclusion/Exclusion Criteria	9 (4.6)	1 (1.0)	10 (3.4)
Received Prohibited Medication or Therapy	14 (7.1)	3 (3.1)	17 (5.8)
Received Study Drug not as Randomized	0	1 (1.0)	1 (0.3)
HGB collection visit outside of scheduled windows in first and/or second treatment Period	51 (26.0)	24 (24.7)	75 (25.6)

Note: Visit outside of scheduled window indicates that a baseline value was measured not within 14-day prior to first dose date of the corresponding TP or week 5 value was measured not within 35 (+-10) days post the corresponding TP first dose date.

Table 52: Use of Prohibited Medication and Therapy by WHO Drug Prefered Term

Intent-to-treat Population

	Ferumoxytol (N=196)	Iron Sucrose (N=97)	Total (N=293)
Number and Percetage of Subject Using Prohibited Medication and Therapy	14 (7.1)	3 (3.1)	17 (5.8)
Ferric Sodium Gluconate Complex	1 (0.5)	0	1 (0.3)
Ferrous Sulfate	2 (1.0)	0	2 (0.7)
Iron	1 (0.5)	1 (1.0)	2 (0.7)
Saccharated Iron Oxide	12 (6.1)	2 (2.1)	14 (4.8)

Outcomes and estimation

Primary efficacy endpoint

Table 53: Mean Change in Hemoglobin at Week 5 – ITT Population (CSR)

Treatment Period[1]	Ferumoxytol Mean Change HgB (g/dL) Mean ± SD (n) N=196	Iron Sucrose Mean Change HgB (g/dL) Mean ± SD (n) N=97	LS mean and 95% Confidence Interval for difference	p-value for difference
TP1	0.5 ± 0.97 (195)	0.4 ± 0.97 (94)	0.13 (-0.11,0.36)	0.2811
TP2	0.6 ± 0.96 (167)	0.3 ± 1.03 (88)	0.30 (0.06,0.55)	0.0158
TP3	0.6 ± 1.10 (130)	0.4 ± 0.87 (64)	0.27 (-0.01,0.56)	0.0592
TP4	0.5 ± 1.12 (81)	0.6 ± 1.11 (32)	-0.21 (-0.63,0.20)	0.3134
TP5	0.4 ± 1.14 (48)	0.3 ± 0.96 (17)	0.05 (-0.54,0.63)	0.8745
TP6	0.5 ± 1.21 (22)	-0.3 ± 1.00 (8)	0.64 (-0.42,1.69)	0.2253

[1] Includes only treatment periods for which n>5 for both treatment groups.

Source: Table 14.2.1.1.1

Table 54: Mean Change in Hemoglobin at Week 5 – Evaluable Population (CSR)

Treatment Period[1]	Ferumoxytol N=181 Mean Change HgB (g/dL) Mean ± SD (n)	Iron Sucrose N=83 Mean Change HgB (g/dL) Mean ± SD (n)	LS mean and 95% Confidence Interval for difference	p-value for difference
TP1	0.5 ± 0.96 (180)	0.5 ± 0.89 (82)	0.05 (-0.19,0.29)	0.6968
TP2	0.5 ± 0.96 (159)	0.3 ± 1.10 (76)	0.29 (0.02,0.55)	0.0347
TP3	0.6 ± 1.09 (124)	0.5 ± 0.83 (58)	0.20 (-0.09,0.50)	0.1822
TP4	0.5 ± 1.13 (78)	0.7 ± 1.14 (28)	-0.23 (-0.68,0.22)	0.3081
TP5	0.5 ± 1.15 (47)	0.3 ± 0.54 (13)	-0.03 (-0.65,0.59)	0.9274
TP6	0.6 ± 1.23 (21)	-0.3 ± 1.07 (7)	0.66 (-0.47,1.79)	0.2408

[1] Includes only treatment periods for which n>5 for both treatment groups. Source: Table 14.2.1.2.

Table 55: Mean Change in Hemoglobin by Month – ITT Population (CSR)

	Ferumoxytol N=196		Iron Sucrose N=97	
Month	Hemoglobin (g/dL) Mean ± SD (n)	Mean Change from baseline (g/dL) Mean ± SD (n)	Hemoglobin (g/dL) Mean ± SD (n)	Mean Change from baseline (g/dL) Mean ± SD (n)
Baseline	10.4 ± 0.74 (196)		10.3 ± 0.81 (95)	
Month 1	10.9 ± 1.11 (188)	0.5 ± 0.98 (188)	10.7 ± 1.10 (92)	0.4 ± 0.98 (90)
Month 2	11.1 ± 1.16 (169)	0.6 ± 1.10 (169)	11.0 ± 1.12 (82)	0.6 ± 1.11 (80)
Month 3	10.9 ± 1.12 (154)	0.4 ± 1.18 (154)	10.7 ± 1.11 (73)	0.3 ± 1.15 (72)
Month 4	10.9 ± 1.13 (147)	0.4 ± 1.13 (147)	10.8 ± 1.18 (77)	0.4 ± 1.19 (75)
Month 5	10.8 ± 1.05 (158)	0.4 ± 1.18 (158)	10.7 ± 1.13 (81)	0.4 ± 1.21 (80)
Month 6	10.7 ± 1.13 (139)	0.3 ± 1.27 (139)	10.8 ± 1.08 (73)	0.4 ± 1.19 (72)
Month 7	10.9 ± 1.02 (139)	0.4 ± 1.22 (139)	10.7 ± 1.06 (78)	0.3 ± 1.37 (76)
Month 8	10.7 ± 1.09 (137)	0.2 ± 1.19 (137)	10.7 ± 1.00 (69)	0.4 ± 1.38 (67)
Month 9	10.7 ± 1.22 (132)	0.3 ± 1.24 (132)	10.9 ± 1.02 (69)	0.4 ± 1.21 (67)
Month 10	10.7 ± 1.18 (131)	0.3 ± 1.23 (131)	10.8 ± 0.99 (67)	0.5 ± 1.23 (65)
Month 11	10.8 ± 1.09 (136)	0.3 ± 1.21 (136)	10.9 ± 0.91 (72)	0.5 ± 1.20 (70)
Month 12	10.9 ± 1.12 (128)	0.4 ± 1.31 (128)	10.7 ± 0.99 (72)	0.4 ± 1.23 (70)
Month 13	10.7 ± 1.14 (116)	0.2 ± 1.38 (116)	10.9 ± 0.94 (54)	0.6 ± 1.16 (53)

Source: Table 14.2.1.3.

Secondary Efficacy Endpoints

Transferrin Saturation (TSAT)

Table 56: Mean Change in TSAT at Week 5 – ITT Population (CSR)

Treatment Period[1]	Ferumoxytol N=196 Mean Change TSAT (%) Mean ± SD (n)	Iron Sucrose N=97 Mean Change TSAT (%) Mean ± SD (n)	LS mean and 95% Confidence Interval for difference
TP1	6.6 ± 9.2 (195)	9.5 ± 11.97 (95)	-3.06 (-5.57,-0.55)
TP2	8.2 ± 12.95 (169)	11.3 ± 14.68 (88)	-3.22 (-6.74,0.31)
TP3	8.5 ± 10.56 (129)	9.1 ± 11.13 (63)	-0.83 (-4.12,2.47)
TP4	9.8 ± 14.76 (80)	10.0 ± 14.76 (32)	0.15 (-5.93,6.23)
TP5	6.3 ± 9.77 (48)	14.4 ± 17.05 (17)	-7.36 (-14.28,-0.44)
TP6	7.1 ± 16.62 (21)	5.1 ± 12.84 (8)	2.04 (-12.88,16.96)

[1] Includes only treatment periods for which n>5 for both treatment groups. Source: Table 14.2.2.1.1.

Table 57: Mean Change in TSAT by Month – ITT Population (CSR)

	Ferumoxytol N=196		Iron Sucrose N=97	
Month	TSAT level Mean ± SD (n)	Mean Change from baseline (%) Mean ± SD (n)	TSAT level Mean ± SD (n)	Mean Change from baseline (%) Mean ± SD (n)
Baseline	21.9 ± 5.74 (196)		22.2 ± 5.50 (96)	
Month 1	28.9 ± 10.22 (189)	6.9 ± 9.27 (189)	32.3 ± 13.19 (92)	10.0 ± 11.98 (91)
Month 2	31.6 ± 11.34 (168)	9.8 ± 11.36 (168)	35.9 ± 16.08 (83)	12.8 ± 15.28 (82)
Month 3	30.2 ± 10.98 (154)	7.9 ± 11.16 (154)	34.7 ± 12.51 (74)	12.2 ± 13.24 (73)
Month 4	31.8 ± 11.85 (147)	9.8 ± 11.95 (147)	34.7 ± 13.07 (76)	12.3 ± 13.34 (75)
Month 5	32.3 ± 11.91 (157)	10.4 ± 12.19 (157)	35.2 ± 11.15 (81)	13.0 ± 11.09 (81)
Month 6	31.8 ± 10.55 (139)	10.0 ± 10.63 (139)	36.1 ± 15.60 (73)	13.4 ± 15.80 (72)
Month 7	31.9 ± 10.31 (136)	10.2 ± 10.84 (136)	34.3 ± 13.38 (78)	11.9 ± 13.98 (77)
Month 8	31.8 ± 11.64 (137)	10.0 ± 12.05 (137)	35.3 ± 11.42 (67)	13.3 ± 12.72 (66)
Month 9	32.7 ± 12.90 (131)	10.7 ± 13.41 (131)	35.9 ± 15.53 (71)	13.8 ± 16.32 (70)
Month 10	32.0 ± 10.64 (132)	10.2 ± 10.98 (132)	34.2 ± 10.93 (67)	12.1 ± 12.03 (66)
Month 11	34.3 ± 12.95 (134)	12.1 ± 12.77 (134)	35.1 ± 11.73 (71)	13.3 ± 12.12 (70)
Month 12	33.9 ± 14.06 (126)	12.0 ± 13.68 (126)	33.0 ± 12.36 (71)	10.9 ± 13.38 (70)
Month 13	31.5 ± 12.76 (116)	9.2 ± 12.58 (116)	34.8 ± 13.35 (53)	12.7 ± 14.46 (52)

Source: Table 14.2.2.2.

Subjects with an increase in hemoglobin of ≥1 g/dL at any time from TP baseline to Week 5

Table 58: Subjects With Increase in Hemoglobin of ≥1 g/dL at Any Time From TP Baseline to Week 5 (ITT Population) (CSR)

Treatment Period[1]	Ferumoxytol N=196 Proportion (%) of subjects with ≥1.0 g/dL Hgb increase	Iron Sucrose N=97 Proportion (%) of subjects with ≥1.0 g/dL Hgb increase	LS mean and 95% Confidence Interval for percent difference
TP1	55/196 (28.1)	23/97 (23.7)	4.35 (-6.20,14.90)
TP2	55/173 (31.8)	13/88 (14.8)	17.02 (6.86,27.17)
TP3	42/133 (31.6)	19/65 (29.2)	2.35 (-11.24,15.94)
TP4	20/85 (23.5)	10/33 (30.3)	-6.77 (-24.86,11.31)
TP5	13/49 (26.5)	3/18 (16.7)	9.86 (-11.33,31.06)
TP6	5/22 (22.7)	1/8 (12.5)	10.23 (-18.61,39.07)

[1] Includes only treatment periods for which n>5 for both treatment groups.
Source: Table 14.2.1.4.1

Cumulative IV iron exposure per subject over the course of the study

The mean cumulative IV iron exposure was 3502.5±1759.78 mg for ferumoxytol and 3117.6±1549.61 mg for iron sucrose. The median values were 3060.0 mg for ferumoxytol and 3000.0 mg for iron sucrose indicating that for each treatment a median of 3 cycles and a total of approximately 3 g was delivered over a 1-year period.

Proportion of subjects requiring blood transfusion

The number of subjects requiring a blood transfusion in each treatment group was similar (18/196 (9.2%) for ferumoxytol and 8/97 (8.2%) for iron sucrose. (Safety Population). Four subjects receiving ferumoxytol required 3 or more transfusions; no subjects treated with iron sucrose required more than 2 transfusions.

Proportion of subjects who had a change in ESA dose over the course of the study

Table 59: Conversion of Weekly Darbepoetin Alpha (ug) dose to Monthly Epoetin Units (IU) (CSR)

Weekly Darbepoetin Alpha (ug)	Monthly epoetin (units/IU)
5-6.5	8000
10	13600
12.5	15000
18.75-20	24000
25	32000
30	44000
40	58000
45	64000
50	72000
60-62.5	120000
65-75	136000
100	248000
125	320000
200-250	360000

Source: ARANESP PI (FDA) and Online Conversion (AMGEN) at http://www.aranesp.com/professional/nephrology/conversion_to_aranesp.html

Table 60: Conversion of Monthly MIRCERA dosing to Epoetin Units (IU) (CSR)

Table 15: Conversion of Monthly MIRCERA dosing to Epoetin Units (IU)

Monthly methoxy polyethylene glycol-epoetin beta (MIRCERA)	Monthly epoetin (units/IU)
75	16000
150	28000
240	55000
500	100000
750	150000

Source: MIRCERA PI (FDA)

The original exploratory endpoint of this study was to evaluate the frequency and proportion of subjects with a greater than 20% increase or decrease over baseline ESA dose during the course of treatment. However, it was determined by discussion with investigators that during the course of this long term evaluation various extraneous events unrelated to clinical status could affect the dose and agent prescribed. Therefore, these data are described only through the use of monthly total doses received. Further, within the data there were outliers which greatly skewed the arithmetic mean. For example, at baseline the dose range in the entire study population was from 0 to 360000 units. Therefore, medians are used to describe the data.

Table 61: Median ESA use (IU) by month (CSR)

Month	Ferumoxytol ESA Dose Median (Range) (n)	Iron Sucrose ESA Dose Median (Range) (n)	All Subjects ESA Dose Median (Range) (n)
Baseline	26400 (0, 248000) (191)	23400 (0, 360000) (93)	26000 (0, 360000) (284)
Month 1	28600 (0, 240000) (191)	23400 (0, 360000) (92)	27000 (0, 360000) (283)
Month 2	28600 (0, 236000) (189)	23250 (0, 360000) (92)	26400 (0, 360000) (281)
Month 3	25200 (0 , 231000) (189)	20600 (0 , 360000) (88)	23900 (0 , 360000) (277)
Month 4	24000 (0, 248000) (179)	17600 (0, 360000) (86)	20000 (0, 360000) (265)
Month 5	22000 (0, 320000) (175)	19800 (0, 360000) (86)	20000 (0, 360000) (261)
Month 6	20000 (0, 248000) (170)	18400 (0, 360000) (84)	19800 (0, 360000) (254)
Month 7	18000 (0, 248000) (165)	19800 (0, 360000) (79)	18900 (0, 360000) (244)
Month 8	21800 (0, 256300) (158)	20800 (0, 360000) (78)	21400 (0, 360000) (236)
Month 9	22000 (0, 429000) (157)	17600 (0, 360000) (78)	19800 (0, 429000) (235)
Month 10	20000 (0, 192000) (154)	17600 (0, 360000) (75)	19800 (0, 360000) (229)
Month 11	19200 (0, 228000) (148)	19800 (0, 360000) (74)	19800 (0, 360000) (222)
Month 12	18500 (0, 158400) (142)	17900 (0, 144300) (72)	18000 (0, 158400) (214)
Month 13	18000 (0, 120500) (137)	17600 (0, 248000) (71)	17800 (0, 248000) (208)

Source: Table 14.2.6.1.

Ancillary analyses

Further post hoc analyses (e.g., subgroup analyses, sensitivity analyses to the primary efficacy analysis) are requested.

All-cause IDA: AMAG-FER-IDA-301

A Phase III Randomized, Double -Blind, Placebo-Controlled Trial of Ferumoxytol for the Treatment of Iron Deficiency AnemiaMethods

Methods

Study Participants

Key inclusion criteria included:

- Male and female subjects ≥18 years of age
- IDA with a screening Hgb value <10.0 g/dL and TSAT <20%
- History of unsatisfactory oral iron therapy or could not use oral iron, which included subjects who remained anaemic despite oral iron therapy, had side effects that precluded the use of oral iron therapy, or who could not otherwise take oral iron

Key exclusion criteria included:

- History of allergy to IV iron
- Allergy to 2 or more classes of drugs.
- Subjects on dialysis or with an eGFR <30 mL/min/1.73 m2
- Screening Hgb ≤7.0 g/dL

- Screening serum ferritin level >600 ng/mL
- Parenteral iron therapy within 4 weeks prior to screening, oral iron therapy within 2 weeks prior to screening, or red blood cell (RBC)/whole blood transfusion within 2 weeks prior to screening or planned during the study
- Erythropoiesis-stimulating agent (ESA) therapy initiated, stopped, or dose changed by >20% within 4 weeks prior to screening, or an anticipated ESA dose change of >20% during the study

Treatments

Subjects who met the entry criteria were randomized in a 3:1 ratio to receive either ferumoxytol or placebo:

• Ferumoxytol Treatment Group: IV injection of ferumoxytol, 510 mg (17 mL) at Baseline (Day 1) with a second dose 2 to 8 days after Dose 1, for a total cumulative dose of 1.02 g

• Placebo Treatment Group: IV injection of 17 mL of normal saline at Baseline (Day 1) with a second injection 2 to 8 days after the first.

Subjects received two injections of either ferumoxytol or saline placebo administerd with a minimum duration of 17 seconds and a maximum duration of 1 minute. Any intervention that could influence study outcome was prohibited during the study period.

Ferumoxytol was given at a fixed dose regardless of bodyweight.

Objectives

The objective of this study was to evaluate the efficacy and safety of a 1.02g course of IV ferumoxytol, administered as two doses of 510 mg each compared with placebo (normal saline) for the treatment of IDA in adult patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.

Outcomes/endpoints

The **primary efficacy endpoint** was defined as the **mean change in haemoglobin from Baseline to Week 5**

Secondary Efficacy Endpoints

- Proportion of subjects achieving a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5
- Proportion of subjects who achieved a haemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5
- Mean change in TSAT from Baseline to Week 5
- Time to haemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline

Underlying Condition Subgroup Analyses

1. Proportion of subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other who achieved a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5

2. Mean change in haemoglobin from Baseline to Week 5 in subjects with AUB, Cancer, GI Disorders, Postpartum Anaemia and Other.

Exploratory efficacy endpoints included PRO measures and blood transfusion.

Analyses of blood tests were performed by a central laboratory to ensure consistency of results and reference ranges across study sites.

The primary analysis supporting the EU registration was defined following scientific advice received by EU competent authorities. The primary endpoint supporting the FDA licensing process was the proportion of subjects achieving a ≥2.0 g/dL increase in Hgb at any time from Baseline to Week 5.

Sample size, Randomisation and blinding (masking)

The sample size of 800 subjects provided 99% power for the assessment of superiority of ferumoxytol to placebo. Subjects were assigned to ferumoxytol exposure and placebo following a 3:1 ratio. The randomization was stratified by Baseline haemoglobin level (>7.0 to ≤8.5 g/dL; > 8.5 to <10.0g/dL) and by underlying condition (AUB, Cancer, GI Disorders, Postpartum Anemia, and Other). The European population, however, were only 6.7% randomised at the very end of study enrolment. Further analyses are requested.

This study was double-blinded with respect to treatment assignment administration of study drug, and relevant laboratory parameters.

Statistical methods

The ITT Population served as the **primary efficacy analysis** population and the Evaluable Population as supportive evaluation of the primary efficacy endpoint (mean change in hemoglobin from Baseline to Week 5); the analysis will be based upon actual treatment received.

The point estimate and 95% CI and p-value for the treatment difference were calculated using an **analysis of covariance (ANCOVA) model**, adjusted for Baseline hemoglobin and underlying condition. Statistical significance was established if the p-value was ≤ 0.05. If the Week 5 hemoglobin value was missing, the change from Baseline was conservatively imputed to be zero, consistent with no increase in hemoglobin. Sensitivity analyses for the primary efficacy parameter assessed the impact of imputation of missing data using multiple imputation (MCMC) methods.

According to the Statistical Analysis Plan and Study Protocol a further sensitivity analysis has been planned using last observation carried forward (LOCF) approach for missing data imputation. No such Analysis has been described or provided in the Clinical Study Report. The submission of the results of this analysis is requested.

The secondary efficacy endpoints were analysed for superiority in a sequential manner with fixed sequences using hierarchical ordering to control alpha at an overall 0.05 level.

1. Proportion of subjects achieving a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5
2. Proportion of subjects who achieved a hemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5
3. Mean change in TSAT from Baseline to Week 5
4. Time to hemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline

The point estimate and 95% CI for the treatment difference of ferumoxytol minus placebo for the two **proportional endpoints** were presented based on large sample size assumption. The p-value was calculated from the **Cochran-Mantel-Haenszel test**, adjusted for Baseline hemoglobin and underlying condition. Statistical significance was established if the p-value was ≤ 0.05.

The point estimate for continuous endpoint, **mean change in TSAT** from baseline to Week 5, were calculated using the same approach as for the primary endpoint analysis.

For the **time-to-response endpoint**, the time (days) to this response (i.e., increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline) was calculated for each treatment arm using a **Kaplan-Meier curve**, and the p-value was obtained from the **log-rank test**. Subjects who did not have a hemoglobin increase of ≥2.0 g/dL or to a hemoglobin level ≥12.0 g/dL were censored at their last laboratory visit date. Subjects who did not have any post-Baseline study visits were not included in the analysis. All suggested analysis approaches are supported.

For subgroup analyses (secondary endpoints 1 and 2 under Underlying Condition Subgroup Analyses, below), the analyses were conducted sequentially. If a subgroup was assessed to be not statistically significant, the remaining subgroup and /or subsequent subgroup analyses were considered descriptive.

Underlying Condition Subgroup Analyses

1. Proportion of subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other who achieved a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5

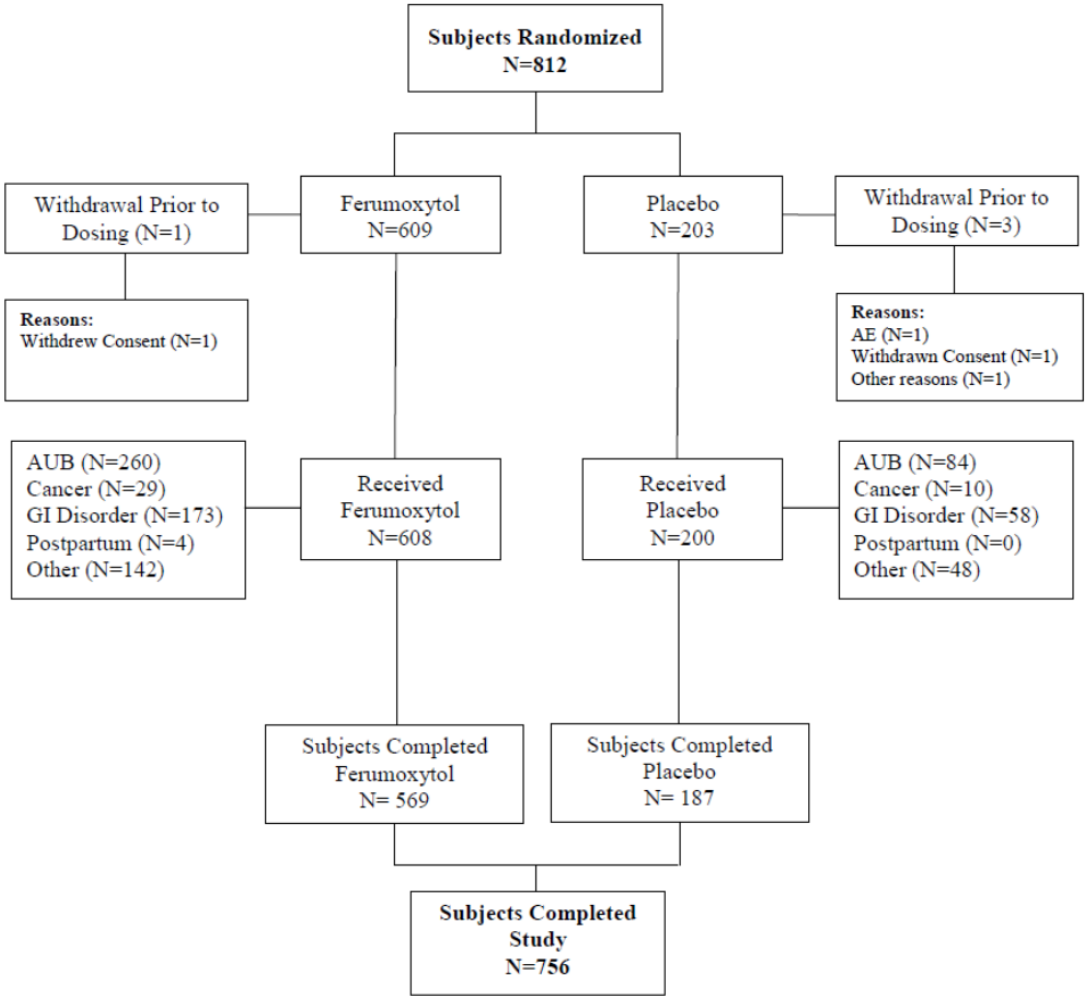
2. Mean change in hemoglobin from Baseline to Week 5 in subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other.

Adjustment for multiple comparison and the proposed subgroup analyses are accepted.

Results

Participant flow

Figure 2: Subject Disposition in Study AMAG-FER-IDA-301



Recruitment

Date first subject enrolled: 19 June 2010

Date last subject completed: 27 February 2012

Conduct of the study

Protocol Amendments

The original study protocol (16 March 2010) was amended once (Protocol Amendment 1, 10 March 2011), clarifying certain subgroups, excluding lactating women and prohibiting the use of a butterfly needle for infusions.

Protocol Deviations

Overall (N=808), 37 subjects (4.6%) failed to meet the Inclusion/Exclusion criteria for the study (33 [5.4%] ferumoxytol vs. 4 [2.0%] placebo). Other protocol deviations/ violations in the study included: received incorrect dosage of study drug (6 [1.0%] subjects in the ferumoxytol group) and received

prohibited medication or therapy (13 [2.1%] subjects in the Ferumoxytol Treatment Group vs. 5 [2.5%] subjects in the Placebo Treatment Group).

8.5% of subjects in the verum and only 4.5% of subjects in the placebo arm reported protocol deviations. The majority of deviations is in the category "Failed to meet Inclusion/Exclusion criteria". In the provided listings, the exclusion criterion most often violated was: Major surgery or invasive intervention within 4 weeks prior to screening, organ transplant within 6 months prior to screening, or any planned surgery or intervention during the course of the study.

The influence of these subjects on the outcomes can be gauged by comparing the efficacy analyses in the ITT Population to the Evaluable (PP) Population.

Baseline data

Nearly 90% of the study population is female, reflecting the greater incidence of IDA in women. Approximately half of subjects are White, and about 80% were recruited in the US and Canada and about 6% in EU countries. An extremely broad range of bodyweights was observed in the study population, reaching from extremely underweight (28kg) to extremely overweight (203kg).

More than half of the study population had either side effects leading to discontinuation of oral iron use or failed to improve after more than 1 month of oral iron treatment. About a quarter had both of these concerns. Less than a fifth had a known condition precluding oral iron use.

Numbers analysed

Table 5: Subject Population (All Randomized Subjects)

Subject Population	Treatment Group		Total N=812
	Ferumoxytol N=609	Placebo N=203	
	n (%)	n (%)	n (%)
ITT Population	**608 (99.8)**	**200 (98.5)**	**808 (99.5)**
Excluded Subjects	1 (0.2)	3 (1.5)	4 (0.5)
Did not Receive Study Drug	1 (0.2)	3 (1.5)	4 (0.5)
Evaluable Population	**531 (87.2)**	**182 (89.7)**	**713 (87.8)**
Excluded Subjects	78 (12.8)	21 (10.3)	99 (12.2)
Violated inclusion/exclusion criteria	33 (5.4)	4 (2.0)	37 (4.6)
Did Not Receive Complete Dosing	32 (5.3)	11 (5.4)	43 (5.3)
No Post-Baseline Hemoglobin Data	19 (3.1)	4 (2.0)	23 (2.8)
Received Blood Transfusion	9 (1.5)	5 (2.5)	14 (1.7)
Received Incorrect Dose Volume	6 (1.0)	0	6 (0.7)
Change of Therapy to Control Bleeding	4 (0.7)	0	4 (0.5)
ESA Violation	1 (0.2)	0	1(0.1)
Significant Protocol Violation/Deviation [1]	0	0	0
Received Off-Study IV Iron Therapy	0	0	0
Safety Population	**608 (99.8)**	**200 (98.5)**	**808 (99.5)**
Excluded Subjects	1 (0.2)	3 (1.5)	4 (0.5)
Did not Receive Study Drug	1 (0.2)	3 (1.5)	4 (0.5)

Note: All percentages based on number of subjects enrolled in the study.

[1] There were no additional significant protocol violations/deviations identified in this study.

Outcomes and estimation

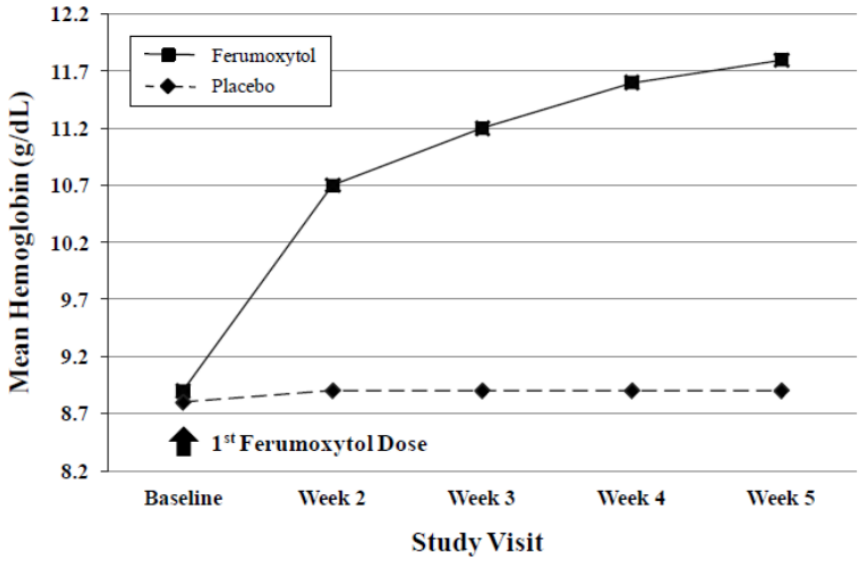
Primary Efficacy Endpoint

Table 26: Primary Efficacy Endpoint: Mean Change in Hemoglobin from Baseline to Week 5 (ITT Population and Evaluable Populations)

Mean Change in Hemoglobin from Baseline to Week 5	Treatment Group		Difference			
	Ferumoxytol	Placebo	Difference	95% CI[1]	p-value[1]	Superiority
Intent-to-Treat Population						
N	608	200				
Mean (SD)	2.6 (1.52)	0.1 (0.89)				
LS mean	2.7	0.1	2.54	(2.33, 2.75)	<0.0001	Yes
Median	2.8	0.0				
Q1, Q3	1.7, 3.7	-0.4, 0.4				
Min, Max	-2.9, 7.0	-3.5, 4.5				
Evaluable Population*						
N	531	182				
Mean (SD)	2.8 (1.46)	0.0 (0.77)				
LS mean	2.8	0.1	2.70	(2.49, 2.90)	<0.0001	Yes
Median	3.0	0.0				
Q1, Q3	2.0, 3.7	-0.4, 0.3				
Min, Max	-2.9, 7.0	-2.4, 3.9				

Note: Baseline was the Day 1 value (prior to injection of study drug). The screening or most recent value prior to Day 1 was used for any subject with missing Day 1 information. Change from Baseline used an imputed value of 0 for missing values at post-baseline visits.

Figure 7: Mean Weekly Hemoglobin from Baseline to Week by Treatment Group (ITT Population)

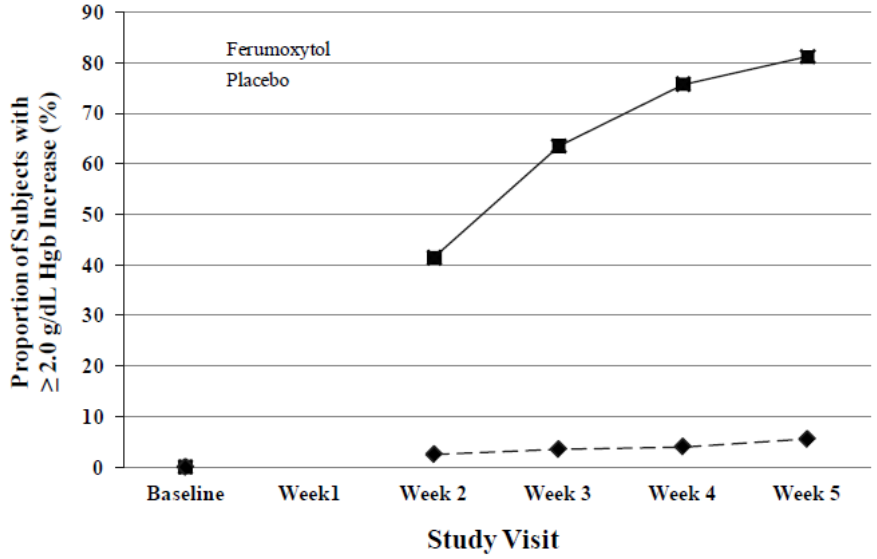


Source Data: Table 14.2.2.1

Secondary Efficacy Endpoints

Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase in Haemoglobin at Any Time from Baseline to Week 5

Figure 8: Proportion of Subjects who Achieved a ≥2.0 g/dL Increase in Hemoglobin at Any Time from Baseline to Week 5 (ITT Population)



Data Source: Table 14.2.1.1

Proportion of Subjects Achieving a Hemoglobin Level ≥12.0 g/dL at Any Time from Baseline to Week 5

Baseline hgb levels were 8.9 and 8.8 for verum and placebo patients, respectively. About 50% of subjecst treated with ferumoxytol achieved a haemoglobin level of ≥12g/dL in contrast to 3% of placebo subjects.

Mean Change in TSAT from Baseline to Week 5

A superior increase in TSAT was reported for the verum group (11.0) compared to placebo patients (-0.1).

Time to Haemoglobin Increase of ≥2.0 g/dL or to a Haemoglobin Level of ≥12.0 g/dL from Baseline

It took about three weeks to reach the full effect of the provided iron substitution on hgb levels for ferumoxytol treated patients.

The *exploratory endpoints* investigated PROs, blood transfusion and ESA usage. The majority of subjects in this study (ferumoxytol, 98.5%; placebo, 97.5%) did not require blood transfusion, and only 1 subject in the ferumoxytol treatment group stopped ESA therapy during the study, but later reinitiated ESA usage.

The 3 PRO instruments (FACIT-Fatigue score, SF-36 health survey, and QoL LASA) demonstrated consistent, significant improvements in fatigue/tiredness, vitality and energy above previously defined MIDs of 3.0 and above that seen in placebo-treated subjects. Baseline scores mirrored those reported in anemic cancer subjects and post–ferumoxytol treatment scores increased, approaching that of general nonanemic population norms.

Ferumoxytol-treated subjects demonstrated significantly greater ($p<0.0001$) improvements in FACIT-Fatigue scores (+11.7 points) relative to placebo-treated subjects (+6.8) from Baseline to Week 5 with a treatment difference of 4.9 points.

In the SF-36 (vitality domain scores) and LASA (energy, ADL, QoL) ferumoxytol-treated subjects also showed statistically significant changes from Baseline to Week 5 compared with placebo (p<0.001).

Ancillary analyses

Underlying Condition Subgroup Analyses

Table 62 Mean Change in Hgb (g/dL) From Baseline to Week 5 by IDA Underlying Condition, ITT Population (IDA-301)

Treatment Subgroups	Treatment Groups Ferumoxytol	Placebo	Treatment Difference (95% CI)	p-value
IDA-301				
AUB n	260	84		
Mean (SD) baseline Hgb (g/dL)	8.8 (0.91)	8.7 (0.96)		
Mean (SD) change from Baseline to Week 5	2.8 (1.37)	0.0 (0.83)		
LS mean change from Baseline to Week 5 (a)	2.8	-0.0	2.78 (2.48, 3.08)	<0.0001
Cancer n	29	10		
Mean (SD) baseline Hgb (g/dL)	9.2 (0.69)	8.8 (1.11)		
Mean (SD) change from Baseline to Week 5	1.3 (1.59)	0.6 (0.86)		
LS mean change from Baseline to Week 5 (a)	1.3	0.5	0.76 (-0.35, 1.87)	0.1745
GI disorders n	173	58		
Mean (SD) baseline Hgb (g/dL)	8.9 (0.89)	8.7 (0.73)		
Mean (SD) change from Baseline to Week 5	2.8 (1.50)	-0.1 (0.63)		
LS mean change from Baseline to Week 5 (a)	2.8	-0.1	2.89 (2.51, 3.27)	<0.0001
Postpartum anemia n	4	0		
Mean (SD) baseline Hgb (g/dL)	8.7 (1.84)	0		
Mean (SD) change from Baseline to Week 5	3.8 (1.51)	0	NE	NE
Other n	142	48		
Mean (SD) baseline Hgb (g/dL)	9.0 (0.85)	9.1 (0.86)		
Mean (SD) change from Baseline to Week 5	2.3 (1.61)	0.2 (1.20)		
LS mean change from Baseline to Week 5 (a)	2.3	0.3	2.01 (1.53, 2.49)	<0.0001
Postpartum anemia or other (b) n	146	48		
Mean (SD) baseline Hgb (g/dL)	9.0 (0.88)	9.1 (0.86)		
Mean (SD) change from Baseline to Week 5	2.3 (1.62)	0.2 (1.20)		
LS mean change from Baseline to Week 5 (a)	2.3	0.3	2.04 (1.56, 2.52)	<0.0001

The provided subgroup analysis is considered descriptive only, as superiority over placebo could not be shown for each subgroup.

AMAG-FER-IDA-302

A Phase III, Randomized, Open-label, Active-Controlled Trial Comparing Ferumoxytol with Iron Sucrose for the Treatment of Iron Deficiency Anemia

Methods

Study Participants

Key inclusion criteria included:

- Male and female subjects ≥18 years of age
- IDA with a screening Hgb value <10.0 g/dL and TSAT <20%
- History of unsatisfactory oral iron therapy or could not use oral iron, which included subjects who remained anaemic despite oral iron therapy, had side effects that precluded the use of oral iron therapy, or who could not otherwise take oral iron

Key exclusion criteria included:

- History of allergy to IV iron
- Allergy to 2 or more classes of drugs.
- Subjects on dialysis or with an eGFR <30 mL/min/1.73 m2
- Screening Hgb ≤7.0 g/dL
- Screening serum ferritin level >600 ng/mL
- Parenteral iron therapy within 4 weeks prior to screening, oral iron therapy within 2 weeks prior to screening, or red blood cell (RBC)/whole blood transfusion within 2 weeks prior to screening or planned during the study
- Erythropoiesis-stimulating agent (ESA) therapy initiated, stopped, or dose changed by >20% within 4 weeks prior to screening, or an anticipated ESA dose change of >20% during the study

Treatments

Subjects who met the entry criteria were randomized in a 2:1 ratio to either ferumoxytol or iron sucrose and received the following:

• Ferumoxytol: IV injection of ferumoxytol, 510 mg (17 mL) at Baseline (Day 1) with a second dose 2 to 8 (5±3) days after Dose 1, for a total cumulative dose of 1.02 g

• Iron sucrose: IV injection or infusion of iron sucrose, 200 mg on Day 1 and at 4 other visits on non-consecutive days over a 14-day period, for a total cumulative dose of 1.0 g

Subjects received either two injections of ferumoxytol or five slow injections/infusions of iron sucrose. Any intervention that could influence study outcome was prohibited during the study period.

As in trial IDA-301, ferumoxytol was given at a fixed dose regardless of bodyweight. Instructions for using a lower dose in subjects with low bodyweight and a haemoglobin value >10-≤12 g/dl are included in section 4.2 of the SmPC.

Objectives

The purpose of this study was to evaluate the efficacy and safety of a 1.02 g course of IV ferumoxytol, administered as 2 doses of 510 mg each, compared with a 1.0 g course of iron sucrose, administered as 5 doses of 200 mg each for the treatment of IDA in patients with a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.

Outcomes/endpoints

The **primary efficacy endpoint** was defined as the **mean change in haemoglobin from Baseline to Week 5**

Secondary Efficacy Endpoints

- Proportion of subjects achieving a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5
- Proportion of subjects who achieved a haemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5
- Mean change in TSAT from Baseline to Week 5
- Time to haemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline

Underlying Condition Subgroup Analyses

1. Proportion of subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other who achieved a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5

2. Mean change in haemoglobin from Baseline to Week 5 in subjects with AUB, Cancer, GI Disorders, Postpartum Anaemia and Other.

Exploratory efficacy endpoints included PRO measures and blood transfusion.

Analyses of blood tests were performed by a central laboratory to ensure consistency of results and reference ranges across study sites.

Analogous to study AMAG-FER-IDA 301, the primary analysis supporting the EU registration was defined following scientific advice received by EU competent authorities. The primary endpoint supporting the FDA licensing process was the proportion of subjects achieving a ≥2.0 g/dL increase in Hgb at any time from Baseline to Week 5.

Sample size, Randomisation and blinding (masking)

The sample size of 600 subjects is considered large enough to provide sufficient power. Subjects were assigned to ferumoxytol and iron sucrose exposure following a 2:1 ratio. The randomization was stratified by Baseline haemoglobin level (>7.0 to ≤8.5 g/dL; > 8.5 to <10.0g/dL) and by underlying condition (ongoing AUB, Cancer, GI Disorders, Postpartum Anemia, and Other). The stratification factors are endorsed and the randomization scheme indicated their balanced allocation in both treatment arms.

The study drug was not blinded.

Statistical methods

Statistical analyses for the primary, secondary, and exploratory endpoints were performed on the ITT Population. Analysis for the primary endpoint were repeated on the Evaluable Population.

The point estimate and 95% CI for the treatment difference based on the primary endpoint (mean change in haemoglobin from Baseline to Week 5) was assessed using an analysis of covariance (ANCOVA) model, adjusting for Baseline hemoglobin and underlying condition. If the Week 5 hemoglobin value was missing, the change from Baseline was conservatively imputed to be zero.

Non-inferiority was concluded if the lower bound of the 95% CI was ≥-0.5; superiority was concluded if the lower bound of the 95% CI was >0.

Secondary efficacy endpoints were analysed for superiority in a sequential manner with fixed sequences using hierarchical ordering to control alpha at an overall 0.05 level.

1. Proportion of subjects achieving a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5
2. Proportion of subjects who achieved a hemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5
3. Mean change in TSAT from Baseline to Week 5
4. Time to hemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline
5. Proportion of subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other who achieved a ≥2.0 g/dL increase in hemoglobin at any time from Baseline to Week 5
6. Mean change in hemoglobin from Baseline to Week 5 in subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other.

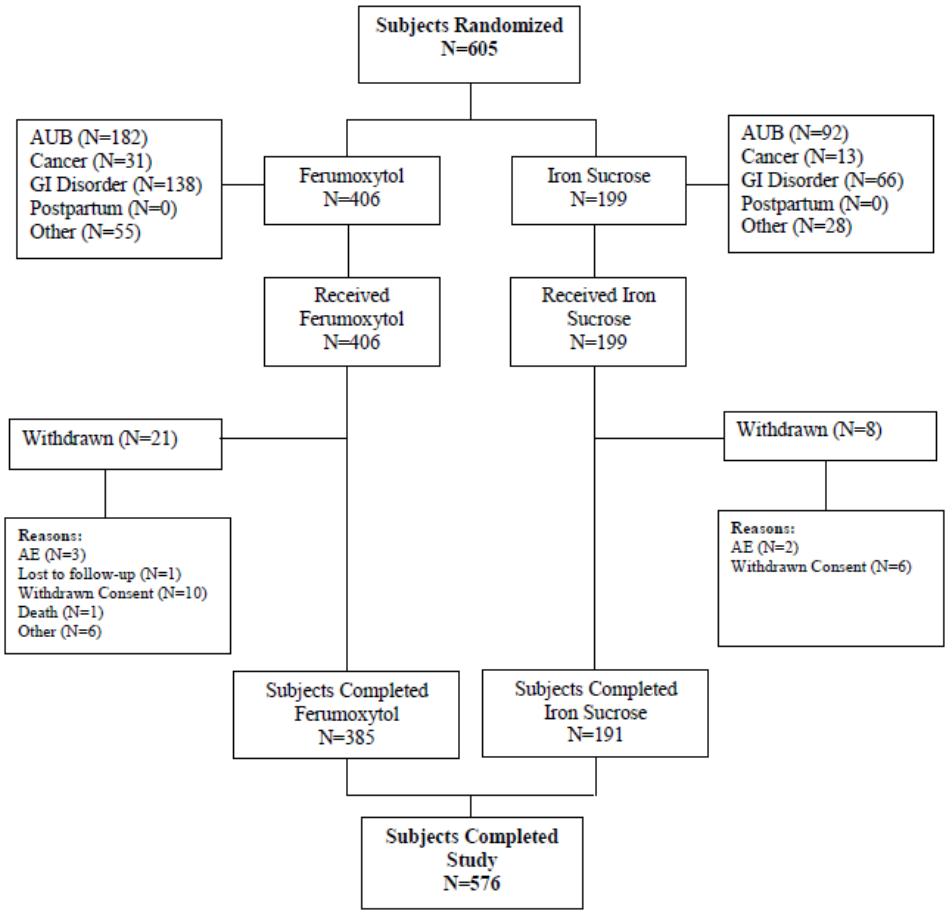
The primary endpoint and the continuous secondary endpoint were analysed using ANCOVA model, adjusted for Baseline hemoglobin and underlying condition. To analyse the proportional secondary endpoints Cochran-Mantel-Haenszel test, adjusted for Baseline hemoglobin and underlying condition was used and for the Time-to-hemoglobin-increase secondary endpoint a Kaplan-Meier curve and the p-value was obtained from the log-rank test.

Additional analyses by subgroup were performed by 1) Underlying Conditions Subgroups (included subjects with AUB, Cancer, GI Disorders, Postpartum Anemia and Other), 2) Baseline Hemoglobin Subgroups (included subjects with Baseline Hgb levels between >7.0 and ≤8.5 g/dL or >8.5 to <10.0 g/dL) and 3) Prior History of IV Iron Use Subgroups.

Results

Participant flow

Figure 2: Subject Disposition in Study AMAG-FER-IDA-302 (ITT Population)



Recruitment

Date first subject enrolled: 10 August 2010
Date last subject completed: 09 November 2011

Conduct of the study

Protocol Amendments

There were no changes to the conduct of the study and the original approved protocol was used throughout the conduct of the entire study.

Protocol Deviations

Overall (N=605), 18 subjects (3.0%) failed to meet the inclusion/exclusion criteria for the study (16 [3.9%] ferumoxytol vs. 2 [1%] iron sucrose). Other protocol deviations/violations in the study included signed informed consent after study participation (1 subject (0.5%) in the iron sucrose group), received incorrect dosage of study drug (1 (0.2%) ferumoxytol vs. 3 (1.5%) iron sucrose) and received prohibited medication or therapy (12 (3.0%) ferumoxytol vs. 3 (1.5%) iron sucrose).

7.1% of subjects in the ferumoxytol and 4.5% of subjects in the iron sucrose arm reported protocol deviations. The majority of deviations is in the category "Failed to meet Inclusion/Exclusion criteria" or "Received prohibited medication or therapy". In the provided listings, the exclusion criterion most often

violated was: Major surgery or invasive intervention within 4 weeks prior to screening, organ transplant within 6 months prior to screening, or any planned surgery or intervention during the course of the study.

The influence of these subjects on the outcomes can be gauged by comparing the efficacy analyses in the ITT Population to the Evaluable (PP) Population.

Baseline data

Similar to the population of pivotal trial AMAG-FER-IDA 301, more than 80% of the study population is female, reflecting the greater incidence of IDA in women. Greater than 80% of subjects are White, and about 70% were recruited in Europe and about 10% in South Africa. A broad range of bodyweights was observed in the study population, spanning from underweight (38kg) to overweight (136kg).

Numbers analysed

Table 6: Subject Population (All Enrolled Subjects)

Subject Population	Treatment Group		Total (N=605)
	Ferumoxytol N=406	Iron Sucrose N=199	
	n (%)	n (%)	n (%)
Randomized	406	199	605
ITT Population	406 (100.0)	199 (100.0)	605 (100.0)
Excluded Subjects	0	0	0
Safety Population	406 (100.0)	199 (100.0)	605 (100.0)
Excluded Subjects	0	0	0
Evaluable Population	372 (91.6)	180 (90.5)	552 (91.2)
Excluded Subjects	34 (8.4)	19 (9.5)	53 (8.8)
Violated inclusion/exclusion criteria	16 (3.9)	2 (1.0)	18 (3.0)
Significant Protocol Violation/Deviation [1]	0	0	0
Did Not Receive Complete Dosing	11 (2.7)	11 (5.5)	22 (3.6)
Received Blood Transfusion	5 (1.2)	4 (2.0)	9 (1.5)
ESA Violation	0	0	0
Received Off-Study IV Iron Therapy	0	0	0
Change of Therapy to Control Bleeding	6 (1.5)	-	6 (1.0)
No Post-Baseline Hemoglobin Data	6 (1.5)	1 (0.5)	7 (1.2)

Note: All percentages based on number of subjects enrolled in the study.

[1] There were no additional significant protocol violations/deviations identified in this study.

Data Source: Table 14.1.1 and Table 14.1.2.5.

Outcomes and estimation

Primary Efficacy Endpoint

Table 19: Primary Efficacy Endpoint: Mean Change in Hemoglobin from Baseline to Week 5 (ITT Population and Evaluable Populations)

Mean Change in Hemglobin from Baseline to Week 5	Treatment Group		Difference			
	Ferumoxytol	Iron Sucrose	Difference	95% CI[1]	P-value[1]	Non-inferiority[2]
Intent-to-Treat Population						
N	406	199				
Mean (SD)	2.9 (1.62)	2.7 (1.30)				
LS mean	2.7	2.4	0.29	(0.06, 0.52)	0.0124	Yes
Median	3.2	2.9				
Q1, Q3	2.0, 4.1	2.0, 3.5				
Min, Max	-2.6, 7.4	-0.4, 6.0				
Evaluable Population						
N	372	180				
Mean (SD)	3.0 (1.57)	2.7 (1.23)				
LS mean	2.7	2.4	0.30	(0.07, 0.53)	0.0095	Yes
Median	3.2	2.9				
Q1, Q3	2.1, 4.1	2.1, 3.4				
Min, Max	-2.6, 7.4	-0.4, 6.0				

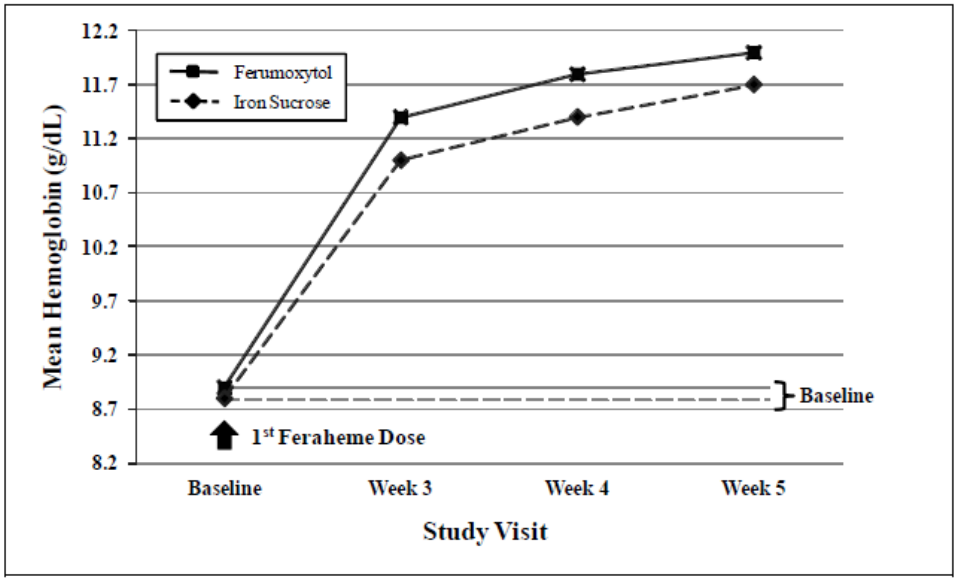
Note: Baseline was defined as the Day 1 value (prior to injection of study drug). The screening or most recent value prior to Day 1 was used for any subject with missing Day 1 information. Change from Baseline used an imputed value of 0 for missing visits.

[1] Treatment difference, 95% confidence interval and p-value were derived from an analysis of covariance model, adjusted for Baseline hemoglobin and underlying condition.

[2] Lower bound of the 95% CI was ≥ -0.5 g/dL (pre-defined non- inferiority margin).

Source Data: Table 14.2.2.1 and 14.2.2.2.1

Figure 6: Mean Change in Hemoglobin from Baseline to Week by Treatment Group (ITT Population)

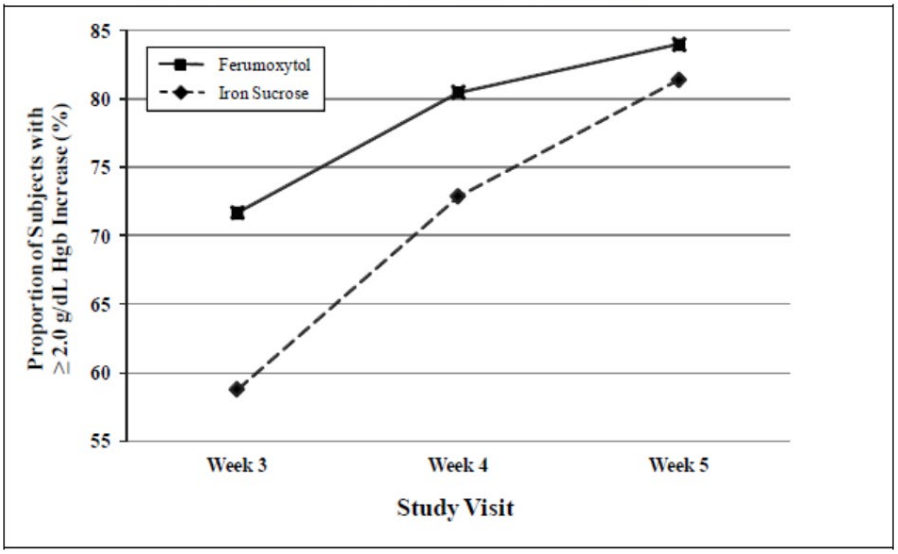


Source Data: Table 14.2.2.1

Secondary Efficacy Endpoints

Proportion of Subjects Who Achieved a ≥2.0 g/dL Increase in Haemoglobin at Any Time from Baseline to Week 5

Figure 7: Proportion of Subjects who Achieved a ≥2.0 g/dL Increase in Hemoglobin at Any Time from Baseline to Week 5 (ITT Population)



Data Source: Table 14.2.1.1

Proportion of Subjects Achieving a Hemoglobin Level ≥12.0 g/dL at Any Time from Baseline to Week 5

Baseline hgb levels were 8.9 and 8.8 for ferumoxytol and iron sucrose patients, respectively. 66.7% of subjecst treated with ferumoxytol achieved a haemoglobin level of ≥12g/dL in contrast to 48.2% of subjects who received iron sucrose.

Mean Change in TSAT from Baseline to Week 5

A superior increase in TSAT was reported for the ferumoxytol group (14.5) compared to iron sucrose treated patients (10.6).

Time to Haemoglobin Increase of ≥2.0 g/dL or to a Haemoglobin Level of ≥12.0 g/dL from Baseline

It takes about three weeks to reach the full effect of the provided iron substitution, with ferumoxytol showing a trend towards an earlier treatment effect.

The *exploratory endpoints* investigated PROs, blood transfusion and ESA usage. The majority of subjects in this study (ferumoxytol, 98.8%; iron sucrose, 98.0%) did not require blood transfusion, and none of the subjects in either treatment group required an increase in dose by >20% or initiation of ESA therapy.

The 3 PRO instruments (FACIT-Fatigue score, SF-36 health survey, and QoL LASA) demonstrated consistent, significant improvements in fatigue/tiredness, vitality and energy above the previously defined MIDs of 3.0, with similar changes observed in both the ferumoxytol and iron sucrose treatment groups. However no statistically significant changes were observed at Week 5 between the treatment groups.

Ancillary analyses

Underlying Condition Subgroup Analyses

Table 63 Mean Change in Hgb (g/dL) From Baseline to Week 5 by IDA Underlying Condition, ITT Population (IDA-302)

Treatment Subgroups	Ferumoxytol	Iron Sucrose	Treatment Difference (95% CI)	p-value
IDA-302				
AUB n	182	92		
Baseline Hgb (g/dL) (SD)	8.9 (0.97)	8.9 (0.99)		
Mean (SD) change from Baseline to Week 5	3.4 (1.32)	3.0 (1.25)		
LS mean change from Baseline to Week 5(a)	3.4	3.0	0.38 (0.10, 0.66) (c)	0.0077
Cancer n	31	13		
Baseline Hgb (g/dL)	8.8 (0.99)	9.0 (0.86)		
Mean (SD) change from Baseline to Week 5	1.9 (1.87)	1.9 (1.72)		
LS mean change from Baseline to Week 5(a)	1.9	2.0	-0.09 (-1.28, 1.10)	0.8811
GI disorders n	138	66		
Baseline Hgb (g/dL)	8.8 (0.92)	8.7 (0.88)		
Mean (SD) change from Baseline to Week 5	2.7 (1.70)	2.5 (1.15)		
LS mean change from Baseline to Week 5(a)	2.7	2.5	0.21 (-0.23, 0.65) (c)	0.3516
Other n	55	28		
Baseline Hgb (g/dL)	9.0 (0.87)	8.9 (1.00)		
Mean (SD) change from Baseline to Week 5	2.6 (1.64)	2.4 (1.31)		
LS mean change from Baseline to Week 5(a)	2.6	2.3	0.34 (-0.33, 1.01) (c)	0.3145

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

3.2.4.3. Summary of main efficacy results

Efficacy-tables.docx

3.2.4.4. Clinical studies in special populations

No studies were conducted in patients with impaired liver function.

The following table was not filled.

	Age (Older subjects number /total number) 65-74	Age (Older subjects number /total number) 75-84	Age (Older subjects number /total number) 85+
Controlled Trials			
Non Controlled trials			

3.2.4.5. In vitro biomarker test for patient selection for efficacy

Not applicable

3.2.4.6. Analysis performed across trials (pooled analyses and meta-analysis)

An integrated Summary of Effectiveness was provided, dated 16 November 2007.

The results were presented for all randomized subjects (represented by all Subjects treated in the Randomized Phases of the three pivotal efficacy studies (Protocols 62,745-6, 62,745-7, and 62,745-5 – presented separately and pooled) as well as for non-randomized subjects (Readmission phase) separately for subjects with and without previous exposure to ferumoxytol. In the following, only the pooled data for the randomised phase of studies 62,745-6/-7/-5 are presented.

Subject disposition

Table 64: Subject Disposition, All Randomized Subjects (Excerpt)

	Randomized Subjects N	Withdrawn Prior to Initial Dose n (%)	Modified ITT Population n (%)	Withdrawn Post-initial Dose by Reason n (% of randomized subjects)					Completed Study n (%)
				Adverse Event	Lost to Follow-Up	Death	Withdrew Consent	Other [a]	
All Protocols									
Ferumoxytol 2 x 510 mg	633	28 (4.4)	605 (95.6)	9 (1.4)	3 (0.5)	4 (0.6)	3 (0.5)	7 (1.1)	579 (91.5)
Ferumoxytol 4 x 255 mg	62	2 (3.2)	60 (96.8)	3 (4.8)	0	0	0	2 (3.2)	55 (88.7)
Oral Iron 200 mg/day	291	12 (4.1)	279 (95.9)	25 (8.6)	1 (0.3)	1 (0.3)	1 (0.3)	6 (2.1)	245 (84.2)
All Subjects	986	42 (4.3)	944 (95.7)	37 (3.8)	4 (0.4)	5 (0.5)	4 (0.4)	15 (1.5)	879 (89.1)

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

Baseline data

Demographics

Table 65: Demographics, All Randomized Subjects (Modified ITT Population) (Excerpt)

	N	Age (Years) Mean±SD	Gender (%) Male/Female	Race (%) C/B/O [a]

All Protocols				
Ferumoxytol 2 x 510 mg	605	63.39±14.55	42.6/57.4	54.9/39.3/5.8
Ferumoxytol 4 x 255 mg	60	58.55±14.86	43.3/56.7	35.0/53.3/11.7
Oral Iron 200 mg/day	279	63.24±12.70	46.6/53.4	49.5/45.9/4.7
All Subjects	944	63.04±14.08	43.9/56.1	52.0/42.2/5.8

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

Across all pivotal studies, the largest proportion of randomized subjects were located in the South (48.1%), followed by the Northeast (22.7%), Midwest (15.3%), and West (14.0%). The majority of subjects in the 2 x 510 mg ferumoxytol treatment group were located in the South (52.4%). The largest proportion of subjects in the 4 x 255 mg ferumoxytol treatment group were located in the Northeast (41.7%), followed by the South (33.3%), West (23.3%), and Midwest (1.7%). In the oral iron treatment group, the largest proportion of subjects were in the South (41.9%), followed by the Northeast (25.8%), Midwest (18.6%), and West (13.6%).

Stage of kidney disease

Table 66: *Stage of Chronic Kidney Disease at Baseline, All Randomized Subjects (Modified ITT Population) (Excerpt)*

	Stage of CKD at Baseline using eGFR [a] (mL/min/1.73m^2) n (%)					
	N	Stage 1 or 2	Stage 3	Stage 4	Stage 5	Stage 5D on HD
All Protocols						
Ferumoxytol 2 x 510 mg	605	7 (1.2)	162 (26.8)	204 (33.7)	55 (9.1)	168 (27.8)
Ferumoxytol 4 x 255 mg	60	0	0	0	0	60 (100.0)
Oral Iron 200 mg/day	279	3 (1.1)	58 (20.8)	75 (26.9)	12 (4.3)	130 (46.6)
All Subjects	944	10 (1.1)	220 (23.3)	279 (29.6)	67 (7.1)	358 (37.9)

a. eGFR=186 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.21 if African-American) (57).
Stage 1 or 2: eGFR≥60; Stage 3: eGFR=30-59; Stage 4: eGFR=15-29; Stage 5: eGFR<15.
b. In Protocol 62,745-6, the CKD stage was not obtained for four subjects in the ferumoxytol treatment group.
c. In Protocol 62,745-7, the CKD stage was not obtained for five subjects in the ferumoxytol treatment group and one subject in the oral iron treatment group.
Note: There were no randomised subjects with CKD stage 5D on peritoneal dialysis.
Abbreviations: CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; HD=hemodialysis; ITT=intent-to-treat.

Kidney Transplant Status

Of the randomized subjects across all protocols (n=944), the majority of subjects at Baseline had native kidney function (58.8%) with CKD stages 1-5. A total of 3.3% of subjects had functioning kidney transplants and 37.9% of subjects were on dialysis. The majority of randomized subjects in the 2 x 510 mg ferumoxytol and oral iron treatment groups had native kidney function at Baseline (68.4% and 50.5%, respectively). All subjects in the 4 x 255 mg ferumoxytol treatment group were on dialysis (stage 5D).

Use of Erythropoiesis Stimulating Agents

Table 67: Use of Erythropoiesis Stimulating Agents, All Randomized Subjects (Modified ITT Population) (Excerpt)

	Use of ESA Therapy			
	N	Not Receiving ESA Therapy n (%)	Received Stable ESA Therapy n (%)	Started ESA Therapy or Dose Change >25% [a] n (%)
All Protocols				
Ferumoxytol 2 x 510 mg	605	267 (44.1)	267 (44.1)	71 (11.7)
Ferumoxytol 4 x 255 mg	60	0	34 (56.7)	26 (43.3)
Oral Iron 200 mg/day	279	84 (30.1)	157 (56.3)	38 (13.6)
All Subjects	944	351 (37.2)	458 (48.5)	135 (14.3)

a. The ESA therapy dose change could be an increase or decrease >25% at any time between Day -10 and Day 35.
Abbreviations: ESA= Erythropoiesis stimulating agent(s); ITT=intent-to-treat.

Concomitant medication

Use of ACE Inhibitors/ARB and Anticoagulants

Angiotensin antagonism (ACE inhibitors or ARB) is well described to inhibit erythropoiesis, and the use of anticoagulants (including aspirin, warfarin, heparin and other agents such as clopidogrel) may enhance bleeding. The possible effect of these agents may be to blunt the mean change from Baseline in Hgb at five weeks, relative to subjects who are not on these agents.

Table 68: Use of ACE Inhibitors/ARB and Anticoagulants, All Randomized Subjects (Modified ITT) (Excerpt)

	Use of ACE Inhibitors/ARB and Anticoagulants				
	N	ACE Inhibitors/ARB n (%)	Anticoagulants n (%)	ACE Inhibitors/ARB and Anticoagulants n (%)	Neither ACE Inhibitors/ARB nor Anticoagulants n (%)
All Protocols					
Ferumoxytol 2 x 510 mg	605	182 (30.1)	111 (18.3)	220 (36.4)	92 (15.2)
Ferumoxytol 4 x 255 mg	60	7 (11.7)	23 (38.3)	18 (30.0)	12 (20.0)
Oral Iron 200 mg/day	279	59 (21.1)	69 (24.7)	101 (36.2)	50 (17.9)
All Subjects	944	248 (26.3)	203 (21.5)	339 (35.9)	154 (16.3)

Abbreviations: ACE=Angiotensin converting enzyme; ARB= angiotensin receptor blocker; ITT=intent-to-treat.
Data Source: Statistical Table 12.1

Use of Calcium-Containing Compounds

The effect of concurrent therapy with oral calcium-containing products, which are commonly used for lowering phosphorus in patients with CKD, may be to impair oral iron absorption.

Table 69: Use of Calcium-Containing Compounds, All Randomized Subjects (Modified ITT) (Excerpt)

	Use of Calcium-Containing Compounds		
	N	No Calcium-containing Compounds n (%)	Calcium-containing Compounds n (%)
All Protocols			
Ferumoxytol 2 x 510 mg	605	436 (72.1)	169 (27.9)
Ferumoxytol 4 x 255 mg	60	29 (48.3)	31 (51.7)
Oral Iron 200 mg/day	279	162 (58.1)	117 (41.9)
All Subjects	944	627 (66.4)	317 (33.6)

Abbreviations: ITT=intent-to-treat.
Data Source: Statistical Table 13.1

Hemoglobin at Baseline

Table 70: Hemoglobin at Baseline, All Randomized Subjects (Modified ITT Population) (Exerpt)

	Hemoglobin at Baseline (g/dL) n (%)					
	N	<9.0	9.0 to <10.0	10.0 to <11.0	11.0 to <12.0	≥12.0
All Protocols						
Ferumoxytol 2 x 510 mg	605	50 (8.3)	181 (29.9)	289 (47.8)	85 (14.0)	0
Ferumoxytol 4 x 255 mg	60	0	3 (5.0)	18 (30.0)	39 (65.0)	0
Oral Iron 200 mg/day	279	18 (6.5)	57 (20.4)	148 (53.0)	56 (20.1)	0
All Subjects	944	68 (7.2)	241 (25.5)	455 (48.2)	180 (19.1)	0

Abbreviation: ITT=Intent-to-treat.

Ferritin at Baseline, All Randomized Subjects

Table 71: Ferritin at Baseline, All randomized subjects (Mod ITT) (Excerpt)

	Ferritin at Baseline (ng/mL) n (%)				
	N	<150	150 to <300	300 to <450	≥450
All Protocols					
Ferumoxytol 2 x 510 mg	605	322 (53.2)	148 (24.5)	77 (12.7)	58 (9.6)
Ferumoxytol 4 x 255 mg	60	12 (20.0)	19 (31.7)	13 (21.7)	16 (26.7)
Oral Iron 200 mg/day	279	115 (41.2)	67 (24.0)	46 (16.5)	51 (18.3)
All Subjects	944	449 (47.6)	234 (24.8)	136 (14.4)	125 (13.2)

Abbreviation: ITT=Intent-to-treat.
Data Source: Statistical Table 11.1

Study Medication Exposure

A total of 605 subjects in Protocols 62,745-6, 62,745-7, and 62,745-5 were exposed to two doses of 510 mg ferumoxytol over 5(±3) days, for a mean cumulative iron dose of 1002.10 mg. An additional 60

subjects received four doses of 255 mg ferumoxytol over sequential dialysis sessions, for a mean cumulative iron dose of 980.85 mg. The mean cumulative ferumoxytol doses across the three studies were similar, ranging from 996.27 mg under the Post-amendment Phase of Protocol 62,745-5 to 1006.59 mg under Protocol 62,745-6. Cumulative IV iron doses for individual ferumoxytol-treated subjects ranged from 210 to 1050 mg.

A total of 279 subjects in Protocols 62,745-6, 62,745-7, and 62,745-5 were exposed to 200 mg/day of elemental oral iron for 21 days, for a mean cumulative oral elemental iron dose of 3795.34 mg. Using a conservative estimate of gastrointestinal absorption of oral iron of ≥40%, this would translate into an elemental iron exposure of >1500 mg in the oral iron treatment group. The mean cumulative iron doses across the three studies were similar, ranging from 3734.51 mg under Post-amendment Phase of Protocol 62,745-5 to 3935.29 mg under the Pre-amendment Phase of Protocol 62,745-5. Cumulative iron doses for individual oral iron-treated subjects ranged from 100 to 5000 mg.

Re-treatment: A total of 69 subjects from the three pivotal studies who were previously randomized to ferumoxytol were re-entered to receive a second course of two 510 mg ferumoxytol doses over 5(±3) days during the Readmission Phase of the study, for a mean cumulative iron dose of 2018.78 mg. The mean cumulative iron doses across the three studies were similar, ranging from 1984.29 mg under the Readmission Phase of Protocol 62,745-7 to 2040.33 mg under the Readmission Phase of Pre-amendment Protocol 62,745-5. Cumulative iron doses for individual subjects ranged from 1380 mg to 2046 mg.

Efficacy Analyses

Table 72: Summary of Primary and Secondary Efficacy Endpoints, All Randomized Subjects (Modified ITT Population) (Excerpt)

	N	Primary Efficacy Endpoint Mean Change from Baseline in Hgb (g/dL) at Week 5		Secondary Efficacy Endpoint Hgb Responders (%) at Week 5		Secondary Efficacy Endpoint Mean Change from Baseline in Ferritin (ng/mL) at Week 3
		Mean±SD	p-value [a]	Yes N (%)	p-value [c]	Mean±SD
All Protocols						
Ferumoxytol 2 x 510 mg	605	1.03±1.23	<0.0001* [b]	283 (46.8)	<0.0001*	461.93±282.43
Ferumoxytol 4 x 255 mg	60	0.89±1.16	0.0142* [b]	29 (48.3)		454.36±262.13
Oral Iron 200 mg/day	279	0.42±1.05		64 (22.9)		-14.33±80.93

Abbreviations: ITT=Intent-to-treat; SD=standard deviation.
Note: Subjects with a missing change from Baseline calculation had a value of zero or no change from Baseline imputed.
* Indicates statistically significant at a p-value <0.05.

a. Two sample t-test for protocols with two treatment groups for evaluating a treatment difference. A single factor ANOVA for protocols with more than two treatment groups for evaluating a treatment difference. A p-value <0.05 is considered statistically significant. In Pre-amendment Protocol 62,745-5, no pairwise comparisons were significant at alpha 0.05 level.
b. Pairwise comparison with Bonferroni adjustment for multiple comparisons between 2 x 510 mg ferumoxytol and oral iron indicates a p-value <0.0001, and a comparison between 4 x 255 mg ferumoxytol and oral iron indicates a p-value= 0.0142. A comparison between the 4 x 255 mg and 2 x 510 mg was not statistically significantly different.
c Two-sided exact Pearson's Chi-square test for evaluating a treatment difference. A p-value <0.05 is considered statistically significant.

Primary endpoint: Mean Change from Baseline in Hemoglobin at five weeks (Day 35) post-initial dose of study medication

Table 73: Mean Change from Baseline in Hemoglobin, All Randomized Subjects (Modified ITT Population) (Excerpt)

	N	Baseline (g/dL)	Primary Efficacy Endpoint Week 5 Change from Baseline (g/dL)		Week 3 Change from Baseline (g/dL)	
		Mean±SD	Mean±SD	p-value [a]	Mean±SD	p-value [a]

All Protocols						
Ferumoxytol 2 x 510 mg	605	10.15±0.81	1.03±1.23	<0.0001* [b]	0.79±1.00	<0.0001* [c]
Ferumoxytol 4 x 255 mg	60	11.11±0.59	0.89±1.16	0.0142* [b]	0.74±0.95	0.0053* [c]
Oral Iron 200 mg/day	279	10.33±0.78	0.42±1.05		0.32±0.83	

Abbreviations: ITT=Intent-to-treat; SD=standard deviation.
Note: Subjects with a missing change from Baseline calculation had a value of zero or no change from Baseline imputed.
* Indicates statistically significant at a p-value <0.05.
a. Two sample t-test for protocols with two treatment groups for evaluating a treatment difference. A single factor ANOVA for protocols with more than two treatment groups for evaluating a treatment difference. A p-value <0.05 is considered statistically significant. In Pre-amendment Protocol 62,745-5, no pairwise comparisons were significant at alpha 0.05 level.

b. Pairwise comparison with Bonferroni adjustment for multiple comparisons between 2 x 510 mg ferumoxytol and oral iron indicates a p-value <0.0001, and a comparison between 4 x 255 mg ferumoxytol and oral iron indicates a p-value= 0.0142. A comparison between the 4 x 255 mg and 2 x 510 mg was not statistically significantly different.
c. Pairwise comparison with Bonferroni adjustment for multiple comparisons between 2 x 510 mg ferumoxytol and oral iron indicates a p-value <0.0001, and a comparison between 4 x 255 ferumoxytol and oral iron indicates a p-value =0.0053. A comparison between the 4 x 255 mg and 2 x 510 mg was not statistically significantly different.

Hemoglobin Responders

A secondary efficacy endpoint for the pivotal efficacy studies was the proportion of Hgb responders at five weeks (Day 35) post-initial dose of study medication.

Table 74: Hemoglobin Responders, All Randomized Subjects (Modified ITT Population) (Excerpt)

		Secondary Efficacy Endpoint Week 5 (Hgb Responders)		Week 3 Improvement in Hgb of at Least 1 g/dL		Overall, at either Week 5 or Week 3 Improvement in Hgb of at Least 1 g/dL	
	N	Yes N (%)	p-value [a]	Yes N (%)	p-value [a]	Yes N (%)	p-value [a]
All Protocols							
Ferumoxytol 2 x 510 mg	605	283 (46.8)	<0.0001*	229 (37.9)	<0.0001*	325 (53.7)	<0.0001*
Ferumoxytol 4 x 255 mg	60	29 (48.3)		24 (40.0)		32 (53.3)	
Oral Iron 200 mg/day	279	64 (22.9)		47 (16.8)		76 (27.2)	

Abbreviations: ITT=intent-to-treat.
* Indicates statistically significant at a p-value <0.05.
a. Two-sided exact Pearson's Chi-square test for evaluating a treatment difference. A p-value <0.05 is considered statistically significant.

Mean Change from Baseline in Ferritin

Table 75: Mean Change from Baseline in Ferritin, All Randomized Subjects (Modified ITT Population) (Excerpt)

	N	Baseline (ng/mL) Mean±SD	Secondary Efficacy Endpoint Week 3 Change from Baseline (ng/mL) Mean±SD	Week 5 Change from Baseline (ng/mL) Mean±SD
All Protocols				
Ferumoxytol 2 x 510 mg	605	184.74±160.06	461.93±282.43	334.36±243.58
Ferumoxytol 4 x 255 mg	60	312.19±167.02	454.36±262.13	324.74±220.50
Oral Iron 200 mg/day	279	242.31±186.39	-14.33±80.93	-25.21±95.52

Abbreviations: ITT=Intent-to-treat; SD=standard deviation.
Note: Subjects with a missing change from Baseline calculation had a value of zero or no change from Baseline imputed.

Mean Change from Baseline in Transferrin Saturation

Table 76: Mean Change from Baseline in Transferrin Saturation, All Randomized Subjects (Modified ITT Population) (Excerpt)

	N	Baseline (%) Mean±SD	Week 3 Change from Baseline (%) Mean±SD	Week 5 Change from Baseline (%) Mean±SD
All Protocols				
Ferumoxytol 2 x 510 mg	605	12.14±6.57	9.50±10.94	8.29±10.12
Ferumoxytol 4 x 255 mg	60	16.95±5.41	7.43±11.67	4.71±7.98
Oral Iron 200 mg/day	279	12.96±6.43	1.83±8.11	0.60±6.85

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

Erythropoiesis Stimulating Agent Dose Percent Change from Baseline

Table 77: Erythropoiesis Stimulating Agent Dose Percent Change from Baseline, All Randomized Subjects (Modified ITT Population) (Excerpt)

	Week 5 Change from Baseline (%)	
	N	Mean±SD
All Protocols		
Ferumoxytol 2 x 510 mg	159	4.71±31.09
Ferumoxytol 4 x 255 mg	38	11.78±69.22
Oral Iron 200 mg/day	83	6.37±34.50

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

Subgroup analyses

Subgroup analyses

Table 78: Mean Change from Baseline in Haemoglobin by Treatment Group and Demographic Subgroups, Integrated Analyses for All Randomized Subjects (Modified ITT Population)

	Ferumoxytol 2 x 510 mg			Ferumoxytol 4 x 255 mg			Oral Iron 200 mg/day		
	N	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD
Age									
<50 years	105	10.22±0.96	1.06±1.38	18	11.02±0.71	0.66±0.80	38	10.16±0.96	0.58±1.42
50 to <65 years	192	10.14±0.80	1.00±1.13	20	11.07±0.60	1.15±1.49	112	10.40±0.79	0.43±1.07
65 to <75 years	163	10.14±0.76	0.94±1.20	12	11.13±0.53	0.49±0.91	70	10.33±0.75	0.46±0.89
≥75 years	145	10.10±0.74	1.17±1.27	10	11.32±0.42	1.28±1.10	59	10.28±0.69	0.25±0.89
Gender									
Male	258	10.15±0.84	1.17±1.27	26	11.09±0.57	0.75±1.02	130	10.37±0.78	0.47±1.11
Female	347	10.15±0.78	0.93±1.18	34	11.12±0.61	1.00±1.25	149	10.28±0.79	0.38±0.99
Race									
Caucasian	332	10.11±0.77	1.11±1.24	21	11.12±0.60	1.03±1.04	138	10.29±0.77	0.28±1.00
Black or African-American	238	10.20±0.83	0.94±1.21	32	11.09±0.55	0.64±1.05	128	10.36±0.80	0.59±1.10
Other	35	10.08±0.92	0.96±1.26	7	11.13±0.82	1.63±1.68	13	10.42±0.81	0.16±0.71

Table 79: Mean Change from Baseline in Hemoglobin by Treatment Group and Other Subgroups, Integrated Analyses for All Randomized Subjects (Modified ITT Population)

	Feraheme 2 x 510 mg			Feraheme 4 x 255 mg			Oral Iron 200 mg/day		
	N 605	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N 60	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N 279	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD
CKD Stage									
Stage 1 or 2	7	9.85±1.16	1.74±1.59	0	-	-	3	9.40±1.30	1.80±1.72
Stage 3	162	9.99±0.65	1.17±1.16	0	-	-	58	9.99±0.70	0.45±0.90
Stage 4	204	9.87±0.72	1.02±1.23	0	-	-	75	9.94±0.75	0.26±1.08
Stage 5	55	9.90±0.63	0.82±1.59	0	-	-	12	9.93±0.80	0.32±1.04
Stage 5D on HD	168	10.76±0.72	0.96±1.11	60	11.11±0.59	0.89±1.16	130	10.75±0.59	0.48±1.06
Kidney Transplant Status									
Native Kidney Function (Stages 1-5)	414	9.94±0.70	1.04±1.27	0	-	-	141	9.96±0.74	0.40±1.01
Functioning Kidney Transplant (Stages 1-5)	23	9.45±0.81	1.39±1.25	0	-	-	8	9.84±0.81	-0.16±1.33
Dialysis (Stage 5D)	168	10.76±0.72	0.96±1.11	60	11.11±0.59	0.89±1.16	130	10.75±0.59	0.48±1.06
Baseline Haemoglobin									
<9.0 g/dl	50	8.45±0.47	1.69±1.30	0	-	-	18	8.33±0.39	0.97±1.04
9.0 to <10.0 g/dl	181	9.59±0.28	1.24±1.34	3	9.50±0.38	2.60±0.95	57	9.62±0.27	0.52±1.15
10.0 to <11.0 g/dl	289	10.44±0.27	0.90±1.14	18	10.59±0.21	1.02±1.02	148	10.49±0.27	0.31±0.95
11.0 to <12.0 g/dl	85	11.32±0.24	0.66±0.99	39	11.47±0.22	0.70±1.13	56	11.24±0.21	0.44±1.12
Baseline Ferritin									
<150 ng/ml	322	10.00±0.77	1.15±1.28	12	11.07±0.41	1.24±0.78	115	10.04±0.84	0.49±1.04
150 to <300 ng/ml	148	10.22±0.74	0.97±1.23	19	11.03±0.65	1.18±1.28	67	10.37±0.77	0.15±0.96
300 to <450 ng/ml	77	10.32±0.87	0.80±1.10	13	11.15±0.71	0.73±1.24	46	10.60±0.61	0.47±1.09
≥450 ng/ml	58	10.54±0.91	0.83±0.99	16	11.19±0.56	0.41±1.06	51	10.67±0.57	0.57±1.08
ESA Therapy									
Not Receiving ESA Therapy	267	9.94±0.70	0.79±1.05	0	-	-	84	10.04±0.70	0.20±0.77
Received Stable ESA Therapy	267	10.23±0.86	1.29±1.32	34	11.25±0.46	0.87±1.01	157	10.45±0.78	0.53±1.09
Started ESA Therapy or Dose Change >25%[a]	71	10.62±0.73	0.99±1.30	26	10.92±0.69	0.92±1.35	38	10.45±0.83	0.45±1.29
ACE Inhibitors/ARB and Anticoagulants									
ACE Inhibitors/ARB (AA only)	182	10.06±0.86	0.94±1.30	7	11.45±0.24	1.08±0.98	59	10.22±0.77	0.31±1.07
Anticoagulants (AC only)	111	10.24±0.80	1.14±1.17	23	11.26±0.52	0.98±1.12	69	10.35±0.87	0.68±0.91
ACE Inhibitors/ARB and Anticoagulants (both AA and AC)	220	10.13±0.70	1.02±1.20	18	10.97±0.45	0.36±1.15	101	10.28±0.70	0.40±1.02

	Feraheme 2 x 510 mg			Feraheme 4 x 255 mg			Oral Iron 200 mg/day		
	N 605	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N 60	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD	N 279	Baseline (g/dl) Mean±SD	Week 5 Change from Baseline (g/dl) Mean±SD
Neither ACE Inhibitors/ARB Nor Anticoagulants (neither AA nor AC)	92	10.24±0.93	1.10±1.22	12	10.83±0.87	1.40±1.15	50	10.51±0.84	0.24±1.19
Calcium-containing Compounds									
No	436	10.08±0.79	1.07±1.27	29	11.01±0.67	0.87±1.24	162	10.22±0.81	0.43±1.01
Yes	169	10.33±0.82	0.94±1.11	31	11.20±0.49	0.91±1.09	117	10.47±0.73	0.41±1.10

a. The ESA therapy dose change could be an increase or decrease >25% at any time between Day -10 and Day 35.
Abbreviations: AC=anticoagulants; ACE= angiotensin converting enzyme, ARB= angiotensin receptor blocker, CKD=chronic kidney disease; ESA=Erythropoiesis stimulating agent(s); ITT=Intent-to-Treat; SD=standard deviation.

3.2.4.7. Supportive studies

Supportive studies - CKD IDA

Study 401 - Oxidative and MRI substudies

Within study -401, two exploratory substudies were to be run concurrently with the main study: an oxidative stress substudy to examine the varying degrees to which iron sucrose and ferumoxytol may or may not induce *oxidative stress in vitro* in subjects undergoing hemodialysis, and an MRI substudy to assess the potential for *deposition of iron in cardiac, hepatic, and pancreatic tissues* and changes in laboratory parameters over a 2-year period.

Oxidative stress substudy

Methods

Design

Approximately 100 of the subjects in the main study were to participate in the oxidative stress substudy. Approximately 50% of patients entering the substudy were to be from the ferumoxytol group and the iron sucrose group, respectively. All subjects participating in the main study had the opportunity to participate in this substudy. Total subject participation in the oxidative stress substudy was to be 5 weeks, running concurrently with the initial treatment period of the main study. Participating subjects were to have blood samples collected for the analysis of biomarkers of oxidative stress/inflammation during the initial treatment period. Samples were collected pre/post dose 1, pre/post dose 2, and at week 5 in the ferumoxytol group, and pre/post dose 1, pre/post dose 10, and week 5 in the iron sucrose group. There were two changes to the planned analysis of the study: 1) An exploratory analysis was added to the analysis to investigate changes in markers of oxidative stress at the intermediate time points between baseline and week 5, and 2) The oxidative stress markers 13-HODE and 4-HNE were not analysed because an assay could not be developed that yielded values consistent with those previously reported. The evaluable population was defined as all subjects who received two doses of ferumoxytol (1.02 g) or all 10 doses of iron sucrose at the initial TP, and had evaluable data for blood biomarkers of oxidative stress/inflammation at the TP Baseline and Week 5.

Outcomes/Endpoints

The exploratory safety endpoints were mean change from baseline to week 5 of the initial TP in the main study in the following blood biomarkers: protein carbonyl content; Monocyte chemoattractant protein-1 (MCP-1); Neutrophil gelatinase-associated lipocalin (NGAL); High sensitivity IL-6; 13-HODE and 4-HNE were planned but not conducted.

Results

Table 80 shows the changes in markers of oxidative and inflammatory stress. All the 95% confidence intervals derived from the t-test for the difference between treatment in the change from baseline to week 5 encompassed zero and thus none of the differences were statistically different.

Table 80: Baseline and Week 5 values for Oxidative Stress Parameters

	Ferumoxytol		Iron Sucrose	
Time Point	Parameter Mean ± SD (n)	Change from baseline Mean ± SD (n)	Parameter Mean ± SD (n)	Change from baseline Mean ± SD (n)
Protein Carbonyl Content				
Baseline	0.4 ± 0.20 (48)		0.4 ± 0.22 (37)	
Week 5	0.4 ± 0.34 (54)	0.0 ± 0.26 (47)	0.4 ± 0.26 (38)	0.0 ± 0.25 (36)
Monocyte Chemoattractant Protein-1 (MCP-1)				
Baseline	319.8 ± 118.49 (55)		347.9 ± 140.94 (37)	
Week 5	340.1 ± 130.38 (54)	26.2 ± 107.04 (54)	408.1 ± 469.19 (38)	70.3 ± 470.76 (36)
Neutrophil Gelatinase-Associated Lipoprotein (NGAL)				
Baseline	950.1 ± 370.23 (57)		982.0 ± 339.89 (37)	
Week 5	936.7 ± 289.31 (57)	-13.3 ± 260.77 (57)	947.5 ± 368.89 (35)	-31.7 ± 220.45 (35)
High Sensitivity IL-6				
Baseline	4.6 ± 4.34 (55)		5.9 ± 6.15 (37)	
Week 5	5.1 ± 5.12 (54)	0.5 ± 3.90 (54)	11.1 ± 21.37 (39)	4.9 ± 19.43 (37)

Source: Tables 14.2.7, 14.2.10, 14.2.11 and 14.2.12.

An exploratory analysis using all subjects included in the substudy and evaluating all time points at which samples were drawn was performed. No statistically significant change in any oxidative stress or inflammatory biomarker following administration of a single dose or after an entire course of therapy with an IV iron was detected.

MRI substudy

Methods

Design

Approximately 70 of the subjects in the main study were to participate in the MRI substudy. Approximately 50% of patients entering the substudy were to be from the ferumoxytol group and the iron sucrose group, respectively. Study subjects were males and females ≥18 years of age with IDA and hemodialysis-dependent CKD who were enrolled in the Main Study (inclusion/exclusion criteria were the same as in the main study, with amendments (contraindications to MR imaging, baseline cardiac T2* value < 20ms). Total subject participation was to be approximately 24 months, with the first ~13 months during the course of the main study, and for approximately 11 months following completion of the main study. Subjects were scheduled for MRI visits at baseline, at 6 and 12 months in the main study, and after completion of the main study at 24 months. However, the study was terminated early at the month 13 visit due to low enrolment. The evaluable population was defined as all subjects who received study drug and had evaluable data for MRI at Baseline and at least one post-dose time point.

Outcomes/Endpoints

The primary endpoint was the absolute change in cardiac T2* from Baseline to each follow-up evaluation. Secondary endpoints were the proportion of subjects who develop cardiac T2* value <20ms as well as <10ms at any time point, change in liver iron concentration (LIC) as determined by T2* from Baseline to each follow-up evaluation, change in pancreatic T2* from Baseline to each follow-up period, change in mean ferritin, TSAT, liver function test, and thyroid function test values from Baseline to each follow-up evaluation, and change in blood glucose and Hemoglobin A1c from Baseline to each follow-up evaluation.

Sample size

The sample size of approximately 70 subjects in this Substudy is based on being able to detect changes in the primary endpoint of myocardial T2* greater than 0.2 ms with a standard deviation of 0.4 ms. For 75% power at a significance level of 5% (single arm, two-sided test), a sample size of 30 is required. Assuming a 15% dropout rate, a total of 35 subjects are required for each treatment arm. There is no statistical comparison between the two treatment groups on the primary endpoint.

- **MRI analysis set**: All subjects enrolled in MRI Substudy and had any exposure to study drug during the MRI Substudy
- **Study completion:** Subjects enrolled in MRI Substudy will be early terminated at month 13 visit, the Main Study ending time, due to early termination of the MRI Substudy.
- **Handling of Missing Data**: All of the endpoints will be analyzed using MRI Substudy evaluable population. No missing data imputation will be used.

Results

The MRI substudy was terminated early due to low enrollment related to logistical issues for patients. Additionally, there was marked attrition of participants willing to have follow up MRIs beyond the 12 month period. At the time the study was halted 46 subjects (26 ferumoxytol and 20 iron sucrose) had been enrolled in the substudy. Twenty-five subjects (15 ferumoxytol and 10 iron sucrose) had a baseline MRI and at least one follow up measurement and were evaluable for the MRI Substudy. Due to the early termination, subject data was only available at 6 and 12 months and not for the full 2 years.

The primary endpoint for this study was the mean change in cardiac T2* and secondary endpoints included the proportion of subjects with a cardiac T2* value of <20 ms and <10 ms. Table 81 shows that cardiac T2* was essentially unchanged at both 6 and 12 month for both treatment groups. Changes in cardiac T2* that are within the normal range ie, >20ms are felt to be clinically not significant. The mean ± standard deviation change for ferumoxytol at 6 and 12 months was -1.90 ± 9.317 and -2.74 ± 7.000 respectively. The corresponding values for iron sucrose were -1.04 ± 6.459 and 0.56 ± 6.547 respectively. No value<20 ms or <10 ms was detected for either Treatment Group at either time point. A secondary endpoint for this study was to assess the change from baseline in liver iron concentration as measured by liver T2*. Table 81 shows that the liver iron concentration rose at 6 and 12 month in each treatment group but the increase was larger for ferumoxytol. The mean ± standard deviation change for ferumoxytol at 6 and 12 months was 13.33 ± 9.317 and 14.21 ± 9.405 respectively. The corresponding values for iron sucrose were 4.05 ± 2.027 and 2.95 ± 2.129 respectively. Since the total amount of iron administered to both groups were statistically identical as well as the responses in hemoglobin level, serum iron and iron saturation, it is likely that the three-fold larger LIC values observed in the ferumoxytol group are an artefact due to the paramagnetic properties of ferumoxytol. Systematic overestimation of liver iron values by MRI has been previously described in normal volunteers receiving ferumoxytol for diagnostic imaging (Storey et al., MRI assessment of hepatic iron clearance rates after USPIO administration in healthy adults. Invest Radiol. 2012 Dec;47(12):717-24. doi: 10.1097/RLI.0b013e31826dc151.)

Table 81: MRI Measurements Over Time for MRI Substudy – Evaluable Patients

	Ferumoxytol		Iron Sucrose	
Time Point	Parameter Mean ± SD (n)	Change from baseline Mean ± SD (n)	Parameter Mean ± SD (n)	Change from baseline Mean ± SD (n)
Cardiac T2* (msec)				
Baseline	37.48 ± 8.409 (15)		35.54 ± 3.615 (10)	
6 Months	35.61 ± 4.578 (14)	-1.90 ± 9.317 (14)	34.66 ± 4.374 (9)	-1.04 ± 6.459 (9)
12 months	32.67 ± 4.695 (9)	-2.74 ± 7.000 (9)	36.06 ± 4.784 (8)	0.56 ± 6.547 (8)
Liver T2* (msec)				
Baseline	2.90 ± 1.407 (15)		2.34 ± 0.934 (10)	
6 Months	16.30 ± 6.969 (14)	13.33 ± 6.955 (14)	6.33 ± 2.412 (9)	4.05 ± 2.027 (9)
12 months	17.43 ± 9.468 (11)	14.21 ± 9.405 (11)	5.35 ± 2.532 (8)	2.95 ± 2.129 (8)

Source: Table 14.2.14.3 and Table 14.2.13

There were no significant difference in other laboratory determinations such as liver function tests, thyroid function tests and hemoglobin A1c.

Readmission phase Studies 62,745-6; -7; -5

The following analyses are presented as provided in the Integrated Summary of Effectiveness.

Subject Disposition, Nonrandomized, Second-course Ferumoxytol Subjects (Integrated Summary of Effectiveness)

Screening for entry into the Readmission Phase of the study occurred not only at Day 35, but at any time after Day 35 but prior to site close-out.

Table 82: Subject Disposition, Nonrandomized, Second-course Ferumoxytol Subjects (Modified ITT Population)

	Number of Subjects N	Withdrawn Prior to Initial Dose n (%)	Modified ITT Population n (%)	Withdrawn Post-initial Dose by Reason n (%)					Completed Study n (%)
				Adverse Event	Lost to Follow-Up	Death	Withdrew Consent	Other [a]	
Readmission Phase of Protocol 62,745-6									
Ferumoxytol 2 x 510 mg	22	0	22 (100.0)	1 (4.5)	0	0	0	0	21 (95.5)
Readmission Phase of Protocol 62,745-7									
Ferumoxytol 2 x 510 mg	21	0	21 (100.0)	1 (4.8)	0	0	0	0	20 (95.2)
Readmission Phase of Post-amendment Protocol 62,745-5									
Ferumoxytol 2 x 510 mg	8	0	8 (100.0)	0	0	0	0	0	8 (100.0)
Readmission Phase of Pre-amendment Protocol 62,745-5									
Ferumoxytol 2 x 510 mg	18	0	18 (100.0)	0	0	0	0	0	18 (100.0)
All Protocols/All Subjects									
Ferumoxytol 2 x 510 mg	69	0	69 (100.0)	2 (2.9)	0	0	0	0	67 (97.1)

a. Other reasons for withdrawal include protocol violation, lack of compliance, and administrative reasons for withdrawal.
Abbreviations: ITT=Intent-to-treat.
Data Source: Statistical Table 1.3

Baseline Characteristics

Table 83: Demographics, Nonrandomized, Second-course Ferumoxytol Subjects (Modified ITT Population)

	N	Age (Years) Mean±SD	Gender (%) Male/Female	Race (%) C/B/O [a]
Readmission Phase of Protocol 62,745-6				
Ferumoxytol 2 x 510 mg	22	62.32±13.68	50.0/50.0	68.2/18.2/13.6
Readmission Phase of Protocol 62,745-7				
Ferumoxytol 2 x 510 mg	21	63.38±14.67	23.8/76.2	66.7/33.3/0
Readmission Phase of Post-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	8	64.88±10.71	37.5/62.5	50.0/50.0/0
Readmission Phase of Pre-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	18	58.39±14.23	38.9/61.1	66.7/33.3/0
All Protocols/All Subjects				
Ferumoxytol 2 x 510 mg	69	61.91±13.73	37.7/62.3	65.2/30.4/4.3

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

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

Data Source: Statistical Table 2.3, Statistical Table 4.3, and Statistical Table 5.3

Stage of CKD

In the Readmission Phase of Protocol 62,745-6 at Readmission Baseline, subjects had CKD stage 3 (36.4%), stage 4 (40.9%), or stage 5 (22.7%). In the Readmission Phase of Protocol 62,745-7 at Readmission Baseline, all subjects had CKD stages 1-4, and the majority of subjects had CKD stage 3 (57.1%); the CKD stage was not obtained for one subject.

In the Readmission Phase of Post- and Pre-amendment Protocols 62,745-5 at Readmission Baseline, all subjects (100.0%) had CKD stage 5D on HD. Across all protocols for nonrandomized, second-course ferumoxytol subjects at Readmission Baseline (n=69), the largest percentage of subjects had CKD stage 5D on HD (37.7%), followed by stage 3 (29.0%), and stage 4 (23.2%).

Kidney Transplant Status

In the Readmission Phase of Protocol 62,745-6 at Readmission Baseline, all (100.0%) subjects had native kidney function. In the Readmission Phase of Protocol 62,745-7 at Readmission Baseline, the majority of subjects had native kidney function (90.5%).

In the Readmission Phase of Post- and Pre-amendment Protocols 62,745-5 at Readmission Baseline, all (100.0%) subjects were on dialysis (stage 5D).

Across all protocols for nonrandomized, second-course ferumoxytol subjects at Readmission Baseline (n=69), the majority of subjects entered the Readmission Phase with native kidney function (59.4%, n=41), compared with dialysis (stage 5D) (37.7%, n=26) and functioning kidney transplant (2.9%, n=2).

Use of Erythropoiesis Stimulating Agents

In the Readmission Phase of Protocols 62,745-6 and 62,745-7, most subjects were not receiving ESA therapy (68.2% and 71.4%, respectively).

In the Readmission Phase of Post-amendment Protocol 62,745-5, the majority of subjects received stable ESA therapy (75.0%). In the Readmission Phase of Pre-amendment Protocol 62,745-5, the percentage of subjects who received stable ESA therapy was 44.4%, and the percentage of subjects who started ESA therapy or changed the ESA dose by >25% was 55.6%.

Across all protocols for nonrandomized, second-course ferumoxytol subjects (n=69), the largest number of subjects were not receiving ESA therapy (43.5%), followed by those subjects who received stable ESA therapy (36.2%) or changed the ESA dose by >25% (20.3%).

Hemoglobin at Readmission Baseline

In the Readmission Phase of Protocol 62,745-6 at Readmission Baseline, the largest percentage of subjects had Hgb in the range of 10.0 to <11.0 g/dL (45.5%) or 9.0 to <10.0 g/dL (36.4%). In the Readmission Phase of Protocol 62,745-7 at Readmission Baseline, the majority of subjects had Hgb in the range of 10.0 to <11.0 g/dL (71.4%).

In the Readmission Phase of Post-amendment Protocol 62,745-5 at Readmission Baseline, the majority of subjects had Hgb in the range of 10.0 to <11.0 g/dL (62.5%), and in the Readmission Phase of Pre-amendment Protocol 62,745-5, the majority of subjects had Hgb in the range of 11.0 to <12.0 g/dL (66.7%).

Across all protocols for nonrandomized, second-course ferumoxytol subjects at Readmission Baseline (n=69), the majority of subjects had Hgb in the range of 10.0 to <11.0 g/dL (52.2%), followed by 11.0 to <12.0 g/dL (23.2%). One subject had Hgb ≥12.0 g/dL.

Ferritin at Readmission Baseline

In the Readmission Phase of Protocol 62,745-6 at Readmission Baseline, the percentage of subjects was similar across all ferritin ranges (27.3% in each of ferritin ranges, 300 to <450 ng/mL and ≥450 ng/mL; and 22.7% in each of ranges, <150 ng/mL and 150 to <300 ng/mL). In the Readmission Phase of Protocol 62,745-7 at Readmission Baseline, the largest percentage of subjects had ferritin in the range of 150 to <300 ng/mL (33.3%), followed by <150 ng/mL (23.8%), 300 to <450 ng/mL (23.8%), and ≥ 450 ng/mL (19.0%).

In the Readmission Phase of Post-amendment Protocol 62,745-5 at Readmission Baseline, an equal percentage of subjects had ferritin in the range of 150 to <300 ng/mL (37.5%) and ≥450 ng/mL (37.5%), with the remainder of the subjects in the range of 300 to <450 ng/mL (25.0%). In the Readmission Phase of Pre-amendment Protocol 62,745-5 at Readmission Baseline, the largest percentage of subjects had ferritin in the range of 300 to <450 ng/mL (44.4%), followed by ≥450 ng/mL (27.8%), 150 to <300 ng/mL (16.7%), and <150 ng/mL (11.1%).

Across all protocols for nonrandomized, second-course ferumoxytol subjects (n=69), the largest percentage of subjects at Readmission Baseline had ferritin in the range of 300 to <450 ng/mL (30.4%), followed by 150 to <300 ng/mL (26.1%), ≥450 ng/mL (26.1%), and <150 ng/mL (17.4%). Overall, the mean Readmission Baseline ferritin was 340.11 ng/mL in subjects entering the Readmission Phase following a first-course of treatment with ferumoxytol.

Efficacy results

Mean Change from Readmission Baseline in Hemoglobin

Table 84: *Mean Change from Readmission Baseline in Hemoglobin, Nonrandomized, Second-course Ferumoxytol Subjects (Modified ITT Population)*

	N	Readmission Baseline (g/dL) Mean±SD	Change from Readmission Baseline	
			Week 5 (g/dL) Mean±SD	Week 3 (g/dL) Mean±SD
Readmission Phase of Protocol 62,745-6				
Ferumoxytol 2 x 510 mg	22	9.91±0.83	0.55±0.89	0.50±0.86
Readmission Phase of Protocol 62,745-7				
Ferumoxytol 2 x 510 mg	21	10.06±0.82	0.31±0.66	0.47±0.89
Readmission Phase of Post-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	8	10.95±0.57	1.19±0.91	0.59±0.98
Readmission Phase of Pre-amendment Protocol 62,745-5				
Ferumoxytol 2 x 510 mg	18	11.23±0.49	0.37±0.80	0.28±0.75
All Protocols				
Ferumoxytol 2 x 510 mg	69	10.42±0.91	0.50±0.83	0.44±0.84

Abbreviations: ITT=Intent-to-treat; SD=standard deviation.
Note: Subjects with a missing change from Baseline calculation had a value of zero or no change from Baseline imputed.
Data Source: Statistical Table 15.3.1, Statistical Table 15.3.4, and Statistical Table 15.3.5.1

Hemoglobin Responders

Across all protocols for nonrandomized, second-course ferumoxytol subjects (n=69), the proportion of subjects who demonstrated a further response to ferumoxytol and were Hgb Responders in the Readmission Phase at Week 5 was 26.1%, and the proportion of subjects who had an improvement in Hgb of at least 1 g/dL at Week 3 or overall (at either Week 5 or Week 3) was 21.7% and 31.9%, respectively.

Overall, In the Readmission Phase of Protocols 62,745-6, 62,745-7, and 62,745-5 for subjects receiving a second-course of treatment with ferumoxytol, ferumoxytol treatment resulted in additional Hgb Responders that ranged from 14.3% to 50.0%.

Mean Change from Readmission Baseline in Ferritin

Across all protocols for nonrandomized, second-course ferumoxytol subjects, ferumoxytol treatment resulted in further increases from Readmission Baseline in ferritin (383.87 ng/mL at Week 3 and 255.31 ng/mL at Week 5). At Readmission Baseline, the mean ferritin was 340.11 ng/mL.

Overall, Nonrandomized subjects in the Readmission Phases of each pivotal study (Protocols 62,745-6, 62,745-7, and 62,745-5) who were previously treated with ferumoxytol demonstrated that treatment with a second-course of ferumoxytol resulted in further substantial increases in serum ferritin at Week 3 and Week 5.

Phase 2 Study 62,745-3

Study 62,745-3 was a phase 2, open-label multi-centre study (5 sites in the USA) of the safety and efficacy of two parenteral dose regimens of ferumoxytol compared with oral iron as an iron replacement therapy in chronic hemodialysis patients on ESA therapy. The primary objective of this clinical study was to assess the impact of ferumoxytol dosing on hemoglobin and iron saturation levels. 36 patients (21 males, 15 females) were enrolled in the study: 15 patients in group 1 (8 x 128 mg ferumoxytol, 11 patients in group 2 (2 x 510 mg ferumoxytol), and 10 patients in group 3 (325 mg daily oral iron maintained for a minimum of 8 sequential dialysis sessions). Ferumoxytol was administered as bolus doses within 30 minutes after starting dialysis. There was 1 protocol amendment, dated 11 March 2003, which clarified dosing for ferumoxytol patients: Dosing for group 1 patients was to be completed within a period of 4 weeks; 6 of 8 doses were considered sufficient for completion. Dosing for group 2 patients was to be completed within 2 weeks. No signed amendment was submitted in this MAA. The first patient's dose was administered on 20 January 2003, the last patient's dose administration ended on 19 June 2003.

Eligible subjects were male or female patients, 18 years of age or older, undergoing chronic hemodialysis who have received stable supplemental EPO therapy (± 25%) for ≥ 4 weeks; Hb ≤12 g/dl; TSAT ≤30%. Exclusion criteria were similar to the pivotal HD-CKD study (62,745-5), and further included exclusion criteria for iron overload (ie, TSAT ≥50%, ferritin ≥800 ng/ml), androgen therapy within 12 weeks of enrolment, and ALT or AST levels 2 times the upper limit of normal.

The primary efficacy endpoints were the mean changes from baseline in hemoglobin and TSAT for 8 weeks following the initial dose of study drug. Additionally, the change from baseline was evaluated for hematocrit, serum iron, serum ferritin, and reticulocytes. The times to maximum response (level) for hemoglobin, hematocrit, TSAT, and serum ferritin were secondary endpoints in this study.

Efficacy was assessed at screening and within 3 days predose, then weekly for 8 weeks following the initial dose of ferumoxytol. For oral iron patients, haematology and iron parameters were evaluated at screening and when initially enrolled into the control group, then weekly for 8 weeks.

Of the 36 enrolled patients, 31 were evaluable for efficacy analyses. 5 patiens were excluded from the EEP due to deviations in dosing administration (2 patients only received 4/8 scheduled doses, 3 patients reveived only 3/8 scheduled doses; no further information was provided). 4 patients in the oral iron group received another IV product following the three weeks of oral iron and are included in the EEP only up to the date of IV iron dosing. Number of evaluable patients was: 10/15 in group 1, 11/11 in group 2, and 10/10 in group 3.

The maximum Hb increases from baseline in the ferumoxytol groups were 0.55 g/dl at week 4 in group 1 (8 x 128 mg) and 0.8 g/dl at week 5 in group 2 (2 x 510 mg ferumoxytol). Maximum Hb increase from baseline in the oral iron group was 0.29 g/dl at week 2. Maximum TSAT increases in the ferumoxytol groups were 7.38% at week 4 in group 1 and 10.91% at week 2 in group 2. In the oral iron group, maximum TSAT increase was 5.67% at week 8.

Phase 2 Study 62,745-4

Study 62,745-4 was a phase 2, uncontrolled, open-label, multi-centre study (3 sites in the USA) of the safety and efficacy of two parenteral dose regimens of ferumoxytol as an iron replacement therapy in patients with CKD (not on HD) or patients on peritoneal dialysis. The primary objective was to assess the impact of ferumoxytol dosing on hemoglobin and iron saturation levels. 21 patients (9 males, 12 females) were enrolled in the study: 10 patients in group 1 (4 IV doses of 255 mg ferumoxytol), and 11 patients in group 2 (2 IV doses of 510 mg ferumoxytol). Ferumoxytol was administered as bolus doses

with 2 to 3 days between doses in group 1 and with 2 to 7 days between doses in group 2. The first dose of study drug was administered on 7 October 2002, the last on 27 December 2002.

Eligible subjects were male or female patients, 18 years of age or older, with chronic renal failure not on HD or who were undergoing PD; Hb ≤12 g/dl; TSAT ≤30%. Exclusion criteria were the same as in study 62,745-3 and similar to the pivotal CKD studies.

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

Efficacy parameters were assessed at screening (within 1 to 4 weeks of dosing), within 3 days predose, then weekly for 8 weeks.

All 21 enrolled patients completed the dosing regimen and received all scheduled doses.

The maximum Hb increases from baseline in group 1 (4 x 255 mg ferumoxytol) was 0.88 g/dl at week 4, and in group 2 (2 x 510 mg ferumoxytol) 1.00 g/dl at week 6. Maximum TSAT increases were 19.70% at week 1 in group 1 and 12.46% at week 2 in group 2.

Supportive studies - All-cause IDA

AMAG-FER-IDA-303

AMAG-FER-IDA-303 was a phase 3, open-label, single-arm, multicenter, extension study of pivotal trial IDA-301. The objective of this study was to evaluate the safety and efficacy of ferumoxytol for the episodic repeat treatment of IDA over a 6-month period. Subjects, who previously enrolled in IDA-301, received any dose of study drug and completed the study, and met the inclusion/exclusion criteria were eligible to enroll in this Extension Study. Once enrolled in IDA-303, subjects were evaluated for IDA on a monthly basis (ie, every 30±5 days) during the 6-month Observation Period, beginning at the time of enrollment until completion of the study or at the end of subject participation in the study. Subjects found to have persistent or recurrent IDA, defined as hemoglobin <11.0 g/dL and TSAT <20%, at any evaluation visit (with the exception of the Visit 7/Study Termination visit), began a 5-week Treatment Period (TP) and received 2 doses of ferumoxytol (510 mg). The first dose of ferumoxytol was administered on TP Day 1 (Baseline) and the second 2 to 8 days later, with the response assessed at TP Week 5. The effects of ferumoxytol on Hgb, iron parameters, and PRO measures were evaluated. The primary efficacy endpoint for this study was the Mean change in Hgb from TP Baseline to TP Week 5 following the first course of ferumoxytol.

A substantial proportion (~83%) of those subjects who completed study IDA-301 rolled over into study IDA-303. 61% of those subjects who received ferumoxytol in study IDA-301 did not require further iron substitution in the extension trial. Nearly all a subjects rolling over from the placebo arm received their first course of ferumoxytol in IDA-303, and replicating the effect seen in the former IDA-301 ferumoxytol subjects, about 60% of these former placebo patients did not require further iron substitution beyond this first treatment course.

151 subjects who stemmed from the placebo arm of IDA-301 satisfied treatment eligibility criteria in IDA-303 and received their first treatment course with Feraheme in this study. The baseline hgb level was 8.7g/dL and the primary efficacy outcome, the Mean change in hgb level from Baseline to Week 5, was 2.6g/dL.

AMAG-FER-IDA-304

AMAG-FER-IDA-304 was a Phase 3, randomised, active-controlled, double-blind study in subjects with IDA (Hgb <12.0 g/dL for females and <14.0 g/dL for males and TSAT ≤20% or ferritin ≤100 ng/mL) and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used. The objective of the study was to evaluate the safety of 1.020 g of intravenous ferumoxytol, administered as 2 doses of 510 mg each, compared to 1.500 mg of IV ferric carboxymaltose (FCM), administered as 2 doses of 750mg each. IDA-304 was intended to provide safety and efficacy data for the new, slower method of administration, which is an infusion diluted in normal saline lasting at least 15 minutes. In contrast to this method, ferumoxytol was administered as an injection lasting a 17 to 30 seconds in the pivotal trials IDA-301 and IDA-302 and supportive study IDA-303. The primary outcome was safety and analyses for two secondary efficacy endpoints were provided. For the two secondary efficacy endpoints (mean change in hemoglobin from Baseline to Week 5 and Mean change in haemoglobin per gram of iron administered from Baseline to Week 5), noninferiority tests were performed first sequentially; if non-inferiority was achieved, superiority tests were further conducted. The pre-defined non-inferiority margin (-0.5 g/dL) was identical to that of pivotal trial IDA-302.

The mean haemoglobin increase from baseline to Week 5 was comparable between ferumoxytol and FCM and non-inferiority could be demonstrated. The absolute increase of haemoglobin (ferumoxytol; 1.382g/dL; FCM: 1.623g/dL) was lower than that observed in the pivotal trials IDA-301 and IDA-302. Another secondary outcome showed the effect of ferumoxytol on hgb change per gram of iron to be larger compared to FCM (1.35 ±1.353 g/dL from Baseline to Week 5 for Feraheme compared with 1.10 ±1.050 g/dL in FCM-treated subjects).

3.2.5. Discussion on clinical efficacy

IDA CKD

Design and conduct of clinical studies

The clinical efficacy dataset of this marketing authorisation application supporting the treatment of IDA in CKD patients is based on the results of three pivotal phase 3 studies **FER-CKD-62,745-5, FER-CKD-62,745-6** and **FER-CKD-62,745-7**. These formed the pivotal basis for the initial approval in the CKD indication. With this new application, two further clinical trials investigating the IV administration of ferumoxytol against IV iron sucrose are submitted, i.e. phase 2 **FER-CKD-201** and phase 4 **FER—CKD-401**. Further, two supportive Phase 2 studies were submitted: study **62,745-3** in chronic HD patients who are receiving supplemental Erythropoietin (EPO) therapy evaluating two regimens of ferumoxytol (8 x 128 mg dose and 2 x 510 mg dose) and one oral iron regimen (325 mg/day); and study **62,745-4** in patients with CKD or patients on peritoneal dialysis (PD) evaluating two regimens of ferumoxytol (4x255 mg with 2-3 days between doses and 2x510mg with 2-7 days between doses).

Studies 62,745-6 and 62,745-7*:* Both studies were phase 3, randomised (3:1), open-label, multicentre studies evaluating the safety and efficacy of ferumoxytol (compared with oral iron) as an iron replacement therapy in subjects with CKD stages 1-5 (not on dialysis). Additional main inclusion criteria were Hgb ≤ 11.0 g/dl, TSAT ≤30% and serum ferritin ≤ 600 ng/ml.

Study 62,745-5 was a phase 3, randomised, open-label, multicentre study evaluating the safety and efficacy of ferumoxytol (compared with oral iron) as an iron replacement therapy in subjects with CKD stage 5D who were on hemodialysis and received supplemental ESA therapy. Additional main inclusion criteria were Hgb ≤ 12.0 g/dl, TSAT ≤30% and serum ferritin ≤ 600 ng/ml.

This study was composed of two distinct parts as a major protocol amendment changed the Hgb entry criterion to ≤11.5 g/dL and removed the 4 x 255 mg ferumoxytol treatment group that was additionally being investigated under the *original protocol* (3:3:1 randomisation) (**Pre-amendment** Randomised Phase). Under the amended protocol, subjects were randomised 1:1 to 2 x 510 mg ferumoxytol (within 5±3 days) or oral iron (**Post-amendment** Randomised Phase).

All subjects who remained iron deficient and anemic and continued to meet the study entry criteria could enter an optional Readmission Phase, where a full treatment course of 1.02 g of IV Ferumoxytol was to be administered as two separate doses. The data generated from these optional readmission phases are regarded supportive only due to important methodological limitations (such as small sample size and potential selection bias).

All study sites of the pivotal studies were located in the US, while studies -401 and -201 additionally included European study sites.

The following issues were critically reviewed in the previous Rienso MAA and, although they were ultimately considered resolved, the respective data addressing the concerns were not submitted within this application and need to be provided:
- justify the representativeness of the oral comparator for the EEA area
- justify that the protocol amendment and changes to the pre-specified analyses of the three pivotal studies did not affect the validity of the study results
- provide additional data on key confounders at baseline (ESA dose [at Baseline, cumulative weekly ESA dose during the study, and the distribution of ESA dose categories differentiating between increase and decrease of dose, stable and no ESA], recent IV iron use and inflammatory processes) and analyses that adjust for these factors
- justify the conduct of the integrated analysis on the modITT and not on the ITT (considering the minor impact on the overall B/R of this pooled analysis, this question will not be further followed)
- provide data on the interval between the first and the second course of therapy in the optional Readmission Phase (since more comprehensive data are expected from study -401, this question is also not further followed)

Lastly, a more complete randomisation scheme list should be provided (**OC**).

The 21 day period of oral iron treatment is considered too short for an appropriate comparison to oral treatment. However, further support is provided by studies -201 and -401, therefore no concern is raised, but conclusions as regards superiority compared to oral iron are considered limited. Efficacy and safety data on long term use were considered insufficient to adequately inform the SmPC about long term re-treatment with Ferumoxytol. Study -401 will provide more robust data on re-treatment, but new analyses are requested (**OC**).

Study FER-CKD-201 was a Phase 2, randomized (1:1), open-label, active-controlled, multicenter clinical trial to evaluate the safety and efficacy of ferumoxytol compared with IV iron sucrose for the treatment of IDA in subjects with CKD.

The in-/exclusion criteria are overall acceptable and representative of a broad CKD population, except for PD patients and patients with very low Hb levels <7 g/dL who were excluded. Concomitant ESA therapy was allowed, if stable (initiated, stopped, or dose changed by >20%) for at least 4 weeks before screening. TSAT levels had to be below 30% and Hb values be >7 g/dL and ≤11 g/dL. Serum ferritin levels were however not restricted, which requires further investigation as regards representativeness of the results with regard to the EEA area, where Best Practice recommendations (*Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement*; doi: 10.1093/ndt/gft033) state that, in non-dialysis dependent

CKD patients, serum ferritin levels >300 ng/mL and TSAT levels>30% should be avoided and in HD patients, a cautious approach is recommended once serum ferritin levels exceed 500 ng/mL (and TSAT levels are above 30%).

At the time of the initial Rienso approval, an *ad hoc* interim analysis was conducted on the ongoing study -201. This is not considered critical in view of a potential Type I error inflation, since no modification in the pre-planned protocol was intended in relation to any outcome of this interim analysis. However, in order to explore whether the interim analysis impacted on the study integrity, the Applicant should provide sensitivity analyses on the primary and secondary/exploratory endpoints separately for the subjects that were enrolled before and after the interim analysis and discuss consistency of results (**OC**).

Even though it is a phase II study of small size, Study FER-CKD-201 is considered important as a head to head comparison with another IV iron treatment and it enrolled EU patients.

Study **AMAG-FER-CKD-401** was a Phase 4, randomised, Open-label, multicentre (35 study sites in the United States, Canada and United Kingdom), active controlled clinical trial designed to evaluate the safety, efficacy, and frequency of use of ferumoxytol compared to iron sucrose for the episodic treatment of IDA in hemodialysis subjects with CKD over a 1-year period.

Monthly Observation visits were pre-scheduled and 5-week treatment periods (TPs) were implemented whenever treatment criteria were met at these visits or any final week 5 visit of any TP (i.e., persistent or recurrent IDA, defined as a hemoglobin <11.5 g/dL and TSAT <30%).

This study included an **MRI substudy** to assess the potential for deposition of iron in cardiac, hepatic and pancreatic tissues and changes in the laboratory parameters over a two year period in subjects with baseline cardiac T2* value < 20ms (cut-off for abnormal values indicating iron overload). Subjects were scheduled for MRI visits at baseline, at 6 and 12 months in the main study, and after completion of the main study at 24 months. However, the study was terminated early at the month 13 visit due to low enrolment.

The cut-off values for TSAT and serum ferritin for study eligibility are considered rather high, in particular in subjects not on hemodialysis (HD). Dose adequacy should be discussed with regard to the fixed dose and the potential concern on iron excess, comparing the results on dose compliance across studies and discuss reasons for incompliance. It should be discussed how many patients would have fulfilled *initial* and *re-treatment* criteria according to European treatment guidelines (*Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement*; Nephrol Dial Transplant (2013) 28: 1346–1359 doi: 10.1093/ndt/gft033) and whether the long term data generated in study -401 are representative for patients in the EEA. The proportions of subjects with Ferritin values TSAT values ≥ 30% AND Ferritin values ≥ 500 ng/mL (post treatment) in the absence of CRP elevation shoud be provided as well (**OC**).

For the Non-inferiority (NI) studies -201 and -401, the NI margin of 0.5 g/dL for the primary efficacy analysis should be justified in accordance with EMA guidance on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99). It is currently not clear whether superiority over placebo can be ensured (**OC**).

Due to different dose administrations with different time lines, a double-blind (double-dummy) design would have been more difficult to implement, but would have been feasible and preferred. Given the objective nature of the endpoints, the open label design of the studies can be accepted, however.

The statistical methods are by and large acceptable. However, additional sensitivity analyses are requested (see 'Efficacy data and additional analyses' below).

All studies investigated mean change from Baseline in Hgb at 5 weeks (Day 35 visit) post-initial dose of study medication as primary efficacy endpoint. Secondary/exploratory endpoints were responder rates

(proportion of subjects with an increase of at least 1.0 g/dL in Hgb at week 5 alone or in combination with an increase of at least 160 ng/mL in ferritin at D21 or week5, the latter being evaluated in the pivotal studies only), and mean changes in serum ferritin and TSAT levels (data not provided for study -401, **OC**), further supported by other markers such as reticulocyte counts and, for the pivotal studies, HCr. The endpoints that were evaluated are overall appropriate to provide a comprehensive picture on the efficacy of ferumoxytol. For study -401, additional analyses are requested sub-dividing patients with long term use by treatment periods actually received (exactly two, three, four etc), as the current analyses use subgroup that use subjects more than once (at least 2 periods, 3 periods, etc) (**OC**).

Efficacy data and additional analyses

The available efficacy database for the proposed dose of 2 × 510mg given two to eight days apart for the treatment of IDA in subjects with CKD consists of 64 and 114 subjects on HD and concomitant ESA therapy for pre- and post-amendment, respectively, in study **62,745-5**; in 228 and 227 non-dialysis-dependent CKD patients **for studies 62,745-6** and **62,745-7**, respectively. This is complemented by 80 additional HD and non-HD patients in study **CKD-201** and 196 HD patients in study **CKD-401** in subjects. Patients with functional kidney transplants were included in the non-dialysis dependent population, and patients on peritoneal dialysis were excluded in all main studies.

No formal dose response studies were conducted. Some efficacy and safety data were provided for different dose regimens (4x128 mg, 2x255 mg) which were largely comparable to the intended dose regimen 2x510mg, except that in HD patients, the results of study 62,745-5 pre-amendment part suggest that the 4 x 255 mg dosing scheme was slightly more effective compared to the 2 x 510 mg scheme. This is of note, since no advantage of the 2 x 510 mg dosage scheme versus 4 x 255 mg can be seen for iron deficient patients on HD. Additional dose response studies for the claimed indication are not requested, but the Applicant will need to justify whether a full treatment course of 2x510 mg is applicable for the broad target population and clarify whether there are sub-populations for whom a dose of 510 mg would be sufficient, based on the study results. Representativeness of the study results for approval in the EEA should be discussed (e.g. proportions of subjects that would qualify for initial treatment or re-treatment according to European treatment recommendations). This should be discussed for the relevant subgroups (patients with CKD on hemodialysis, with and without concomitant ESA therapy as well as patients with CKD not on HD, with and without concomitant ESA therapy) (**OC**).

Study 62,745-6, **62,745-7,** and **62,745-5 (post amendment)**

The protocol amendment was implemented after 148 subjects had been randomised (2x 510 mg ferumoxytol,N=64; 4 x 255 mg ferumoxytol, N=62; oral iron, N=22). After the protocol amendment, a total of 230 patients were randomised in a 1:1 ratio at 44 sites in the US. The latter sample was used for the primary efficacy analysis.

As there are no data supporting the recommendation in the SmPC to use a single dose in patients with body weight lower than 50 kg and Hb 10-12 g/dL, the Applicant is asked to provide an analysis of all subjects ≤ 50 kg who were treated with one and two doses of Feraheme with regard to mean change from baseline to week 5 in tabulated form. In addition, a lower weight limit may need to be included (**OC**).

Mean Baseline values for Hb for ferumoxytol and oral treatment, respectively, were slightly lower in studies -6 and –7 (9.96 and 9.95 g/dL/ 9.85 and 9.94 g/dL) compared to study -5 (10.59 and 10.69 g/dL) and this was comparable to study -401, where also HD patients were included (10.4 g/dL). Mean ferritin were also lower in studies 6-/-7 (146.1 and 143.53 ng/mL / 123.74 and 146.18 ng/mL) compared to study -5 (340.52 and 357.56 ng/mL) or study -401 (around 413 and 397 ng/mL for ferumoxytol and

IS, respectively). Mean TSAT levels for ferumxytol and Oral iron, respectively, were also lower in studies -6/-7 (11.28 and 10.14%/ 9.79 and 10.37%) compared to study -5 (15.71 and 15.91%) and study -401 (21.9 and 22.2%).

For the pivotal studies -5/ -6 and -7, this is (on average) in line with European treatment recommendations (TSAT<25%, ferritin levels < 200 ng/mL if the aim is to increase Hb concentration without starting ESA treatment in ND CKD patients (or <300 ng/ml in HD patients); for patients on ESA therapy TSAT <30%, ferritin <500 nmol/mL, or higher in HD patients *in the presence of hyporesponsiveness to ESA or a risk/benefit ratio going against ESA use).* The question still arises of how many patients were included in the studies that would have fulfilled treatment criteria, had the studies been conducted more recently and not 15 years ago – in line with current treatment recommendations, which changed due to availability of larger datasets pointing to safety concerns in patients with higher Hb levels (12 g/dL) and higer serum ferritin levels (>500/800 ng/mL).

A majority of subjects had CKD stage 4 and 5. No subject was on dialysis (stage 5D) in studies -6/-7, and all subjects were on dialysis in study -5. The majority of subjects were not on concomitant ESA therapy (63.6% and 58.6% in study 62745-6 and 62745-7, respectively), while all patients on HD had concomitant ESA therapy. Further discussion is awaited with regard to the specifics of ESA characteristics and potential imbalances between treatment groups (**OC**).

Subgroup analyses on ESA use should be presented as a forest plot, i.e. presented alongside estimates for other such groupings to prevent overinterpretation (**OC**).

Overall, the study populations are considered representative of the target population, with the open question on baseline serum ferritin levels/ TSAT levels with a view on the representativeness of the European target population and that no data from patients PD seem available. Among the main common exclusion criteria, several relevant exclusion criteria were noted, e.g., subjects with active gastrointestinal bleeding or acute bleeding episodes within 4 weeks of enrolment, subjects who had causes of anaemia other than iron deficiency (e.g., systemic lupus erythematosus, myeloma, rheumatoid arthritis), subjects who were refractory (not responding) to EPO or who were receiving in excess of 25,000 Units/week – 35,000 Units/weeks of EPO. The excluded population in studies evaluating treatment of IDA in CKD should be summarized in SmPC in section 5.1. (**OC**).

The primary endpoint results in the ITT population show superior efficacy of the IV-Feraheme treatment over a 21 day course of oral iron (limitations on study design borne in mind) across all studies. The 95% Confidence intervals (incl. between group comparison) should be provided, as on its own change from baseline may be entangled with regression to the mean (Hgb level was among the inclusion criteria), and p-values on change from baseline are generally not advocated (**OC**).

Given the particularly low response in study -6 and a potential center effect in study -7, possible impact of incompliant subjects in the oral treatment arm on the superiority conclusion should be discussed (**OC**). The primary endpoint results are supported by the results in the Efficacy Evaluable (EE) population, sensitivity analyses with different missing data imputation (except study-6 when worst case imputation was used) and further secondary endpoints. The result for study -6 needs to be borne in mind when evaluating the robustness of effects across all studies. Additional tipping point analyses are requested. The amount of missing data is not immediately evident from the data as presented. A disposition table showing the N's at each scheduled assessment (Days -10, -5, 0, 21 and 35) would be useful. E.g., the degree of imputation is not immediately clear and whether there are any patients with no post-baseline data who must be somehow imputed to satisfy the definition of ITT. It might also help judge the potential value of a repeated measures analysis (**OC**).

A pre-specified subgroup analysis was the use of ESA (Yes/No) for studies 62745-6 and -7. An enhanced mean increase from baseline in Hb (paralleled by higher increases in Hgb responders) was observed in the ESA (+) groups in both studies compared to EAS (-) groups (both treatment groups). For the analysis of Ferritin responders and mean change from baseline in ferritin (at day21), results for the ESA (-) were slightly higher (ferumoxytol group only).

Subgroups analysed across studies (Integrated Summary of Effectiveness) were presented and show largely consistent effects across subgroups, with some differences across different age categories and gender. In addition, the data suggest that with worsening of the kidney function the response to iron replacement therapy is decreasing in the IV-treatment groups. Data from patients with early CKD stages are however too limited to draw firm conclusions, but it is of note that superiority compared to oral therapy could not be shown (n=7 and n= 3 for ferumoxytol and oral therapy). This may further support that a first line treatment indication as claimed by the Applicant may not be most appropriate based on the available dataset and by considering current treatment guidelines.

Overall, the pivotal studies in the CKD population comparing Feraheme with oral IV treatment met the primary endpoint and the results of the secondary efficacy analyses support the results of the primary efficacy analysis. However, due to uncertainties, conclusions on the superiority compared to oral iron remain limited.

Study CKD-201: The majority of subjects were CKD Stage 5, followed by Stage 4 and Stage 3. Only 6.3% of subjects were stage 2 and all were in the IP treatment group. No subjects had stage 1 CKD. This is unfortunate, bearing in mind the uncertainty from the pivotal studies on patients with CKD stage 1-2. 43.2 % subjects were on haemodialysis. Some important baseline characteristics were not (adequately) presented and should be provided (ESA use and dose, mean Hb, ferritin and TSAT levels, previous use of oral and IV iron replacement therapy (IRT), respectively, as well as inflammatory processes) (**OC**). A further concern is raised on the concomitant antianemic therapies (60 vs. 51.2%) (**OC**).

Baseline mean ± SD hemoglobin levels were similar between the ferumoxytol and iron sucrose treatment groups at 10.09±0.92 g/dL vs. 10.04±0.98 g/dL, respectively. The primary efficacy analysis showed non-inferiority of Ferumoxytol compared to IS, using an NI margin of 0.5g/dL. The results from the EE Population and sensitivity analyses parallel these results. Since no per protocol population has been defined, additional analyses are requested to explore the impact of protocol violations on the results. In addition, conservative missing data imputation should be applied (**OC**).

For the iron stores parameters and Hb responder analyses, the 95% CIs for the treatment difference should be provided (**OC**). Additional analyses adjusted for key confounders should also be provided (ESA use, recent IV iron use, inflammatory processes, TSAT levels), similar to what had been requested in the previous Rienso application on the pivotal study results (**OC**).

Subgroup analyses: Point estimates for difference in mean Hb change from baseline were largely consistent across subgroups, with some inconsistencies noted in patients aged 65 to<75 years, males, CKD Stage 1-3 , and non-ESA use. Non-inferiority using the 0.5 NI margin could not be concluded for the following subgroups: Non-Dialysis subjects and subjects with CKD stage 1-3, no ESA use, age 65 to<75 years and <50 years. Overall, the subgroup results need to be cautiously interpreted due to small sample sizes. The Applicant is asked to comment on the differences observed in subgroup analyses for the subgroup 'CKD Stage 1-3' and 'Non-dialysis' in relation to potential differences between treatment groups in baseline characteristics and the results from other studies that included Non-dialaysis CKD patients/ CKD stage 1-3 patients (**OC**).

Overall, the primary efficacy analysis showed non-inferiority of Ferumoxytol compared to IS (LS mean difference: 0.10; 95%CI: -0.21 to 0.41). The secondary and exploratory endpoint results are supportive

of the primary endpoint results. It is considered that study results show comparable efficacy of ferumoxytol and iron sucrose treatments in IDA-CKD, provided the remaining uncertainties can be adequately addressed (see OCs).

Study CKD-401:

The majority of subjects were recruited in the US, with only 3.1 and 5.2% for ferumoxytol and IS, respectively, recruited in Europe (UK).

Mean Hb levels were 10.4 g/dL at baseline in both treatment groups. Mean TSAT und ferritin levels were higher compared to study-5, which would be anticipated based on higher cut-off values of ferritin for study eligibility. Non-inferiority could be concluded for TP1 and TP2 using the pre-specified NI margin of 0.5 g/dL based on the ITT and the Evaluable Population (EP). A question is however raised on the analysis using the EP, since the numbers used for analysis cannot be followed (**OC**). Overall a rather small change from baseline was observed in both treatment groups (0.5 and 0.4 g/dL for ferumoxytol and IS, respectively). Consistency with previous results should be discussed for both treatment groups and the NI margin be justified, in particular whether superiority over placebo could be maintained **(OC**). Additional sensitivity analyses are requested to explore the robustness of the primary endpoint results (**OC**). In addition, certain intercurrent events (ICE) such as non-compliance to the study drug in TP1 or the need for prohibited medications could make a considerable impact regarding a positive non-inferiority conclusion. Therefore, additional analyses are requested that explore their impact on the study outcome (**OC**). The proportions of subjects with concomitant ESA therapy was not provided (**OC**). In addition, sensitivity analyses should be provided, adjusting for important co-variates (ESA use, TSAT levels, serum ferritin levels) (**OC**). The protocol amendment regarding the window to collect Week 5 data being expanded to 35 (±10) days (inclusive) after the first dose of the corresponding treatment period should be justified to still capture the maximum response of both treatment groups (as should be the week 5 time point for the comparator IS) and discuss potential differences between groups in sample collection (**OC**). 'Other antianemic preparations' were used by more patients in the ferumoxytol group (12.2%) compared to the iron sucrose group (5.2%), these should be clarified and justified not to have affected the study outcome (**OC**). Additional subgroup analyses previously conducted for the pivotal studies should also be conducted for the current study and consistency of results be discussed across studies (**OC**).

Re-treatment: Re-treatment rate within one year was slightly higher than initially estimated (at least 85 and 90% for ferumoxytol and IS-treated subjects needed more than one treatment course over one year). The analyses presented do not allow adequate interpretation, since it remains unknown how many patients needed how many treatment courses and at what time point of the study. Hb values over time (by monthly observation periods) barely increased over time. Overall, a conclusion on whether this study is suitable to support any further recommendations in the SmPC for long term administration of Ferumoxytol that go beyond a second treatment course cannot be drawn at this stage of the procedure, further analyses are awaited (**OC**).

MRI substudy: Participant number was low, with 15 subjects in the ferumoxytol group and 10 subjects in the iron sucrose group. In both treatment arms liver iron concentrations were increased at the 6 and 12 month time points. The increase was approximately 3-fold higher in the ferumoxytol group compared to the iron sucrose group. This needs further explanation, in particular since iron deposition in liver and spleen was reported in animal models (**OC**). The respective statements on MRI interference in the SmPC should be justified (SmPC comment).

All-cause IDA indication

Design and conduct of clinical studies

The clinical efficacy dataset of this marketing authorisation application supporting the second-line IDA indication is based on the results of two pivotal and two supportive clinical trials investigating the IV administration of ferumoxytol at a dose of 2 × 510mg , i.e. pivotal Phase 3 trials **AMAG-FER-IDA-301** and **AMAG-FER-IDA-302** with supportive trials **AMAG-FER-IDA-303** and **AMAG-FER-IDA-304**.

AMAG-FER-IDA-301 was a phase 3, randomised, double-blind, placebo-controlled, multicentre clinical study investigating the safety and efficacy of ferumoxytol compared to placebo (superiority design) for the treatment of IDA in adult subjects with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used. IDA was defined as a screening Hgb value <10.0 g/dL and TSAT <20%. Randomised subjects received 2 infusions of either ferumoxytol at a dose of 510mg for a total dose of 1,020mg or normal saline two to 8 days apart. The primary outcome was the Mean change in haemoglobin from Baseline to Week 5, the secondary efficacy endpoints were defined as the Proportion of subjects achieving a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5, the Proportion of subjects who achieved a haemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5, Mean change in TSAT from Baseline to Week 5 and the Time to haemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline. The investigated clinical outcomes are accepted surrogate laboratory parameters used to monitor the severity of iron deficiency anaemia and therefore endorsed. In addition, exploratory endpoints investigated PROs, blood transfusion and ESA usage and thus provided data with regard to the effect on the patients' well-being and if other measures were necessary to alleviate signs and symptoms of IDA. AS IDA-301 enrolled subjects with diverse underlying illnesses, Underlying Condition Subgroup Analyses were provided for the Proportion of subjects with AUB, Cancer, GI Disorders, Postpartum Anaemia and Other who achieved a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5 and for the Mean change in haemoglobin from Baseline to Week 5 in subjects with AUB, Cancer, GI Disorders, Postpartum Anaemia and 'Other'.

AMAG-FER-IDA-302 was a phase 3, randomised, open-label, active-controlled, multicentre clinical study to evaluate the efficacy and safety of ferumoxytol compared with iron sucrose (non-inferiority design) for the treatment of IDA in adult subjects with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used. IDA was defined as a screening Hgb value <10.0 g/dL and TSAT <20%. Randomised subjects received either 2 infusions of ferumoxytol at a dose of 510mg two to 8 days apart for a total dose of 1,020mg or five slow injections/infusions of iron sucrose at a dose of 200 mg, for a total dose of 1,000mg. The efficacy outcomes were identical to those of study IDA-301, with the primary outcome defined as the Mean change in haemoglobin from Baseline to Week 5, the secondary efficacy endpoints defined as the Proportion of subjects achieving a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5, the Proportion of subjects who achieved a haemoglobin level ≥12.0 g/dL at any time from Baseline to Week 5, Mean change in TSAT from Baseline to Week 5 and the Time to haemoglobin increase of ≥2.0 g/dL or to ≥12.0 g/dL from Baseline. Exploratory endpoints and underlying condition subgroup analyses were also provided in a similar way. The justification for the non-inferiority margin is considered acceptable from a clinical point of view, as the selected NI margin preserves 50% of the expected effect of a transfusion of one unit of packed RBCs. In study AMAG-FER-IDA 301, the mean change of Hgb from baseline to week five was observed as >2g/dL in a comparable population treated with the same dose of ferumoxytol, therefore a similar effect size could be expected for this trial.

AMAG-FER-IDA-303 was a phase 3, open-label, single-arm, multicentre, extension study of IDA-301. The objective of this study was to evaluate the safety and efficacy of ferumoxytol for the episodic repeat treatment of IDA over a 6-month period. Subjects, who previously enrolled in IDA-301, received any dose of study drug and completed the study, and met the inclusion/exclusion criteria were eligible to enrol in this Extension Study. Once enrolled in IDA-303, subjects were evaluated for IDA on a monthly

basis (i.e., every 30±5 days) during the 6-month Observation Period, beginning at the time of enrolment until completion of the study or at the end of subject participation in the study. Subjects found to have persistent or recurrent IDA, defined as haemoglobin <11.0 g/dL and TSAT <20%, at any evaluation visit (with the exception of the Visit 7/Study Termination visit), began a 5-week Treatment Period (TP) and received 2 doses of ferumoxytol (510 mg). The first dose of ferumoxytol was administered on TP Day 1 (Baseline) and the second 2 to 8 days later, with the response assessed at TP Week 5. The effects of ferumoxytol on Hgb, iron parameters, and PRO measures were evaluated. The primary efficacy endpoint for this study was the Mean change in Hgb from TP Baseline to TP Week 5 following the first course of ferumoxytol. The primary endpoint, therefore captures the effect of the first treatment cycle, i.e. the first treatment course of those subjects rolled over from the placebo arm of IDA-301, which is not considered to be completely in line with the objectives of the study, as the effect of a single course of treatment with ferumoxytol has already been shown in trials IDA-301 and IDA-302. The secondary efficacy endpoints, which provide analyses of Hgb and TSAT parameters after each treatment course are considered to be more suited to assess the efficacy of repeated treatment with Feraheme.

AMAG-FER-IDA-304 was a Phase 3, randomised, active-controlled, double-blind study in subjects with IDA (Hgb <12.0 g/dL for females and <14.0 g/dL for males and TSAT ≤20% or ferritin ≤100 ng/mL) and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used. The objective of the study was to evaluate the safety of 1.020 g of intravenous ferumoxytol, administered as 2 doses of 510 mg each, compared to 1.500 mg of IV ferric carboxymaltose (FCM), administered as 2 doses of 750mg each. IDA-304 was intended to provide safety and efficacy data for the new, slower method of administration, which is an infusion diluted in normal saline lasting at least 15 minutes. In contrast to this method, ferumoxytol was administered as an injection lasting a 17 to 30 seconds in the pivotal trials IDA-301 and IDA-302 and supportive study IDA-303. The primary outcome was safety and analyses for two secondary efficacy endpoints were provided. For the two secondary efficacy endpoints (mean change in haemoglobin from Baseline to Week 5 and Mean change in haemoglobin per gram of iron administered from Baseline to Week 5), non-inferiority tests were performed first sequentially; if non-inferiority was achieved, superiority tests were further conducted. The pre-defined non-inferiority margin (-0.5 g/dL) was identical to that of IDA-302.

Efficacy data and additional analyses

Efficacy data for the proposed dose of 2 × 510mg given two to 8 days apart in the second line all-cause IDA indication are available from the 3 single treatment period studies IDA-301 (n=608), IDA-302 (n=406) and IDA-304 (n=1000). In addition, IDA-303 provides data for repeated treatment for up to 5 treatment cycles in subjects who rolled over from parent study IDA-301. Data characterising the effect of two treatment courses are available from 244 subjects, three courses in 69 subjects, 4 courses in 18 subjects and 5 courses in 4 subjects.

In study **IDA-301** nearly 90% of the study population was female, reflecting the greater incidence of IDA in women. Approximately half of subjects were White, and about 80% were recruited in the US and Canada and about 6% in EU countries. A broad range of bodyweights was observed in the study population, reaching from extremely underweight (28kg) to extremely overweight (203kg).

The Applicant should summarize main inclusion criteria for studies in IDA indication in section 5.1 of SmPC, e.g., key eligibility criteria included all patients with IDA associated with underlying conditions other than CKD who had a history of unsatisfactory oral iron therapy or in whom oral iron could not be used, a Hgb <10.0 g/dL and a TSAT <20% (**OC**).

The primary outcome, mean change of haemoglobin from baseline to week 5, shows clear superiority of the ferumoxytol arm (2.7 g/dL) over the placebo arm (0.1 g/dL). The result is unambiguous and shown in the ITT as well as the PP population. The mean (SD) Baseline haemoglobin was comparable between

the two treatment groups (ferumoxytol, 8.9 g/dL ±0.89; placebo, 8.8 ±0.89). The majority of ferumoxytol-treated subjects (81.1%, 493/608 subjects) had a ≥2.0 g/dL increase in haemoglobin at any time from Baseline to Week 5 compared with 5.5% (11/200 subjects) of placebo-treated subjects. About 50% of subjects treated with ferumoxytol achieved a haemoglobin level of ≥12g/dL in contrast to 3% of placebo subjects. A superior increase in TSAT was reported for the verum group compared to placebo patients, further demonstrating the ability of the body to metabolise the provided iron. The mean time to reach an Hgb increase ≥2 g/dL was approximately three weeks for the verum group. The exploratory efficacy outcomes were able to show treatment effects mainly with regard to improvement of fatigue.

In trial **IDA-302**, similar to the population of trial IDA 301, more than 80% of the study population was female. Greater than 80% of subjects were White, and about 70% were recruited in Europe and about 10% in South Africa. A broad range of bodyweights was observed in the study population, spanning from underweight (38kg) to overweight (136kg).

The primary outcome, mean change of haemoglobin from baseline to week 5, shows non-inferiority of the ferumoxytol arm (2.7 g/dL) to the iron sucrose arm (2.4 g/dL). The result is shown in the ITT as well as the PP population. The mean (SD) Baseline haemoglobin was comparable between the two treatment groups (ferumoxytol, 8.9 g/dL ±0.94; iron sucrose, 8.8 ±0.95). A similar proportion of patients treated with Feraheme (84.0%, 341/406 subjects) or iron sucrose (81.4%,162/199 subjects) achieved an increase of ≥2g/dL of haemoglobin during the 5 week treatment period, demonstrating the comparable ability to utilise and metabolise the iron contained in both preparations. A higher proportion of subjects treated with ferumoxytol (66.7%, 271/406 subjects) achieved a haemoglobin level of ≥12g/dL at any time until Week 5 than subjects treated with iron sucrose (48.2%, 96/199 subjects). A superior increase in TSAT was reported for the ferumoxytol group compared to iron sucrose treated patients. The time to an increase in Hgb of ≥2 g/dL was approximately three weeks for both iron preparations, with ferumoxytol showing a trend towards an earlier treatment effect. This is likely due to the splitting of the intended dose into only two instead of five infusions, resulting in an earlier availability of a meaningful amount of elemental iron. The exploratory efficacy outcomes were able to show treatment effects mainly with regard to improvement of fatigue at a level comparable between the two tested medicinal products.

A substantial proportion (~83%) of those subjects who completed study IDA-301 rolled over into study **IDA-303**. 61% of those subjects who received ferumoxytol in study IDA-301 did not require further iron substitution in the extension trial. Nearly all a subjects rolling over from the placebo arm received their first course of ferumoxytol in IDA-303, and replicating the effect seen in the former IDA-301 ferumoxytol subjects, about 60% of these former placebo patients did not require further iron substitution beyond this first treatment course. This underlines the difficulty of investigating repeated treatment courses in an IDA population. It is not possible to simply randomise subjects to receive a second or third administration of iron or placebo, because the need for continued treatment is not present in a significant proportion of patients. The patient population included in trial IDA-303 is comprised of those subjects who were willing to undergo further study visits for a 6-month duration, and less than half of those patients did require repeated iron administrations.

151 subjects who stemmed from the placebo arm of IDA-301 satisfied treatment eligibility criteria in IDA-303 and received their first treatment course with Feraheme in this study. The baseline Hgb level was 8.7g/dL and the primary efficacy outcome, the Mean change in Hgb level from Baseline to Week 5, was 2.6g/dL. The secondary endpoints provide relevant surrogate outcomes over up to 5 treatment cycles. Due to the small number of subjects treated more often than twice, the results have to be interpreted with caution. However, over successive treatment rounds, an increase in Hgb values as well as an increase in TSAT can be observed. Baseline Hgb before the second and all following rounds are higher than before the first treatment, reflecting the effect of the initial iron substitution.

Trial **IDA-304** investigated the safety of administering Feraheme as an infusion given over 15 minutes in contrast to the rapid injection method used in the previous studies. Efficacy was defined as a secondary objective, and two efficacy endpoints were analysed. The majority of subjects were female (76.1%) and White (71.4%). More than 80% of subjects were from the US, and about 15% from European countries. The range of bodyweight reached from 44kg to 252kg.

The mean haemoglobin increase from baseline to Week 5 was comparable between ferumoxytol and FCM and non-inferiority could be demonstrated. As FCM was dosed at 1.5g and Feraheme at 1.02g, the effect of 68% of the administered iron dose on Hgb is considered impressive. The absolute increase of haemoglobin (ferumoxytol; 1.382g/dL; FCM: 1.623g/dL) was lower than that observed in the pivotal trials IDA-301 and IDA-302. This is very likely the effect of the higher baseline Hgb levels in IDA-304 (10.42g/dL) compared to the other studies (IDA-301: 8.9 g/dL ; IDA-302: 8.9 g/dL). Another secondary outcome showed the effect of ferumoxytol on Hgb change per gram of iron to be larger compared to FCM (1.35 ±1.353 g/dL from Baseline to Week 5 for Feraheme compared with 1.10 ±1.050 g/dL in FCM-treated subjects).

In the pivotal trials IDA-301 and IDA-302, regarding efficacy, the unambiguous superiority over placebo and noninferiority to active comparator has been shown. IDA-303 and IDA-304 serve for other purposes such as re-treatment or comparison of different administration methods, and are considered as supportive data.

An **underlying condition subgroup analysis** in subjects with AUB, cancer, GI disorders, and other underlying conditions was provided for studies IDA-301, IDA-302 and IDA-303. However, the number of subjects in several subgroups is very small, therefore the outcomes should only be interpreted with caution. A positive trend is evident for each subgroup, which is expected due to the pharmacodynamic mechanism of action. In addition, no compelling reason exists for any subgroup to assume that intravenously administered and therefore 100% bioavailable iron should not influence the iron metabolism and in consequence, erythropoiesis in a beneficial way. The underlying mechanism causing anaemia is more complex and difficult to treat in cancer patients and is also influenced by type of chemotherapy etc., therefore the trend towards lower Hgb increases observed in this subgroup are not surprising. The current ESMO Clinical Practice Guidelines for the management of anaemia and iron deficiency in patients with cancer recommend IV iron substitution for both cancer patients with absolute as well as functional iron deficiency given as a single dose of 1000mg iron or an equivalent total dose in several infusions as feasible with available i.v. iron formulations. These recommendations recognize the beneficial influence of IV over oral iron substitution in cancer-associated anaemia.

Ferumoxytol was given at a **fixed dose** of 2 x 510mg regardless of bodyweight in all four studies supporting all-cause IDA. Blood volume does increase with increasing bodyweight, but at a lower rate. Therefore newer iron dosing recommendations using the Ganzoni formula recommend using the ideal bodyweight for obese patients and the actual bodyweight for underweight patients. Thus a fixed dose might lead to overdosing of patients with low bodyweight. Instructions for using a lower dose of 1 x 510mg in subjects with low bodyweight and a haemoglobin value >10-≤12 g/dl are included in section 4.2 of the SmPC. This approach to avoid overdosing could be considered acceptable in principle. However, as there are no data supporting this recommendation, the Applicant is asked to provide an analysis of all subjects ≤ 50 kg who were treated with one and two doses of Feraheme with regard to mean change from baseline to week 5 in both pivotal IDA trials in tabulated form. A lower border for body weight should also be considered/introduced - derived from the clinical study data - to avoid iron overload and off-label-use in children/adolescents (**OC**).

Wording of indication

A formal major objection is raised on the indication wording, which should be further simplified. The targeted CKD IDA population is considered a subpopulation of IDA patients and clinical findings do not suggest different clinical benefits in CKD patients as compared to patients with IDA due to other causes. In addition, it is considered that ferumoxytol should be reserved for second line treatment, i.e. when the oral route is insufficient or poorly tolerated, based on general safety concerns related to hypersensitivity reactions including anaphylaxis, associated with IV iron products. The following wording is suggested: "Ferumoxytol is indicated for the treatment of iron deficiency anemia in adults when oral iron preparations are ineffective or cannot be used (see section 5.1)". This is considered to cover all IDA subpopulations that were investigated and reflects the available dataset and overall study programme. In addition, the sentence "The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2)" should be deleted as it is not considered necessary and determination if a patient fulfils the indication is expected to be covered by general medicinal state-of-the-art knowledge of the treating physician (**MO**).

3.2.6. Conclusions on clinical efficacy

CKD indication

Overall, the main studies were conducted in a patient population largely representative of a broad CKD population. However, patients with stage 1-2 CKD disease were underrepresented and lower effect sizes are noted. The sample size was however too low to draw meaningful conclusions. No subjects on PD were included in the main clinical studies. In order to adequately reflect the study population in section 5.1 of the SmPC, further discussion is needed on the use of previous IV therapy in the recruited (sub)population(s) (e.g. patients not on HD, as per current European treatment recommendations, oral therapy would usually be indicated before switching to IV therapy). Although the primary endpoints were formally met in the three pivotal studies, the results overall need to be cautiously interpreted due to the short oral treatment duration of only 21 days, since maximum response to oral treatment might not have been achieved. In addition, the response to oral treatment was very low in study -6 and in a substantial proportion of study centers in study -7, which casts doubt on the reported treatment compliance in the oral comparator group. Nevertheless, the additionally conducted studies -201 and -401 are sufficient to address any limitations regarding the pivotal studies. Non-inferiority of Ferumoxytol 2x510 mg could be shown based on a pre-specified NI margin of 0.5 g/dL in the primary and secondary analyses, supported by additional sensitivity analyses. However, an overall low treatment response was observed in particular in study -401. Consistency of results with previous studies (and available literature regarding the comparator Iron sucrose) should be discussed. Justifications for the statistical derivation of the margin need to be provided, in particular, whether superiority over placebo would have been ensured with the selected margin. Furthermore, additional sensitivity analyses are needed to further explore the robustness of the primary /secondary results. However, provided these are all in line with the so far presented results and any remaining open questions can be adequately clarified (e.g. on the adequacy of the dosing in subgroups), the efficacy of ferumoxytol 2x510 mg can be considered to be convincingly shown.

All cause IDA indication

In summary, the treatment effect of two administrations of ferumoxytol at a dose of 510mg each could be consistently replicated across four different trials in a study population with IDA that can be considered representative for the intended target population. A beneficial effect on accepted and clinically relevant surrogate laboratory outcomes could be shown in subjects with lower (8.9 g/dL in IDA-301 and IDA-302)

and relatively higher (10.42g/dL in IDA-304) baseline haemoglobin levels as well as over repeated treatment cycles in IDA-303. In addition, non-inferiority to two different iron preparations used as active comparators in trials IDA-302 (iron sucrose) and IDA-304 (ferric carboxymaltose) was demonstrated. After one initial course of treatment, approximately 60% of the subjects who rolled over from IDA-301 into IDA-303 did not require further iron substitution. This effect was replicated in those patients stemming from the placebo arm of IDA-301, who received their first ferumoxytol treatment in the extension study. About 60% of those subjects did not need a further treatment cycle. These data illustrate a satisfactory durability of the treatment effect in subjects with IDA.

The second line indication in patients with all-cause IDA is considered approvable from an efficacy point of view, provided the Applicant satisfactorily addresses the open concerns in the LoQ.

3.2.7. Clinical safety

Clinical safety in CKD patients with IDA

Initial programme supporting the IDA-CKD indication

The ferumoxytol clinical development programme supporting the CKD indication comprised 11 clinical trials that have also been submitted for the initial MAA. A detailed integrated analysis of safety across these 11 studies is presented. For the integrated analyses of safety, data have been presented separately for CKD and non-CKD subjects. Within each of these subject populations, data have been further analysed by study type, treatment exposure and ferumoxytol dosing regimen. A brief summary of the methodology and rationale for these analysis subgroups is presented below.

- Study type: Several study designs were used during the ferumoxytol clinical development programme. The majority of subjects were randomised and not blinded to treatment since the active control was administered orally while ferumoxytol was administered IV. For the integrated safety analyses, studies were classified based on randomisation, blinding, and type of control.
- Treatment exposure: Subjects were broadly grouped by treatment exposure to compare the safety profile of ferumoxytol with that of oral iron and placebo. Exposure to ferumoxytol was further classified as a first or second treatment course. The first ferumoxytol course population includes all subjects not previously treated with ferumoxytol and the second ferumoxytol course population comprised those subjects previously exposed to a therapeutic course of ferumoxytol (i.e., any exposure >1.02 g).
- Ferumoxytol Dosing regimen: Among subjects exposed to ferumoxytol, the safety profiles of different dosing regimens were compared (1 x 125 mg, 1 x 250 mg, 1 x 510 mg, 8 x 128 mg, 4 x 255 mg, 2 x 510 mg, 4 x 255 mg followed by 2 x 510 mg, and 2 x 510 mg followed by 2 x 510 mg), allowing an evaluation of the safety profile of the different doses and regimens of ferumoxytol investigated during the clinical development programme (Note that all doses are given in terms of elemental iron (Fe)).

Additional CKD studies

In addition to the previously submitted studies, the Applicant conducted two post-marketing studies in CKD patients (CKD-201 and CKD-401, please refer to the efficacy section for details on study design). Throughout the safety assessment the results of both studies are presented together with the respective results in each section for comparability.

3.2.7.1. Patient exposure

The initial 11 clinical studies involving 1726 subjects and more than 2800 exposures to ferumoxytol contributed to the safety evaluation.

Table 85 Exposure to Study Medication by Cumulative Dose of Iron (mg) – CKD Subjects (Safety Population , seven studies)

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

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

b. Safety data in the analysis by randomised, open-label, controlled studies were derived from the following protocols: 62,745-5, 62,745-6, and62,745-7.

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

Abbreviations: SD=standard deviation.

CKD-201: 162 received at least one dose of study treatment (80 Ferumoxytol, 82 Iron Sucrose).

CKD-401: A total of 676 Treatment Periods were evaluated for 196 ferumoxytol subjects and 318 for 97 iron sucrose subjects. A complete Treatment Period consisted of 2 scheduled doses (510 mg each) for ferumoxytol and 10 doses (100 mg each) for iron sucrose.

Table 86: Number of Subjects in Each Treatment Period

Treatment Period	Ferumoxytol N=196 Number of Subjects n	Iron Sucrose N=97 Number of Subjects n
1	196	97
2	173	88
3	133	65
4	85	33
5	49	18
6	22	8
7	11	5
8	6	4

3.2.7.2. Adverse events

The overall incidence of TEAEs in the open-label, controlled studies, was lower in subjects following treatment with ferumoxytol 2 x 510 mg (44.0%) than in those following treatment with oral iron (53.9%) (Table 87). Lower incidences in subjects treated with ferumoxytol 2 x 510 mg, compared with oral iron, were also present for all other categories of TEAEs.

Table 87: Summary of Treatment-emergent Adverse Events in Randomised, Open-label, Controlled Studies by Treatment Regimen - CKD Subjects (Safety Population, three studies)

AE Category [a]	Ferumoxytol		Oral Iron N=280 n (%)
	4 x 255 mg N=60 n (%)	2 x 510 mg N=605 n (%)	
TEAEs	21 (35.0)	266 (44.0)	151 (53.9)
Related TEAEs [b]	1 (1.7)	82 (13.6)	52 (18.6)
Serious TEAEs	8 (13.3)	59 (9.8)	34 (12.1)
Related Serious TEAEs [b]	0	1 (0.2)	1 (0.4)
TEAEs Resulting in Temporary Discontinuation of Study Medication	1 (1.7)	7 (1.2)	10 (3.6)
TEAEs Resulting in Permanent Discontinuation of Study Medication	3 (5.0)	11 (1.8)	26 (9.3)
TEAEs Resulting in Hospitalization	6 (10.0)	49 (8.1)	27 (9.6)
TEAEs Resulting in Death	2 (3.3)	8 (1.3)	6 (2.1)

a. Subjects may be counted under more than one AE category.
b. Relationship classified by Investigator as remotely related, probably related, or definitely related.
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.

For the target therapeutic course of ferumoxytol (1.02 g) administered by three different treatment regimens (2 x 510 mg, 4 x 255 mg, or 8 x 128 mg), there was no indication of a consistent relationship between the regimen and the incidence of any of the TEAE parameters. In general, the incidences of all TEAE parameters were comparable between the 4 x 255 mg and 2 x 510 mg regimens. For the 8 x 128

mg regimen, the incidences of four TEAE parameters (all TEAEs; TEAEs resulting in temporary discontinuation of study medication; TEAEs resulting in permanent discontinuation of study medication; and TEAEs resulting in hospitalization) were higher and the incidence of related TEAEs was lower than observed for the 2 x 510 mg regimen. The incidences of all other TEAE parameters were similar between the 8 x 128 mg and 2 x 510 mg regimens.

Table 88: Summary of Treatment-emergent Adverse Events by Ferumoxytol Treatment Regimen and Treatment Exposure - CKD Subjects (Safety Population; Seven Studies)

	Ferumoxytol										Oral Iron	Placebo
AE Category	**1 x 125 mg**	**1 x 250 mg**	**1 x 510 mg**	**8 x 128 mg**	**4 x 255 mg**	**2 x 510 mg**	**4 x 255 -> 2 x 510 mg**	**2 x 510 -> 2 x 510 mg**	**First Course**	**Second Course**		
N	N=10	N=10	N=708	N=15	N=58	N=692	N=12	N=57	N=1562	N=69	N=290	N=711
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
TEAEs	2 (20.0)	2 (20.0)	140 (19.8)	11 (73.3)	25 (43.1)	302 (43.6)	7 (58.3)	41 (71.9)	512 (32.8)	29 (42.0)	155 (53.4)	135 (19.0)
Related TEAEs b	1 (10.0)	0	33 (4.7)	0	1 (1.7)	82 (11.8)	0	8 (14.0)	123 (7.9)	4 (5.8)	52 (17.9)	36 (5.1)
Serious TEAEs	0	1 (10.0)	27 (3.8)	1 (6.7)	7 (12.1)	70 (10.1)	2 (16.7)	9 (15.8)	111 (7.1)	6 (8.7)	34 (11.7)	17 (3.3)
Related Serious TEAEs b	0	0	1 (0.1)	0	0	2 (0.3)	0	0	3 (0.2)	0	1 (0.3)	1 (0.1)
TEAEs Resulting in												
Temporary Discontinuation of Study Medication	0	0	1 (0.1)	2 (13.3)	2 (3.4)	8 (1.2)	0	0	13 (0.8)	0	10 (3.4)	0
Permanent Discontinuation of Study Medication	0	0	5 (0.7)	4 (26.7)	3 (5.2)	13 (1.9)	0	1 (1.8)	25 (1.6)	1 (1.4)	26 (9.0)	6 (0.8)
Hospitalization	0	1 (10.0)	26 (3.7)	2 (13.3)	6 (10.3)	58 (8.4)	1 (8.3)	9 (15.8)	97 (6.2)	6 (8.7)	27 (9.3)	14 (2.0)
Death	0	0	0	0	2 (2.4)	9 (1.3)	0	1 (1.8)	11 (0.7)	1 (1.4)	6 (2.1)	2 (0.3)

a. Subjects may be counted under more than one AE category.
b. Relationship classified by Investigator as remotely related, probably related, or definitely related.

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

Post-marketing study CKD-201:

The overall incidence of AEs irrespective of relationship to study medication was lower in subjects treated with ferumoxytol (47.5%) than in those treated with iron sucrose (64.6%).

Table 89: Overview of TEAEs by Treatment Group and Overall (Safety Population) – CKD-201

	Ferumoxytol (n=80)		Iron Sucrose (n=82)		Total (n=162)	
Adverse Event Category	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**	**Events n**	**Subjects n (%)**
All AEs	86	38 (47.5)	161	53 (64.6)	247	91 (56.2)
Related AEs	8	8 (10.0)	46	13 (15.9)	54	21 (13.0)
SAEs	8	7 (8.8)	11	6 (7.3)	19	13 (8.0)
Related SAEs	1	1 (1.3)	1	1 (1.2)	2	2 (1.2)
AEs of Special Interest [1]	1	1 (1.3)	7	5 (6.1)	8	6 (3.7)
Cardiovascular AEs [2]	2	2 (2.5)	1	1 (1.2)	3	3 (1.9)
AEs Resulting in Temporary Discontinuation of Study Medication	2	2 (2.5)	3	3 (3.7)	5	5 (3.1)
AEs Resulting in Permanent Discontinuation of Study Medication	1	1 (1.3)	7	4 (4.9)	8	5 (3.1)
AEs Resulting in Study Discontinuation	1	1 (1.3)	5	4 (4.9)	6	5 (3.1)
AEs Leading to Death	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)

1 AEs of Special Interest included hypotension and hypersensitivity.

2 Cardiovascular AEs included nonfatal myocardial infarction, heart failure, moderate-to-severe hypertension, and hospitalization due to any cardiovascular cause.

Post-marketing study CKD-401:

The overall incidence of TEAEs was similar between subjects treated with ferumoxytol (80.6%) and those treated with iron sucrose (83.5%).

Table 90 Summary of Treatment-Emergent Adverse Events by Treatment Period for ferumoxytol (Safety Population) - CDK-401

AE Category	Overall		TP1		TP2		TP3		TP4		TP5		TP6	
Ferumoxytol (Events, Subjects (%))														
Number of subjects		196		196		173		133		85		49		22
All AEs	1073	158 (80.6)	198	78 (39.8)	166	65 (37.6)	94	42 (31.6)	56	25 (29.4)	48	20 (41.7)	28	10 (35.7)
Related AEs	14	9 (4.6)	10	6 (3.1)	1	1 (0.6)	2	1 (0.8)	0	0	0	0	1	1 (4.5)
SAEs	259	93 (47.4)	44	27 (13.8)	44	26 (15.0)	14	10 (7.5)	10	8 (9.4)	11	8 (16.3)	8	5 (22.7)
Related SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AEs of Special Interest- protocol defined 1	30	25 (12.8)	14	12 (6.2)	3	3 (1.7)	7	7 (5.3)	2	2 (2.4)	3	3 (6.1)	0	0
Cardiovascular AEs 2	49	29 (14.8)	9	7 (3.6)	8	5 (2.9)	5	4 (3.0)	1	1 (1.2)	3	3 (6.1)	3	3 (13.6)
AEs Resulting in Temporary Discontinuation of Study drug	2	2 (1.0)	0	0	0	0	0	0	0	0	0	0	0	0
AEs Resulting in Permanent Discontinuation of Study drug	11	8 (4.1)	3	2 (1.0)	1	1 (0.6)	1	1 (0.8)	0	0	0	0	0	0
AEs Resulting in Study Discontinuation	30	20 (10.2)	6	4 (2.0)	4	4 (2.3)	4	2 (1.5)	0	0	1	1 (2.0)	0	0
Death 3	22	15 (7.7)	3	2 (1.0)	2	2 (1.2)	3	1 (0.8)	0	0	1	1 (2.0)	0	0
Iron Sucrose (Events, Subjects (%))														
Number of subjects		97		97		88		65		33		18		8
All AEs	612	81 (83.5)	115	45 (46.4)	86	36 (40.9)	77	23 (35.4)	35	13 (39.4)	33	9 (50.0)	13	3 (37.5)
Related AEs	4	4 (4.1)	1	1 (1.0)	0	0	2	2 (3.1)	0	0	0	0	0	0
SAEs	174	49 (50.5)	31	16 (16.5)	28	14 (15.9)	24	10 (15.4)	12	8 (24.2)	13	7 (38.9)	10	3 (37.5)
Related SAEs	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AEs of Special Interest- protocol defined 1	40	26 (26.8)	11	10 (10.3)	9	9 (10.2)	9	9 (13.8)	3	3 (9.0)	7	3 (16.7)	1	1 (12.5)
Cardiovascular AEs 2	44	25 (25.8)	5	5 (5.2)	6	4 (4.5)	10	7 (10.8)	3	3 (9.0)	1	1 (5.5)	2	1 (12.5)
AEs Resulting in Temporary Discontinuation of Study drug	9	3 (3.1)	1	1 (1.0)	0	0	0	0	0	0	4	2 (11.1)	1	1 (12.5)
AEs Resulting in Permanent Discontinuation of Study drug	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AEs Resulting in Study Discontinuation	7	7 (7.2)	2	2 (2.1)	1	1 (1.1)	3	3 (4.6)	0	0	0	0	0	0
Death 3	7	6 (6.2)	2	2 (2.1)	0	0	3	2 (3.1)	0	0	0	0	0	0

[1] AEs of special interest include hypotension and hypersensitivity as defined in the protocol.

[2] Cardiovascular AEs include myocardial infarction, heart failure, moderate to severe hypertension and hospitalization due to any cardiovascular cause.

[3] Reported as unrelated to study drug by the investigator.

Note: Subjects were counted once within the same System Organ Class or Preferred Term. Percentages are based on the number of subjects in each Treatment Group.

Related AEs are those with relationship classified by investigator as related to study drug.

Common Adverse Events

In the initial CKD registrational programme across the main 7 CKD studies (N=1562), the most common AEs (≥2.0% of subjects) among ferumoxytol-treated subjects were diarrhoea (2.4%), hypotension (2.1%), and nausea (2.0%).

For the three Phase III pivotal studies, most of the TEAEs occurred with a higher frequency with oral iron: diarrhea (4.0% vs. 8.2%), nausea (3.1% vs. 7.5%), constipation (2.1% vs. 5.7%), and edema peripheral (2.0% vs. 3.2%), except for dizziness (ferumoxytol, 2.6% vs. oral iron, 1.8%) and hypotension (2.5% vs. 0.4%).

Table 91: Number (Percent) of Subjects with the Most Common Treatment-emergent Adverse Events (Based on >1.0% of Subjects in the Ferumoxytol 2 x 510 mg Treatment Group) in Randomised, Open-label, Controlled Studies by Treatment Regimen - 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)

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.

For the target therapeutic course of ferumoxytol (1.02 g), there was no consistent relationship between the incidences of the most common individual TEAEs and the different treatment regimens (ie, 2 x 510 mg, 4 x 255 mg, or 8 x 128 mg). TEAEs that occurred in ≥2.0% of subjects treated with 2 x 510 mg ferumoxytol were diarrhea, hypotension, nausea, dizziness, and headache. In general, the incidences of most of the individual common TEAEs in the 2 x 510 mg treatment group were lower than or equal to the incidences in the 4 x 255 mg treatment group and lower than or equal to the incidences in the 8 x 128 mg treatment group.

Table 92: Number (Percent) of Subjects with the Most Common Treatment-emergent Adverse Events by Ferumoxytol Treatment Regimen and Treatment Exposure – CKD Subjects (Safety Population, seven studies)

TEAE [a] Preferred Term	Ferumoxytol											Placebo
	1 x 125 mg	1 x 250 mg	1 x 510 mg	8 x 128 mg	4 x 255 mg	2 x 510 mg	4 x 255 mg -> 2 x 510 mg	2 x 510 mg -> 2 x 510 mg	First Course	Second Course	Oral Iron	
	N=10	N=10	N=708	N=15	N=58	N=692	N=12	N=57	N=1562	N=69	N=290	N=711
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Diarrhea	0	0	8 (1.1)	1 (6.7)	0	27 (3.9)	1 (8.3)	4 (7.0)	37 (2.4)	4 (5.8)	23 (7.9)	9 (1.3)
Hypotension	0	0	9 (1.3)	2 (13.3)	1 (1.7)	21 (3.0)	0	0	33 (2.1)	0	1 (0.3)	6 (0.8)
Nausea	0	0	8 (1.1)	1 (6.7)	2 (3.4)	18 (2.6)	0	5 (8.8)	31 (2.0)	3 (4.3)	21 (7.2)	10 (1.4)
Dizziness	0	0	7 (1.0)	2 (13.3)	0	19 (2.7)	0	2 (3.5)	29 (1.9)	1 (1.4)	5 (1.7)	6 (0.8)
Edema Peripheral	0	0	8 (1.1)	0	1 (1.7)	12 (1.7)	0	3 (5.3)	23 (1.5)	1 (1.4)	9 (3.1)	8 (1.1)
Headache	0	0	6 (0.8)	0	0	16 (2.3)	0	1 (1.8)	22 (1.4)	1 (1.4)	6 (2.1)	9 (1.3)
Vomiting	1 (10.0)	0	8 (1.1)	1 (6.7)	2 (3.4)	9 (1.3)	0	3 (5.3)	22 (1.4)	2 (2.9)	14 (4.8)	8 (1.1)
Constipation	0	0	2 (0.3)	0	1 (1.7)	11 (1.6)	0	3 (5.3)	17 (1.1)	0	16 (5.5)	2 (0.3)

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.

Post-marketing study CKD-201:

The most common AEs among ferumoxytol treated subjects were nausea (7.5%) and muscle spasms (5.0%). Adverse events occurring in ≥2.0% of subjects treated with ferumoxytol included: nasopharyngitis, URI, headache, hyperkalemia, and cough (3.8%); peripheral oedema, constipation, diarrhoea, hypotension, hypoglycemia, and anaemia (2.5%).

The most commonly occurring AEs in subjects treated with iron sucrose included: hypotension (9.8%), URI, muscle spasms, and peripheral oedema (7.3%). AEs that occurred in ≥2.0% of subjects treated with iron sucrose included parosmia (4.9%), constipation, nausea, gout, hypoglycemia (3.7%), nasopharyngitis, myalgia, pain in extremity, injection site pain, vomiting, dizziness, and headache (2.4%).

Post-marketing study CKD-401:

The overall incidence of TEAEs was similar between subjects treated with ferumoxytol (80.6%) and those treated with iron sucrose (83.5%). The PTs with the highest incidence in ferumoxytol-treated subjects by MedDRA PT were nausea (11.2%) followed by diarrhea (10.7%), hypotension (8.7%), vomiting (8.2%) and muscle spasms (8.2%).

Infections and infestations were reported by 64 subjects (32.7%) in the ferumoxytol group and 33 subjects (34.0%) in the iron sucrose group. The most commonly reported events were upper respiratory tract infection (7.1% ferumoxytol; 6.2% iron sucrose), urinary tract infection (6.1% ferumoxytol; 3.1% iron sucrose), pneumonia (5.6% ferumoxytol; 3.1% iron sucrose), sepsis (5.1% ferumoxytol; 2.1% iron sucrose), and cellulitis (2.6% ferumoxytol; 6.2% iron sucrose).

Table 93: Treatment Emergent Adverse Events by MedDRA SOC and Treatment Group in Decreasing Relative AE Incidence- All Causality (Safety Population) - Study CKD-401

MedDRA System Organ Class Preferred Term	Treatment Group					
	Ferumoxytol (n=196)		Iron Sucrose (n=97)		Total (n=293)	
	Events	Subjects n (%)	Events	Subjects n (%)	Events	Subjects n (%)
All AEs	1073	158 (80.6)	612	81 (83.5)	1685	239 (81.6)
Gastrointestinal disorders	163	74 (37.8)	85	36 (37.1)	248	110 (37.5)
Nausea	30	22 (11.2)	17	15 (15.5)	47	37 (12.6)
Diarrhoea	25	21 (10.7)	13	12 (12.4)	38	33 (11.3)
Vomiting	20	16 (8.2)	15	12 (12.4)	35	28 (9.6)
Abdominal pain	14	12 (6.1)	9	8 (8.2)	23	20 (6.8)
Injury, poisoning and procedural complications	135	61 (31.1)	101	42 (43.3)	236	103 (35.2)
Arteriovenous fistula site complication	18	14 (7.1)	25	8 (8.2)	43	22 (7.5)
Arteriovenous fistula thrombosis	8	7 (3.6)	7	7 (7.2)	15	14 (4.8)
Fall	7	7 (3.6)	6	6 (6.2)	13	13 (4.4)
Infections and infestations	112	64 (32.7)	61	33 (34.0)	173	97 (33.1)
Upper respiratory tract infection	14	14 (7.1)	7	6 (6.2)	21	20 (6.8)
Urinary tract infection	12	12 (6.1)	3	3 (3.1)	15	15 (5.1)
Pneumonia	12	11 (5.6)	4	3 (3.1)	16	14 (4.8)
Sepsis	10	10 (5.1)	2	2 (2.1)	12	12 (4.1)
Cellulitis	5	5 (2.6)	7	6 (6.2)	12	11 (3.8)
General disorders and administration site conditions	87	57 (29.1)	37	21 (21.6)	124	78 (26.6)
Non-cardiac chest pain	11	10 (5.1)	12	7 (7.2)	23	17 (5.8)
Pyrexia	17	15 (7.7)	1	1 (1.0)	18	16 (5.5)
Musculoskeletal and	127	40 (20.4)	82	25 (25.8)	209	65 (22.2)

connective tissue disorders						
Pain in extremity	16	13 (6.6)	22	11 (11.3)	38	24 (8.2)
Muscle spasms	70	16 (8.2)	37	7 (7.2)	107	23 (7.8)
Arthralgia	8	8 (4.1)	10	7 (7.2)	18	15 (5.1)
Vascular disorders	77	38 (19.4)	38	24 (24.7)	115	62 (21.2)
Hypotension	21	17 (8.7)	8	7 (7.2)	29	24 (8.2)
Hypertension	37	14 (7.1)	14	6 (6.2)	51	20 (6.8)
Nervous system disorders	48	35 (17.9)	48	24 (24.7)	96	59 (20.1)
Dizziness	11	10 (5.1)	18	7 (7.2)	29	17 (5.8)
Headache	12	8 (4.1)	9	7 (7.2)	21	15 (5.1)
Respiratory, thoracic and mediastinal disorders	74	41 (20.9)	30	18 (18.6)	104	59 (20.1)
Cough	14	12 (6.1)	5	5 (5.2)	19	17 (5.8)
Dyspnoea	13	11 (5.6)	6	6 (6.2)	19	17 (5.8)
Cardiac disorders	64	30 (15.3)	33	18 (18.6)	97	48 (16.4)
Cardiac failure congestive	6	6 (3.1)	7	5 (5.2)	13	11 (3.8)
Metabolism and nutrition disorders	51	32 (16.3)	29	15 (15.5)	80	47 (16.0)
Fluid overload	15	14 (7.1)	12	6 (6.2)	27	20 (6.8)
Hyperkalaemia	11	11 (5.6)	7	5 (5.2)	18	16 (5.5)
Skin and subcutaneous tissue disorders	32	19 (9.7)	14	10 (10.3)	46	29 (9.9)
Pruritus	15	12 (6.1)	5	4 (4.1)	20	16 (5.5)
Psychiatric disorders	30	18 (9.2)	11	7 (7.2)	41	25 (8.5)
Investigations	12	11 (5.6)	21	13 (13.4)	33	24 (8.2)
Blood and lymphatic system disorders	20	14 (7.1)	6	6 (6.2)	26	20 (6.8)
Anaemia	12	8 (4.1)	5	5 (5.2)	17	13 (4.4)

Analysis by Treatment Period: An AE was counted as belonging to a TP if the onset time of the event was after the start time of dose 1 of the TP and before the earlier of 65 days from starting time of dose 1 of the TP or start time of dose 1 of the next TP. Events which fell outside of this window are not reflected in this analysis.

Table 94: Subjects Experiencing Adverse Events by Treatment Period - Study CKD-401

System Organ Class	TP1	TP2	TP3	TP4	TP5	TP6
	Ferumoxytol n subjects (%) / Iron Sucrose n subjects (%)					
Number of subjects	196/97	173/88	133/65	85/33	49/18	22/8
Overall	78(39.8) /45(46.4)	65(37.6) /36(40.9)	42(31.6) /23(35.4)	25(29.4) /13(39.4)	20(40.8) /9 (50.0)	10 (45.5) /3 (37.5)
Blood and lymphatic system disorders	3 (1.5) / 2 (2.1)	3 (1.7) / 1 (1.1)	1 (0.8) / 0	1 (1.2) / 1 (3.0)	0 / 2 (11.1)	0 / 0
Cardiac disorders	9 (4.6) / 2 (2.1)	7 (4.0) / 5 (5.7)	3 (2.3) 7 (10.8)	1 (1.2) / 2 (6.1)	2 (4.1) / 0	3 (13.6) / 1 (12.5)
Congenital, familial and genetic disorders	1 (0.5) / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders	0 / 1 (1.0)	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Eye Disorders	0 / 0	1 (0.6) / 0	1 (0.8) / 0	3 (3.5) / 0	0 / 0	0 / 0
Gastrointestinal disorders	20(10.2) /13(13.4)	13(7.5) /10 11.4)	8 (6.0) / 4 (6.2)	4 (4.7) / 3 (9.1)	4 (8.2) / 2 (11.1)	1 (4.5) / 1 (12.5)
General disorders and administration site conditions	16 (8.2) / 9 (9.3)	15 (8.7) / 3 (3.4)	9 (6.8) / 3 (4.6)	4 (4.7) / 1 (3.0)	2 (4.1) / 1 (5.6)	2 (9.1) / 0
Hepatobiliary disorders	0 / 0	1 (0.6) / 0	0 / 0	0 / 0	1 (2.0) / 0	0 / 0
Immune system disorders	2 (1.0) / 1 (1.0)	0 / 0	0 / 1 (1.5)	0 / 0	0 / 0	0 / 0
Infections and infestations	16 (8.2) / 9 (9.3)	13 (7.5) / 9 (10.2)	9 (6.8) / 6 (9.2)	5 (5.9) / 2 (6.1)	9 (18.4) / 4 (22.2)	1 (4.5) / 2 (25.0)
Injury, poisoning and procedural complications	20(10.2) /12(12.4)	21(12.1) /14(15.9)	9 (6.8) / 6 (9.2)	7 (8.2) / 2 (6.1)	2 (4.1) / 2 (11.1)	0 / 1 (12.5)
Investigations	3 (1.5) / 1 (1.0)	0 / 6 (6.8)	2 (1.5) / 2 (3.1)	0 / 0	0 / 1 (5.6)	1 (4.5) / 0
Metabolism and nutrition disorders	6 (3.1) / 2 (2.1)	6 (3.5) / 3 (3.4)	3 (2.3) / 4 (6.2)	1 (1.2) / 2 (6.1)	2 (4.1) / 3 (16.7)	2 (9.1) / 1 (12.5)
Musculoskeletal and connective tissue disorders	11 (5.6) / 9 (9.3)	11 (6.4) / 5 (5.7)	8 (6.0) / 8 (12.3)	5 (5.9) / 2 (6.1)	2 (4.1) / 1 (5.6)	4 (18.2) / 1 (12.5)
Neoplasms benign, malignant and unspecified	1 (0.5) / 1 (1.0)	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Nervous system disorders	9 (4.6) / 5 (5.2)	4 (2.3) / 3 (3.4)	2 (1.5) / 4 (6.2)	1 (1.2) / 5 (15.2)	1 (2.0) / 2 (11.1)	1 (4.5) / 0
Psychiatric disorders	6 (3.1) / 2 (2.1)	5 (2.9) / 1 (1.1)	0 / 1 (1.5)	1 (1.2) / 0	1 (2.0) / 1 (5.6)	1 (4.5) / 0
Renal and urinary disorders	1 (0.5) / 0	3 (1.7) / 0	0 / 1 (1.5)	0 / 0	0 / 0	1 (4.5) / 0
Respiratory, thoracic and mediastinal disorders	11 (5.6) / 8 (8.2)	9 (5.2) / 6 (6.8)	3 (2.3) / 1 (1.5)	4 (4.7) / 2 (6.1)	2 (4.1) / 2 (11.1)	2 (9.1) / 0
Skin and subcutaneous tissue disorders	6 (3.1) / 3 (3.1)	6 (3.5) / 1 (1.1)	4 (3.0) / 2 (3.1)	0 / 0	0 / 1 (5.6)	0 / 0
Vascular disorders	12(6.1) / 10 (10.3)	8 (4.6) / 4 (4.5)	4 (3.0) / 4 (6.2)	3 (3.5) / 2 (6.1)	2 (4.1) / 1 (5.6)	1 (4.5) / 0

Common Adverse Events That Were Severe

The incidences of the individual TEAEs of severe intensity were ≤0.5% in the ferumoxytol 2 x 510 mg treatment group.

Table 95: Number (Percent) of Subjects with the Most Common Treatment-emergent Adverse Events That Were Severe in Intensity and Occurred in More Than One Subject in Any Treatment Group in Randomised, Open-label, Controlled Studies by Treatment Regimen - CKD Subjects (Safety Population, three studies)

Severe 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 (%)
Chest Pain	0	3 (0.5)	0
Abdominal Pain	0	3 (0.5)	1 (0.4)
Cardiac Arrest	0	2 (0.3)	1 (0.4)
Cardiac Failure Congestive	0	2 (0.3)	1 (0.4)
Diarrhea	0	2 (0.3)	5 (1.8)
Hypertension	0	2 (0.3)	0
Nausea	0	2 (0.3)	2 (0.7)
Hyperkalemia	0	2 (0.3)	0
Renal Failure Acute	0	2 (0.3)	1 (0.4)
Syncope	0	2 (0.3)	0
Vomiting	0	1 (0.2)	2 (0.7)
Anaemia	0	0	3 (1.1)
Pneumonia	1 (1.7)	0	2 (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.
Data Source: ISS, Statistical Table 30.4.1.

Table 96: Number (Percent) of Subjects with the Most Common Treatment-emergent Adverse Events That Were Severe in Intensity (Based on Subjects in All Studies Treated with a First Course of Ferumoxytol) by Ferumoxytol Treatment Regimen – CKD Subjects (Safety Population, seven studies)

Severe TEAE a Preferred Term	Ferumoxytol								Placebo n (%)
	1 x 125 mg n (%)	1 x 250 mg n (%)	1 x 510 mg n (%)	8 x 128 mg n (%)	4 x 255 mg n (%)	2 x 510 mg n (%)	4 x 255 mg -> 2 x 510 mg n (%)	2 x 510 mg -> 2 x 510 mg n (%)	
	N=10	N=1	N=708	N=15	N=5	N=692	N=1	N=57	N=711
Diarrhea	0	0	1 (0.1)	1 (6.7)	0	3 (0.4)	0	0	0
Abdominal Pain	0	0	1 (0.1)	0	0	2 (0.3)	0	1	0
Chest Pain	0	0	0	0	0	2 (0.3)	0	1	0
Cardiac Failure	0	0	1 (0.1)	0	0	2 (0.3)	0	1	0
Hypertension	0	0	0	0	0	3 (0.4)	0	0	0
Hypotension	0	0	1 (0.1)	0	0	2 (0.3)	0	0	1
Nausea	0	0	1 (0.1)	0	0	2 (0.3)	0	0	0

Neck Pain	0	0	1 (0.1)	0	0	2 (0.3)	0	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.

First and second course treatment

Table 97: Number (Percent) of Subjects with Treatment-emergent Adverse Events That Were Severe in Intensity and Occurred in More Than One Subject in Any Treatment Group by Treatment Exposure – CKD Subjects (Safety Population, seven studies)

Severe 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	5 (0.3)	0	5 (1.7)	0
Abdominal Pain	4 (0.3)	0	1 (0.3)	0
Cardiac Failure Congestive	3 (0.2)	1 (1.4)	1 (0.3)	0
Chest Pain	3 (0.2)	0	0	0
Hypertension	3 (0.2)	0	0	0
Hypotension	3 (0.2)	0	0	1 (0.1)
Nausea	3 (0.2)	0	2 (0.7)	0
Neck Pain	3 (0.2)	0	0	1 (0.1)
Renal Failure Acute	3 (0.2)	0	1 (0.3)	0
Cardiac Arrest	2 (0.1)	0	1 (0.3)	0
Coronary Artery Disease	2 (0.1)	0	0	0
Headache	2 (0.1)	0	0	0
Hypertensive Crisis	2 (0.1)	0	0	0
Hyperkalemia	2 (0.1)	0	0	0
Hypoglycemia	2 (0.1)	1 (1.4)	1 (0.3)	0
Pain In Extremity	2 (0.1)	0	0	0
Pneumonia	2 (0.1)	0	2 (0.7)	0
Syncope	2 (0.1)	0	0	0
Vomiting	2 (0.1)	0	2 (0.7)	0
Anaemia	0	0	3 (1.0)	0

a. Subjects may be counted under more than one preferred term.
Note: Safety data in this table were derived from the following protocols: 62,745-2, 62,745-3, 62,745-4, 62,745-5, 62,745-6, 62,745-7, and 62,745-8.

Abbreviations: TEAE=treatment-emergent adverse event.

Study CKD-201: The TEAEs of all except 3 (3.8%) subjects in the ferumoxytol group and 1 (1.2%) subject in the iron sucrose group were mild or moderate in severity. Severe TEAEs in the ferumoxytol group each occurred with an incidence of 1.3% (1 subject), were also serious TEAEs, and included abdominal pain, deep vein thrombosis, and anastomotic hemorrhage. Severe TEAEs in the iron sucrose

group occurred in 1 (1.2%) subject and included non-serious iron deficiency anemia and serious renal failure chronic that were unrelated to study medication.

Study CKD-401: The rates of severe TEAEs were comparable between ferumoxytol- and iron sucrose-treated subjects (ferumoxytol, 27.6%; iron sucrose, 30.9%).

In the ferumoxytol treatment group, severe AEs occurring in >2% of subjects were: sepsis (6 events in 6 subjects (3.1%)), mental status changes (6 events in 5 subjects (2.6%)), acute respiratory failure (6 events in 6 subjects (3.1%)), acute myocardial infarction, (4 events in 4 subjects (2.0%)), fluid overload (4 events in 4 subjects (2.0%) and cardio-respiratory arrest (4 events in 4 subjects (2.0%).

In the iron sucrose group severe AEs occurring events in >2% of subjects were: hyperkalaemia (3 events in 3 subjects (3.1%)), acute myocardial infarction, (3 events in 2 subjects (2.1%)), cardiac arrest (2 events in 2 subjects (2.1%)), abdominal pain (2 events in 2 subjects (2.1%)), staphyloccal sepsis (2 events in 2 subjects (2.1%)) and fluid overload (2 events in 2 subjects (2.1%)).

Common Adverse Events Related to Treatment

There were no related TEAEs that occurred with a frequency of ≥2% in the ferumoxytol 2 x 510 mg treatment group. The only related TEAEs that differed by >3% incidence was diarrhea and constipation, which were both higher in the oral iron group than in the ferumoxytol 2 x 510 mg group.

Table 98: Subjects with the Most Common Treatment-emergent Related Adverse Events (Based on >0.5% of Subjects in the Ferumoxytol 2 x 510 mg Treatment Group) in Randomised, Open-label, Controlled Studies by Treatment Regimen - CKD Subjects (Safety Population, three studies)

Related TEAE [a,b] 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	11 (1.8)	16 (5.7)
Dizziness	0	10 (1.7)	1 (0.4)
Constipation	0	9 (1.5)	14 (5.0)
Hypotension	0	8 (1.3)	0
Nausea	0	6 (1.0)	7 (2.5)
Abdominal Pain	0	5 (0.8)	3 (1.1)
Dysgeusia	0	4 (0.7)	1 (0.4)
Flushing	0	4 (0.7)	0
Headache	0	4 (0.7)	1 (0.4)
Rash	0	4 (0.7)	1 (0.4)

a. Subjects may be counted under more than one preferred term.
b. Relationship classified by Investigator as remotely related, probably related, or definitely related.
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.

Table 99: Subjects with Treatment-emergent Related Adverse Events Occurring in >0.1% of Subjects in the Ferumoxytol First Course Treatment Group by Treatment Exposure – CKD Subjects (Safety Population, seven studies)

Related TEAE [a,b] Preferred Term	Ferumoxytol First Course N=1562 n (%)	Ferumoxytol Second Course N=69 n (%)	Oral Iron N=290 n (%)	Placebo N=711 n (%)
Dizziness	15 (1.0)	0	1 (0.3)	4 (0.6)
Diarrhea	14 (0.9)	0	16 (5.5)	2 (0.3)
Hypotension	13 (0.8)	0	0	1 (0.1)
Constipation	11 (0.7)	0	14 (4.8)	0
Nausea	9 (0.6)	0	7 (2.4)	4 (0.6)
Dysgeusia	6 (0.4)	1 (1.4)	1 (0.3)	2 (0.3)
Headache	6 (0.4)	0	1 (0.3)	3 (0.4)
Abdominal Pain	5 (0.3)	0	3 (1.0)	1 (0.1)
Rash	5 (0.3)	0	1 (0.3)	0
Vomiting	5 (0.3)	0	6 (2.1)	1 (0.1)
Infusion Site Swelling	4 (0.3)	0	0	1 (0.1)
Flushing	4 (0.3)	0	0	1 (0.1)
Pruritus	4 (0.3)	0	0	3 (0.4)
Chest Pain	3 (0.2)	0	1 (0.3)	1 (0.1)
Fatigue	3 (0.2)	0	0	3 (0.4)
Feces Discolored	3 (0.2)	0	1 (0.3)	0
Infusion Site Reaction	3 (0.2)	0	0	0
Somnolence	3 (0.2)	0	0	0

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

b. Relationship classified by Investigator as remotely related, probably related, or definitely related.

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.

Table 100: Subjects with the Most Common Treatment-emergent Related Adverse Events (Based on Subjects in All Studies Treated with a First Course of Ferumoxytol) **by Ferumoxytol Treatment Regimen** - CKD Subjects (Safety Population, seven studies)

Related TEAE [a,b] Preferred Term	Ferumoxytol								Placebo n (%)
	1 x 125 mg n (%)	1 x 250 mg n (%)	1 x 510 mg n (%)	8 x 128 mg n (%)	4 x 255 mg n (%)	2 x 510 mg n (%)	4 x 255 mg -> 2 x 510 mg n (%)	2 x 510 mg -> 2 x 510 mg n (%)	
	N=10	N=10	N=708	N=15	N=58	N=692	N=12	N=57	N=711
Dizziness	0	0	4 (0.6)	0	0	10 (1.4)	0	1 (1.8)	4 (0.6)
Diarrhea	0	0	2 (0.3)	0	0	12 (1.7)	0	0	2 (0.3)
Hypotension	0	0	2 (0.3)	0	0	11 (1.6)	0	0	1 (0.1)
Constipation	0	0	2 (0.3)	0	0	8 (1.2)	0	1 (1.8)	0

Nausea	0	0	2 (0.3)	0	0	6 (0.9)	0	1 (1.8)	4 (0.6)
Dysgeusia	0	0	2 (0.3)	0	0	4 (0.6)	0	1 (1.8)	2 (0.3)
Headache	0	0	2 (0.3)	0	0	4 (0.6)	0	0	3 (0.4)

a. Subjects may be counted under more than one preferred term.
b. Relationship classified by Investigator as remotely related, probably related, or definitely related.
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.

Post-marketing study CKD-201:

The incidence of related TEAEs was lower in the ferumoxytol group (10.0%, 8 subjects) than the iron sucrose group (15.9%, 13 subjects).

Among subjects treated with ferumoxytol, all related TEAEs occurred with an incidence of 1.3% (1 subject). Among subjects treated with iron sucrose, TEAEs that occurred in more than 1 subject were parosmia (3 [3.7%] subjects), hypotension (3 [3.7%] subjects), and injection site pain (2 [2.4%] subjects). The majority of related TEAEs in both treatment groups were mild in severity.

A total of 30 related TEAEs of parosmia occurred in 3 (3.7%) subjects in the iron sucrose group compared to none (0.0%) in the ferumoxytol group. All of the related events of parosmia were mild in severity.

Postmarketing study CKD-401:

Fourteen AEs for 9 (4.6%) subjects in the ferumoxytol treatment group and 4 AEs for 4 subjects (4.1%) in the iron sucrose group were reported as related to study drug. None of the AEs was serious and no PT appeared more than once in any treatment group.

Following AEs were reported in ferumoxytol group: hypertension, blood pressure increased, hyperkalaemia, hypocalcaemia, metabolic acidosis, Hypotension, Catheter site pruritus, Pruritus, Urticaria, Nausea.

Following AEs were reported in IS group: Vomiting, myalgia, AF.

Related AEs were seen primarily in TP1 when 10 events were observed for 6 subjects. Each related AE occurred for only 1 subject and were observed across multiple SOCs

3.2.7.3. Serious adverse events and deaths, other significant events

Death

Table 101: All Deaths in the Clinical Development Program

Time relative to final dose of study drug	**FERUMOXYTOL (N=1726)**	**FERUMOXYTOL2 x 510 mg (N=749)**	**ORAL IRON (N=290)**	**PRE-DOSE**
Pre-dose	-	-	-	4
Within 30 days post final dose	12 (0.7%)	6 (0.8%)	4 (1.4%)	-
30-60 days post final dose	4 (0.2%)	3 (0.4%)	3 (1.0%)	-
More than 60 days post final	3 (0.2%)	1 (0.1%)	1 (0.3%)	-
TOTAL	**19 (1.1%)**	**10 (1.3%)**	**8 (2.8%)**	**4**

Post-marketing study CKD-201: No deaths occurred in the post marketing study FER-CKD-201. One death occurred prior to randomization into the study and was reported to US Food and Drug Administration (FDA).

Post-marketing study CKD-401: There were 16 post-treatment deaths reported in the ferumoxytol group (8.2%) and 6 in the iron sucrose group (6.2%). Deaths were unrelated to study drug administration. The death of 1 subject in the ferumoxytol group occurred after the subject had withdrawn from the study and data were no longer being collected but was reported as an SAE.

Other serious adverse events (SAEs)

The overall incidence of SAEs across the main 7 CKD studies (N=1562), irrespective of relationship to study medication and dose of ferumoxytol, was lower in subjects following a first course of treatment with any dose of ferumoxytol (7.1%) than in subjects treated with oral iron (11.7%).

Table 102: Subjects with Treatment-emergent Serious Adverse Events by Ferumoxytol Treatment Regimen and Exposure– CKD Subjects (Safety Population, seven studies) (min 2 subjects in first course ferumoxytol treatment)

	Ferumoxytol											
System Organ Class Preferred Term a	**1 x 125 mg**	**1 x 250 mg**	**1 x 510 mg**	**8 x 128 mg**	**4 x 255 mg**	**2 x 510 mg**	**4 x 255 mg -> 2 x 510 mg**	**2 x 510 mg -> 2 x 510 mg**	**First Course**	**Second Course**	**Oral Iron**	**Placebo**
N	N=10	N=10	N=708	N=15	N=58	N=692	N=12	N=57	N=1562	N=69	N=29	N=711
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Overall	0 (0)	1 (10.0)	27 (3.8)	1 (6.7)	7 (12.1)	70 (10.1)	2 (16.7)	9 (15.8)	111 (7.1)	6 (8.7)	34 (11.7)	17 (2.4)
Cardiac Disorders	0	0	7 (1.0)	0	2 (3.4)	18 (2.6)	0	2 (3.5)	27 (1.7)	2 (2.9)	10 (3.4)	3 (0.4)
Acute myocardial infarction	0	0	1 (0.1)	0	0	1 (0.1)	0	0	3 (0.2)	0	1 (0.3)	0
Angina pectoris	0	0	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)	0	0	1 (0.1)
Angina unstable	0	0	0	0	0	2 (0.3)	0	0	2 (0.1)	0	1 (0.3)	0
Atrial fibrillation	0	0	0	0	0	2 (0.3)	0	1 (1.8)	2 (0.1)	1 (1.4)	0	0
Atrial flutter	0	0	1 (0.10	0	0	1 (0.1)	0	0	2 (0.1)	0	0	0
Cardiac arrest	0	0	0	0	0	2 (0.3)	0	0	2 (0.1)	0	1 (0.3)	0
Cardiac failure congestive	0	0	5 (0.7)	0	1 (1.7)	5 (0.7)	0	1 (1.8)	11 (0.7)	1 (1.4)	3 (1.0)	1 (0.1)
Coronary artery disease	0	0	0	0	0	3 (0.4)	0	0	3 (0.2)	0	0	0
Gastrointestinal Disorders	0	0	4 (0.6)	1 (6.7)	1 (1.7)	5 (0.7)	0	1 (1.8)	11 (0.7)	1 (1.4)	4 (1.4)	1 (0.1)
Abdominal pain	0	0	2 (0.3)	0	0	1 (0.1)	0	0	3 (0.2)	0	0	0
Diarrhea	0	0	0	1 (6.7)	0	1 (0.1)	0	0	2 (0.1)	0	0	0
Gastrointestinal hemorrhage	0	0	0	0	1 (1.7)	1 (0.1)	0	0	2 (0.1)	0	0	0
General Disorders and Administrative Site Conditions	0	0	1 (0.1)	0	0	4 (0.6)	0	1 (1.8)	6 (0.4)	0	3 (1.0)	1 (0.1)
Chest pain	0	0	0	0	0	3 (0.4)	0	1 (1.8)	4 (0.3)	0	0	1 (0.1)
Hepatobiliary Disorders	0	0	0	0	0	2 (0.3)	0	0	2 (0.1)	0	0	0
Cholelithiasis	0	0	0	0	0	2 (0.3)	0	0	2 (0.1)	0	0	0
Infections and Infestations	0	0	5 (0.7)	0	3 (5.2)	18 (2.6)	0	2 (3.5)	26 (1.7)	2 (2.9)	8 (2.8)	8 (1.1)
Cellulitis	0	0	1 (0.1)	0	0	1 (0.1)	0	1 (1.8)	2 (0.1)	1 (1.4)	2 (0.7)	3 (0.4)
Gangrene	0	0	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)	0	1 (0.3)	1 (0.1)
Localized infection	0	0	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)	0	0	0
Osteomyelitis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)	0	0	0

Peritonitis bacterial									2 (0.1)	0	0	0
Pneumonia	0	0	0	0	1 (1.7)	5 (0.7)	0	0	6 (0.4)	0	3 (1.0)	0
Sepsis	0	0	0	0	1 (1.7)	2 (0.3)	0	0	3 (0.2)	0	2 (0.7)	1 (0.1)
Investigations	0	0	4 (0.6)	0	0	0	0	0	4 (0.3)	0	2 (0.7)	0
Haemoglobin decreased	0	0	2 (0.3)	0	0	0	0	0	2 (0.1)	0	0	0
Nervous System Disorders	0	1 (10.0)	1 (0.1)	0	0	8 (1.2)	0	0	10 (0.6)	0	2 (0.7)	0
Syncope	0	0	0	0	0	2 (0.3)	0	0	2 (0.1)	0	0	0
Transient ischemic attack	0	1 (10.0)	0	0	0	1 (0.1)	0	0	2 (0.1)	0	0	0
Psychiatric Disorders	0	0	0	0	0	4 (0.6)	0	1 (1.8)	5 (0.3)	0	0	0
Mental status changes	0	0	0	0	0	3 (0.4)	0	0	3 (0.2)	0	0	0
Renal and Urinary Disorders	0	0	2 (0.3)	0	1 (1.7)	5 (0.7)	0	1 (1.8)	8 (0.5)	1 (1.4)	5 (1.7)	1 (0.1)
Renal failure acute	0	0	1 (0.1)	0	0	3 (0.4)	0	0	4 (0.3)	0	1 (0.3)	0
Renal failure chronic	0	0	0	0	1 (1.7)	2 (0.3)	0	1 (1.8)	3 (0.2)	1 (1.4)	1 (0.3)	0
Respiratory, Thoracic, and Mediastinal Disorders	0	0	2 (0.3)	0	1 (1.7)	4 (0.6)	1 (8.3)	0	7 (0.4)	1 (1.4)	5 (1.7)	0
Chronic obstructive airways disease exacerbated	0	0	1 (0.1)	0	0	1 (0.1)	0	0	2 (0.1)	0	2 (0.7)	0
Pulmonary edema	0	0	0	0	1 (1.7)	1 (0.1)	1 (8.3)	0	2 (0.1)	1 (1.4)	0	0
Vascular Disorders	0	0	1 (0.1)	0	1 (1.7)	7 (1.0)	0	1 (1.8)	9 (0.6)	1 (1.4)	3 (1.0)	0
Hypertensive crisis	0	0	0	0	1 (1.7)	1 (0.1)	0	0	2 (0.1)	0	0	0
Hypotension	0	0	1 (0.1)	0	0	4 (0.6)	0	0	5 (0.3)	0	1 (0.3)	0

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

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

Post-marketing study CKD-201:

The incidence of serious TEAEs across System Organ Classes and Preferred Terms was similar between the ferumoxytol group (8.8%, 7 subjects) and iron sucrose group (7.3%, 6 subjects). In the ferumoxytol group, the highest incidence of serious TEAEs occurred in the Gastrointestinal disorders (2.5%, 2 subjects) System Organ Class, and in the iron sucrose group, the highest incidence of serious TEAEs occurred in the Infections and infestations (3.7%, 3 subjects) System Organ Class.

Post-marketing study CKD-401:

All treatment-emergent SAEs in both groups were unrelated to the study drug.

Table 103: Treatment-Emergent Serious Adverse Events by MedDRA SOC and PT by Treatment Group in Decreasing Total SAE Incidence - All Causality (Safety Population) – Study CDK-401

Preferred Term	Treatment Group					
	Ferumoxytol (n=196)		Iron Sucrose (n=97)		Total	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
Overall	259	93 (47.4)	174	49 (50.5)	433	142 (48.5)
Infections and infestations	49	38 (19.4)	24	17 (17.5)	73	55 (18.8)
Sepsis	10	10 (5.1)	2	2 (2.1)	12	12 (4.1)
Pneumonia	7	7 (3.6)	4	3 (3.1)	11	10 (3.4)
Cellulitis	4	4 (2.0)	2	2 (2.1)	6	6 (2.0)
Gastrointestinal disorders	32	25 (12.8)	21	12 (12.4)	53	37 (12.6)
Abdominal pain	2	2 (1.0)	4	4 (4.1)	6	6 (2.0)
Gastrointestinal haemorrhage	3	3 (1.5)	1	1 (1.0)	4	4 (1.4)
Vomiting	1	1 (0.5)	3	3 (3.1)	4	4 (1.4)
Nausea	0	0	3	3 (3.1)	3	3 (1.0)
Cardiac disorders	31	20 (10.2)	27	15 (15.5)	58	35 (11.9)
Cardiac failure congestive	5	5 (2.6)	7	5 (5.2)	12	10 (3.4)
Acute myocardial infarction	4	4 (2.0)	6	3 (3.1)	10	7 (2.4)
Angina pectoris	4	3 (1.5)	6	4 (4.1)	10	7 (2.4)
Cardiac arrest	5	3 (1.5)	2	2 (2.1)	7	5 (1.7)
Cardio-respiratory arrest	4	4 (2.0)	1	1 (1.0)	5	5 (1.7)
Injury, poisoning and procedural complications	22	18 (9.2)	20	16 (16.5)	42	34 (11.6)
Arteriovenous fistula thrombosis	5	4 (2.0)	4	4 (4.1)	9	8 (2.7)
Hip fracture	3	3 (1.5)	0	0	3	3 (1.0)
Respiratory, thoracic and mediastinal disorders	27	21 (10.7)	9	6 (6.2)	36	27 (9.2)
Acute respiratory failure	7	7 (3.6)	2	2 (2.1)	9	9 (3.1)
Pulmonary oedema	7	6 (3.1)	1	2 (2.1)	8	7 (2.4)
Dyspnoea	4	4 (2.0)	1	1 (1.0)	5	5 (1.7)
Pleural effusion	4	3 (1.5)	0	6 (6.2)	4	3 (1.0)
Metabolism and nutrition disorders	18	17 (8.7)	21	10 (10.3)	39	27 (9.2)
Fluid overload	10	9 (4.6)	9	4 (4.1)	19	13 (4.4)
Hyperkalaemia	5	5 (2.6)	6	4 (4.1)	11	9 (3.1)

Hypoglycaemia	2	2 (1.0)	3	3 (3.1)	5	5 (1.7)
Vascular disorders	14	12 (6.1)	14	13 (13.4)	28	25 (8.5)
Nervous system disorders	16	13 (6.6)	12	9 (9.3)	28	22 (7.5)
General disorders and administration site conditions	10	9 (4.6)	6	6 (6.2)	16	15 (5.1)
Non-cardiac chest pain	5	5 (2.6)	2	2 (2.1)	7	7 (2.4)
Blood and lymphatic system disorders	8	7 (3.6)	5	5 (5.2)	13	12 (4.1)
Anaemia	5	4 (2.0)	4	4 (4.1)	9	8 (2.7)
Psychiatric disorders	11	6 (3.1)	3	2 (2.1)	14	8 (2.7)
Mental status changes	10	5 (2.6)	2	1 (1.0)	12	6 (2.0)
Musculoskeletal and connective tissue disorders	6	3 (1.5)	4	3 (3.1)	10	6 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3	2 (1.0)	1	1 (1.0)	4	3 (1.0)
Immune system disorders	2	2 (1.0)	1	1 (1.0)	3	3 (1.0)
Skin and subcutaneous tissue disorders	1	1 (0.5)	1	1 (1.0)	2	2 (0.7)
Investigations	0	0	2	2 (2.1)	2	2 (0.7)
Ear and labyrinth disorders	0	0	3	2 (2.1)	3	2 (0.7)

Table 104 Serious Adverse Events by Treatment Period – Study CDK-401

System Organ Class	TP1	TP2	TP3	TP4	TP5	TP6
			Ferumoxytol / Iron Sucrose			
Number of subjects	196/97	173/88	133/65	85 / 33	49 / 18	22 / 8
Overall	27(13.8) / 16(16.5)	26(15.0) / 14(15.9)	10(7.5) / 10(15.4)	8(9.4) / 8(24.2)	8 (16.3) / 7 (38.9)	5 (22.7) / 3 (37.5)
Blood and lymphatic system disorders	1 (0.5) / 2 (2.1)	2 (1.2) / 1 (1.1)	1 (0.8) / 0	0 / 1 (3.0)	0 / 1 (5.6)	0 / 0
Cardiac disorders	6 (3.1) / 2 (2.1)	3 (1.7) / 3 (3.4)	2 (1.5) / 7 (10.8)	1 (1.2) / 2 (6.1)	2 (4.1) / 0	2 (9.1) / 1 (12.5)
Gastrointestinal disorders	4 (2.0) / 4 (4.1)	1 (0.6) / 3 (3.4)	0 / 1 (1.5)	2 (2.4) / 1 (3.0)	0 / 1 (5.6)	1 (4.5) / 1
General disorders and administration site conditions	1 (0.5) / 1 (1.0)	1 (0.6) / 0	1 (0.8) / 2 (3.1)			
Hepatobiliary disorders	0 / 0	1 (0.6) / 0	0 / 0	0 / 0	1(2.0) / 0	0 / 0
Immune system disorders	1 (0.5) / 1 (1.0)	0 / 0	0 / 0			
Infections and infestations	9 (4.6) / 4 (4.1)	6 (3.5) / 5 (5.7)	3 (2.3) / 2 (3.1)	1 (1.2) / 1 (3.0)	3 (6.1) / 1 (5.6)	1 (4.5) / 2 (25.0)
Injury, poisoning and procedural complications	5 (2.6) / 2 (2.1)	5 (2.9) / 5 (5.7)	2 (1.5) / 2 (3.1)	1 (1.2) / 0	0 / 1 (5.6)	0 / 0
Investigations	0 / 1 (1.0)	0 / 0	0 / 0			
Metabolism and nutrition disorders	3(1.5) / 1 (1.0)	3 (1.7) / 2 (2.3)	2 (1.5) / 3 (4.6)	0 / 2 (6.1)	2 (4.1) / 2	1 (4.5) / 1
Musculoskeletal and connective tissue	0 / 2 (2.1)	2 (1.2) / 1 (1.1)	1 (0.8) / 1 (1.5)	1 (1.2) / 0	0 / 0	0 / 0
Neoplasms benign, malignant and	1 (0.5) / 1 (1.0)	0 / 0	0 / 0			
Nervous system disorders	3 (1.5) / 1 (1.0)	1 (0.6) / 0	1 (0.8) / 2 (3.1)	0 / 2 (6.1)	0 / 2 (11.1)	0 / 0
Psychiatric disorders	1 (0.5) / 0	3 (1.7) / 1 (1.1)	0 / 0	1 (1.2) / 0	1(2.0) / 1 (5.6)	0 / 0
Renal and urinary disorders	0 / 0	2 (1.2) / 0	0 / 0	0 / 0	0 / 0	1 (4.5) / 0
Respiratory, thoracic and mediastinal	3 (1.5) / 3 (3.1)	5 (2.9) / 2(2.3)	0 / 0	2 (2.4) / 1 (3.0)	0 / 0	0 / 0
Skin and subcutaneous tissue disorders	0 / 1 (1.0)	1 (0.6) / 0	0 / 0			
Vascular disorders	2 (1.0) / 2 (2.1)	3 (1.7) / 2 (2.3)	0 / 1 (1.5)	0 / 1 (3.0)	1(2.0) / 1 (5.6)	1 (4.5) / 0

Treatment-related SAE in CKD subjects

Across all CKD studies in the initial registrational programme, five subjects experienced a total of six treatment-related SAEs. Three subjects reported four SAEs considered related to treatment with ferumoxytol; one oral iron-treated subject and one subject who received placebo also reported a treatment-related SAE.

There were three ferumoxytol cases entailing either anaphylactic reaction or hypotension (AESI).

Post-marketing study CKD-201: There were two related SAEs in the FER-CKD-201 study. In the ferumoxytol treatment group, 1 event of anaphylactic reaction in 1 subject occurred on the same day as the subject's first dose of ferumoxytol. In the iron sucrose treatment group, 1 event of hypotension in 1 subject occurred on the same day as the subject's first dose of iron sucrose.

Post-marketing study CKD-401: There were no treatment-related SAEs for either treatment group.

3.2.7.4. Laboratory findings

Clinical chemistry, haematology, urinalysis, special tests

In CKD subjects, for Hgb and haematocrit, there were larger increases in ferumoxytol groups than in the oral iron group consistent with a greater therapeutic effect with ferumoxytol, and no safety issues related to maximum Hgb concentration or rate of rise in Hgb were observed. There were no clinically meaningful changes in WBC or platelet counts. The proportion of subjects with clinically significant abnormalities or with CTCAE Grade 2 or higher abnormalities did not identify significant safety issues related to ferumoxytol treatment.

For clinical chemistry values, Baseline abnormalities were consistent with the CKD population studied. Clinical chemistry values at Day 35 were judged clinically significant by the Investigator in generally similar proportions of subjects between ferumoxytol and oral iron groups and across ferumoxytol treatment regimens. There was no evidence of a significant reduction in serum phosphorus.

Liver function test elevations (defined as a change >50% of Baseline and above the ULN for alkaline phosphatase, ALT, AST, bilirubin, and GGT) were observed in 6.8% of subjects receiving a ferumoxytol first course, 5.8% receiving a ferumoxytol second course, 2.8% receiving oral iron and 4.2% receiving placebo. Similarly, any liver function test meeting CTCAE Grade 2 or higher were observed in 7.8% of subjects receiving a ferumoxytol first course, 13.0% receiving a ferumoxytol second course, 5.2% receiving oral iron and 7.0% receiving placebo. Most of the ferumoxytol cases were GGT abnormalities.

For iron panel values, the expected increases in serum ferritin, serum iron, and TSAT and decreases in TIBC were observed in subjects receiving iron therapy. The changes were generally greater with ferumoxytol than with oral iron treatment. Following each TP, post-Baseline iron, ferritin and TSAT values rose in both treatment groups, but was consistently higher in the iron sucrose treatment group compared to the ferumoxytol treatment group at all post-Baseline time points with the exception of the TSAT value for TP6. Total iron binding capacity (TIBC) decreased in both treatment groups in each TP except TP6 for iron sucrose.

Table 133.2.1 Laboratory Measures by Ferumoxytol Dosing Regimen - CKD Subjects - Safety Population

Serum Ferritin (ng/mL)

Ferumoxytol Dosing Regimen: Ferumoxytol 2x510 mg N=692

Visit	N	Mean	SD	Min	25th Percentile	Median	75th Percentile	Max
Lab Result								
DAY -10 VISIT	545	196.85	173.61	2.30	54.70	138.00	295.00	1169.0
DAY -5 VISIT	597	183.95	157.39	1.60	51.50	138.00	278.00	704.00
DAY 00 VISIT	21	305.73	253.49	2.00	89.00	209.00	520.00	713.80
DAY 07 VISIT	20	550.86	362.14	38.00	286.00	502.00	714.50	1496.0
DAY 14 VISIT	27	866.97	429.43	205.00	438.00	899.00	1188.0	1737.0
DAY 21 VISIT	650	676.41	334.98	51.90	408.00	650.50	885.00	2112.0
DAY 28 VISIT	21	679.32	414.56	93.00	270.00	696.20	1040.0	1450.0
DAY 35 VISIT	663	539.30	312.45	15.10	298.00	506.00	731.00	2482.0
DAY 42 VISIT	21	563.73	325.74	43.00	376.00	651.30	792.10	1063.0
DAY 49 VISIT	21	570.81	369.70	29.00	234.00	640.70	784.00	1451.0
DAY 56 VISIT	21	528.33	319.87	21.00	177.00	601.00	711.00	1044.0
Change from Baseline								
DAY 07 VISIT	20	328.08	317.91	0.00	149.00	271.15	477.35	1407.0
DAY 14 VISIT	27	594.55	296.52	203.00	334.00	547.00	828.00	1316.0
DAY 21 VISIT	650	490.88	269.39	-174.0	299.00	449.40	634.00	1530.0
DAY 28 VISIT	21	379.79	252.15	37.10	116.00	406.20	520.00	908.00
DAY 35 VISIT	663	354.11	244.31	-276.0	184.60	312.00	473.00	2004.0
DAY 42 VISIT	21	279.86	207.72	-14.90	92.00	288.00	410.00	601.10
DAY 49 VISIT	21	286.94	249.17	-45.90	134.00	245.00	401.00	1005.0
DAY 56 VISIT	21	244.46	216.61	-124.0	38.00	264.70	400.00	598.00

Vital signs and electrocardiography

In CKD Subjects, no clinically meaningful changes in blood pressure or heart rate were observed within the first hour after a first or second course of IV ferumoxytol injections. In subjects on dialysis, the changes in vital signs were associated with the dialysis procedure. There was no evidence of a consistent increase or decrease in blood pressure over time related to ferumoxytol dose.

No meaningful differences in AEs related to hypertension were observed in subjects receiving ferumoxytol, irrespective of dose, or oral iron.

For ferumoxytol-treated subjects, treatment with ESA was associated with a small increase in the proportion of subjects with SBP changes >30% of Baseline, although there was no clear relationship to weekly ESA dose. For subjects in the ferumoxytol and placebo groups, the incidence of SBP increases >30% of Baseline was associated with maximum haemoglobin values higher than 11 g/dL. In the ferumoxytol first course of treatment, subjects with maximum haemoglobin concentrations of <11 g/dL, 11 to <12 g/dL, 12 to <13 g/dL, and ≥13 g/dL had incidences of SBP increases >30% of Baseline of 2.4%, 5.6%, 2.6%, and 4.1%, respectively. A similar trend was observed for subjects treated with oral iron. These trends were not observed in subjects receiving a second course of ferumoxytol. Overall, there did not appear to be an increase in blood pressure related to therapeutic response.

There was no clinically meaningful difference in the incidence of abnormal physical examination findings (1) when subjects in the three pivotal efficacy and safety studies who were exposed to either 2 x 510 mg or 4 x 255 mg ferumoxytol were compared to subjects who received oral iron or (2) when subjects who received one course of ferumoxytol (any dose) were compared with those who received oral iron or placebo and (3) among subjects treated with a second course of ferumoxytol.

An increase in the incidence of abnormal physical examination findings was observed for some body systems with increasing dose of ferumoxytol, including general appearance, eyes, ears, nose, and throat, heart, and extremities.

In CKD-201: Similar changes in iron panel parameter as observed in the integrated analysis were observed in both treatment groups (comparator iron sucrose). Nevertheless substantially higher mean levels of ferritin were observed in the ferumoxytol group compared to the iron sucrose group at all post-

baseline time points, which also peaked sooner in the ferumoxytol group (Week 2, 886.7 ng/mL) than iron sucrose (Week 3, 598.7 ng/mL). Also mean iron levels and TSAT were higher in the ferumoxytol group at all post-baseline time points. TIBC, transferrin levels, and UIBC decreased in both treatment groups post-Baseline and were lower in the ferumoxytol group than the iron sucrose group at all post-Baseline time points.

Other laboratory values were comparable between treatment groups. The only difference observed was that mean values for GGT were higher in the ferumoxytol group than in the iron sucrose group at all study time points, although median values between the treatment groups remained similar throughout the study. This discrepancy might be due to one subject in the ferumoxytol group with extremely high GGT levels. Other measures of hepatic function were similar for the two treatment groups, and showed no clinically meaningful differences between the treatment groups or changes within the treatment groups over time.

In CKD-401: Similar observations as in the integrated analysis and study CDK-201 were made. A slight increase in mean ferritin levels are observed over time. No other trends or safety signals were identified.

3.2.7.5. Special populations

Paediatric population

Paediatric patients are not part of the intended indication.

Paediatric studies CKD 251/252 and CKD-253 were terminated, and paediatric studies AMAG-FER-CKD-354, and AMAG-FER-IDA-352 are ongoing.

Elderly patients

No discussion was provided by the Applicant

Renal impairment

Stage of CKD

In subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were similar across CKD stages 3 to 5D: 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 haemodialysis 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. CKD stages 3-4 generally did not appear to impact the safety profile of ferumoxytol relative to either oral iron (ie, the incidence of events was lower in ferumoxytol-treated subjects vs. oral iron-treated subjects) or placebo (ie, the incidence of events was higher or comparable in ferumoxytol-treated subjects relative to placebo-treated subjects). For CKD stage 1 or 2, incidences of related TEAEs and TEAEs leading to permanent discontinuation of study drug were higher in ferumoxytol-treated subjects than in oral iron-treated or placebo-treated subjects but the number of oral iron-treated (N=3) and placebo-treated (N=13) subjects available for analysis was small. For CKD stage 5D on PD, incidences of TEAEs and related TEAEs were higher in placebo-treated subjects than in ferumoxytol-treated or oral iron-treated subjects; events resulting in permanent discontinuation of study drug were higher in the ferumoxytol-treated subjects. None of the common TEAEs showed a difference in incidence between the ferumoxytol first course and either the placebo or oral iron treatment groups based on CKD stage. No clinically important relationships were found between the most commonly reported TESAEs and CKD stage for a first course of ferumoxytol vs. oral iron and placebo. No TESAEs occurred in subjects with CKD stage 1 or 2.

Kidney Transplant Status

In CKD subjects treated with a first course of ferumoxytol, the overall TEAE incidence rates were 33.7% in 904 subjects with native kidney function, 41.2% in 34 subjects with a functioning kidney transplant, and 30.9% in 624 subjects on dialysis. Kidney transplant status did not appear to impact the safety profile of ferumoxytol relative to either oral iron (ie, the incidence of events was lower in ferumoxytol-treated subjects vs. oral iron-treated subjects) or placebo (ie, the incidence of events was higher or comparable in ferumoxytol-treated subjects relative to placebo-treated subjects). None of the common TEAEs showed a difference in incidence between the ferumoxytol first course treatment group and either the placebo or oral iron group based on kidney transplant status categories. No clinically important relationships were found between the most commonly reported TESAEs and kidney transplant status for a first course of ferumoxytol vs. oral iron and placebo. After treatment with a first dose of ferumoxytol, incidences of cardiac disorders in general were similar (1.4%) for subjects with native kidney function (1.9%; N=904) or subjects on dialysis (1.6%; N=624), and incidences were similar for cardiac failure congestive (0.7% and 0.8%, respectively) and coronary artery disease (0.1% and 0.3%, respectively).

Hepatic impairment

A single AE related to abnormal laboratory tests of liver function was reported in the first course ferumoxytol group. Changes in serologic tests of liver function (alkaline phosphatase, ALT, AST, bilirubin, GGT) >50% of Baseline and above the normal range, and values of grade 2 or higher according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 1 were observed in all treatment groups. In general, CTCAE grade 2 or higher laboratory abnormalities were observed more commonly in the ferumoxytol first course group than in subjects taking oral iron (7.8% vs. 5.2%), but at a similar rate in subjects receiving placebo (7.8% vs. 7.0%). Among ferumoxytol-treated subjects, CTCAE grade 2 or higher values were seen more often after the second course for ALT and GGT. In all treatment groups, the most commonly observed serologic abnormalities were elevations of GGT.

Only a small number of subjects in any treatment group had a positive history of liver cirrhosis. Among those subjects with a history of cirrhosis, the incidence of abnormal liver function serology was higher than for subjects without a history of liver cirrhosis; this generalization held for all treatment groups. For subjects with no history of cirrhosis, subjects treated with the first course of ferumoxytol had generally higher incidence rates of serologic elevations than subjects treated with oral iron or placebo, with no important differences seen for subjects treated with the first and second course of ferumoxytol.

Subjects treated with ferumoxytol were approximately evenly divided into groups with maximum serum ferritin <500 ng/mL, 500 to 800 ng/mL, and >800 ng/mL. Changes in liver function tests to abnormal values >50% above Baseline and values of CTCAE grade 2 or higher after the first course were more common in subjects with a highest serum ferritin >800 ng/mL; this trend was also observed in subjects treated with placebo but not consistently observed in subjects treated with oral iron or in subjects evaluated after the second course of ferumoxytol. In each treatment group, nearly all subjects had maximum transferrin saturation <50%. The incidence of changes in liver-related serum tests in subjects with maximum saturations <50% and in the small number of subjects with maximum saturations ≥50% appeared similar.

Intrinsic Factors - age, gender, race and body weight

In CKD subjects treated with a first course of ferumoxytol, overall similar TEAE incidence rates were observed regarding subgroups for age, gender, race and body weight.

Haemoglobin

In general, Baseline Hgb levels did not appear to impact the safety profile of ferumoxytol relative to placebo.

The rate of Hgb increase did not appear to impact the safety profile of ferumoxytol relative to either oral iron (ie, the incidence of events remained lower in ferumoxytol-treated subjects vs. oral irontreated subjects) or placebo (ie, the incidence of events remained higher in ferumoxytol-treated subjects relative to placebo-treated subjects).

Small differences in the incidences of cardiac disorders in general (17 subjects [1.4%]), and specifically cardiac failure congestive (9 subjects [0.8%]) and coronary artery disease (3 subjects [0.3%]), were observed at an increase in Hgb of <0.5 g/dL per week compared with two TESAEs of cardiac failure congestive in two subjects (0.7%) at an increase of 0.5 to <1.0 g/dL per week, and no TESAEs of coronary artery disease. Three of four TESAEs of chest pain occurred in three subjects (0.3%) at an increase in Hgb of <0.5 g/dL per week; the other occurred in one subject (0.4%) at an increase of 0.5 to <1.0 g/dL per week. For rate of Hgb increase ≥1.0 g/dL per week, there were no cardiac TESAEs.

Serum Ferritin

In CKD subjects treated with a first course of ferumoxytol, there was no consistent increase or decrease in incidence rates of overall TEAEs by Baseline serum ferritin: 33.8% in the <150 ng/mL subgroup; 30.9% in the 150 to <300 ng/mL subgroup; 30.6% in the 300 to <450 ng/mL subgroup; and 35.6% in the ≥ 450 ng/mL subgroup. Baseline serum ferritin levels generally did not appear to impact the safety profile of ferumoxytol relative to either oral iron (ie, the incidence of events was generally lower in ferumoxytol-treated subjects vs. oral iron-treated subjects) or placebo (ie, the incidence of events was generally higher in ferumoxytol-treated subjects relative to placebo-treated subjects).

None of the common TEAEs in subjects treated with a first course of ferumoxytol showed a difference in incidence between the ferumoxytol first course and the oral iron or placebo treatment groups based on Baseline serum ferritin concentration. No clinically important relationships were found between the most commonly reported TESAEs and Baseline serum ferritin levels for a first course of ferumoxytol vs. oral iron and placebo.

Transferrin Saturation

In CKD subjects treated with a first course of ferumoxytol, overall TEAE incidence rates tended to decrease with increasing Baseline TSAT: 36.4% in the <10% subgroup; 31.6% in the 10% to <25% subgroup; 29.3% in the 25% to <50% subgroup; and 0% in the ≥ 50% subgroup. A similar trend was observed for oral-iron treated subjects (59.6%, 50.6%, 47.8%, and 0% with increasing Baseline TSAT levels); however, across subgroups, subjects treated with a first course of ferumoxytol consistently had lower incidence rates relative to subjects treated with oral iron. Baseline TSAT levels did not appear to impact the safety profile of ferumoxytol relative to either oral iron (ie, the incidence of events remained lower in ferumoxytol-treated subjects vs. oral iron-treated subjects) or placebo (ie, the incidence of events remained higher or comparable in ferumoxytol-treated subjects relative to placebo-treated subjects). None of the common TEAEs showed a difference in incidence between the ferumoxytol first course treatment group and the placebo group based on Baseline TSAT. No clinically important relationships were found between the most commonly reported TESAEs and Baseline TSAT for a first course of ferumoxytol vs. oral iron and placebo. All of the TESAEs commonly reported with a first course of ferumoxytol treatment occurred at Baseline TSAT levels of <10% (N=511), and 10% to <25% (N=873). One TESAE of renal failure chronic (1 subject [0.6%]) and one TESAE of hypoglycaemia (1

subject [0.6%]) occurred at a Baseline TSAT of 25% to <50% (N=167); none occurred at a TSAT ≥ 50% (N=4).

3.2.7.6. Safety related to drug-drug interactions and other interactions

In the initial programme in CKD no formal studies to evaluate the interaction of ferumoxytol with other medications were performed.

In Study AMAG-FER-CKD-401 no analyses to examine drug-drug interactions were performed.

Discussions of TEAEs of special interest by various concomitant therapies (including ACE inhibitors and beta blockers, average weekly ESA dose, and anticoagulants) are presented for CKD subject.

General Effect of Average Weekly Erythropoiesis Stimulating Agents (ESA) Dose

In CKD 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 ≥ 40,000 units/week

Hypersensitivity

ACE inhibitors and/or beta-blockers

In CKD patients, in the four ferumoxytol dose groups, incidences of TEAEs associated with acute hypersensitivity, including events related to changes in blood pressure, were similar for subjects treated and not treated with ACE inhibitors and/or beta-blockers.

Thrombotic events

Average Weekly ESA Dose

Among ferumoxytol-treated subjects, the incidence of thrombotic events increased with the dose of ESA. But this trend is based on a very small number of events.

Incidences of any thrombotic event in subgroups treated with:

- No treatment: 0.2% (1 event)
- <20,000 units/week: 1.1% (5 events),
- 20,000 to <40,000 units/week: 3.9% (6 events),
- ≥40,000 units/week: 17.6% (3 events),

No similar trend was evident in subjects treated with the ferumoxytol second course or in subjects treated with oral iron; no placebo subjects were analyzed by ESA dose.

Anticoagulants

Among ferumoxytol-treated subjects, the incidence of thrombotic events was higher among subjects treated with concurrent anticoagulants (1.5%, compared to 0.5% for subjects on no anticoagulants); this trend was not apparent for subjects treated with oral iron or placebo. A single thrombotic event was observed among subjects treated with the ferumoxytol second course, in a subject taking anticoagulants.

3.2.7.7. Discontinuation due to adverse events

Permanent Treatment Discontinuation: In the three Phase III pivotal safety and efficacy studies (Protocols 62,745-5, 62,745-6, and 62,745-7), there was a lower incidence of TEAEs leading to permanent discontinuation of study treatment with 2 x 510 mg ferumoxytol (1.8%) than with oral iron (9.3%) or with 4 x 255 mg ferumoxytol (5.0%).

Temporary Treatment Discontinuation: In the three Phase III pivotal safety and efficacy studies (Protocols 62,745-5, 62,745-6, and 62,745-7), there was a lower incidence of temporary discontinuation of study treatment with 2 x 510 mg ferumoxytol (1.2%) compared with oral iron (3.6%). One TEAE in one subject (1.7% of 60 subjects) treated with 4 x 255 mg ferumoxytol resulted in temporary discontinuation of study treatment.

Post-marketing study CKD-201: Overall (N=162), 5 (3.1%) subjects each had a TEAE that resulted in temporary discontinuation of study medication, 2/80 (2.5%) subjects in the ferumoxytol group and 3/83 (1.2%) subjects in the iron sucrose group. In the ferumoxytol group, 1 was discontinued from study drug due to a related, serious TEAE of anaphylactic reaction. The subject was permanently discontinued from study drug and was withdrawn from the study. In the iron sucrose group, 1 female subject had 1 TEAE that led to permanent study drug discontinuation but not study withdrawal, and 4 male subjects had a total of 5 TEAEs that led to permanent discontinuation of study medication and withdrawal from the study.

Post-marketing study CKD-401

Permanent Discontinuation of Study Drug: Eight subjects in the ferumoxytol group (4.1%) and no subjects in the iron sucrose group were permanently discontinued from the study drug due to AEs. AEs leading to study permanent study drug discontinuation or study discontinuation were also seen mostly in TP1 and TP2.

Temporary Discontinuation of Study Drug: Two subjects in the ferumoxytol group and 3 subjects in the iron sucrose group were temporarily discontinued from the study drug.

Clinical safety in all-cause IDA patients

Initial IDA studies

Pivotal studies IDA- 301 and IDA-302 have already been presented to the EMA as a part of variation to extend the indication to patients with all-cause IDA. The Applicant has pooled together results from studies 301, 302 and 303 and presented them in 3 different integrated analyses, due to the differences of the studies:

Primary IAS:

- Pooled, pivotal safety data from the 2 randomised, controlled phase 3 studies in IDA patients (IDA-301 and IDA-302), which is termed the Initial Treatment Pool.

Secondary IAS:

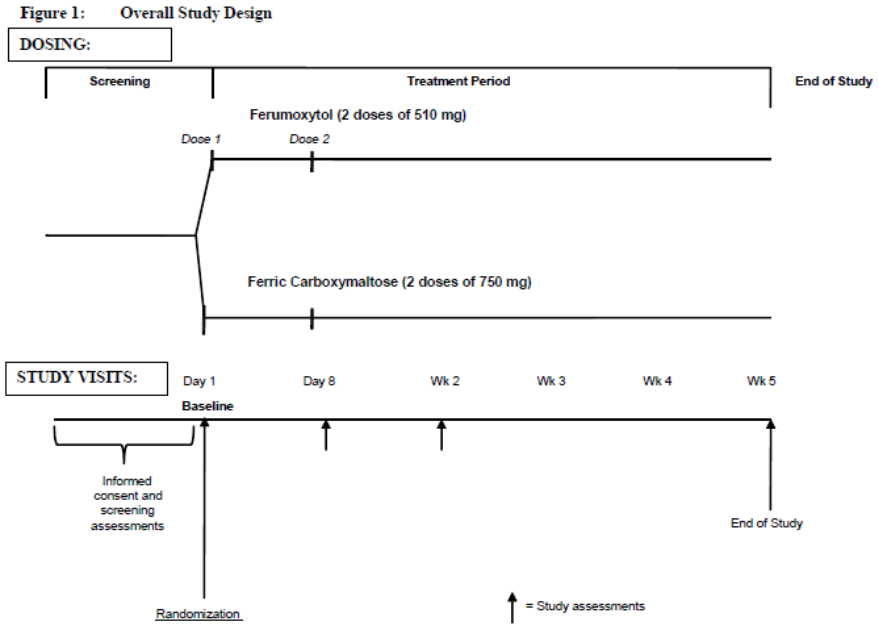
- Pooled safety data from IDA patients from both the randomised, controlled phase 3 study (IDA-301) and the Extension Study (IDA-303), which is termed the Repeat Treatment Pool; this analysis provided follow-up safety data on patients over approximately 7 months (5 weeks in IDA-301, with a 2-week window for rollover, and 6 months follow up in IDA-303) on repeat dosing.

- Pooled, safety data from the 2 randomised, controlled studies of ferumoxytol vs iron sucrose in IDA patients (IDA-302) and in IDA patients with CKD (CKD-201), which is termed the Active Comparator Pool.

The safety study IDA-304 was conducted at a later stage, following safety concerns regarding hypersensitivity reactions. This study was also the first study to investigate the new method of administration i.e. slow infusion in lieu of a rapid injection, which has been used in previous studies. Results from this study have been presented separately by the Applicant and are discussed separately in this report.

Study IDA-304 was a Phase III, randomized, double-blind, multicenter, safety study of 1.020 g of IV ferumoxytol, administered as 2 doses of 510 mg each, compared to 1.500 g of IV FCM, administered as 2 doses of 750 mg each for the treatment of iron deficiency anemia.

Figure 1: Overall Study Design



Mechanisms of Hypophosphatemia Sub-Study

Up to 180 subjects (1:1 ratio to receive either ferumoxytol or FCM) were to be enrolled in the Sub-Study. This substudy was conducted with the aim of gaining additional understanding of the underlying mechanisms associated with changes in phosphorus that occur in patients with iron deficiency anemia of any etiology.

Study participants

Main inclusion criteria:

1. Males and females ≥18 years of age
2. Subjects with IDA and in whom intravenous iron treatment was indicated and defined as:
   a) Subjects with documented hemoglobin <12.0 g/dL for females and <14.0 g/dL for males within 60 days of dosing
   And
   b) Subjects with documented TSAT ≤20% or Ferritin ≤100 ng/mL within 60 days of dosing

3. Documented history of unsatisfactory oral iron therapy or in whom oral iron could not be tolerated, or in whom oral iron was considered medically inappropriate (as per oral iron history questionnaire)
Information on whether oral iron was medically inappropriate was collected as per an oral iron history questionnaire that documented information on past use of oral iron, any side effects experienced, whether or not it was effective, or if the subject had a medical condition for which oral iron was not medically indicated.

Main exclusion criteria:

1. Known hypersensitivity reaction to any component of ferumoxytol or FCM
2. History of allergy to an IV iron
3. History of multiple drug allergies
4. Subjects with dialysis dependent CKD
5. Hemoglobin ≤7.0 g/dL
6. Female subjects who were pregnant, intended to become pregnant, were breastfeeding, had a positive serum/urine pregnancy test or were not willing to use effective contraceptive precautions during the study (including females of childbearing potential who were partners of male subjects)
7. Subject had either baseline measurement of SBP of ≤90 mm Hg or DBP of ≤60 mm Hg
8. Subjects weighing less than 50 kg or 110 lbs

Treatments

Subjects randomized to ferumoxytol received intravenous infusion of ferumoxytol 510 mg diluted (17 mL) in 233 mL 0.9% sodium chloride injection, USP (normal saline) to a final volume of 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.020 g.

Subjects randomized to FCM received intravenous infusion of FCM 750 mg diluted (15 mL) in 235 mL 0.9% sodium chloride injection, USP (normal saline) to a final volume 250 mL, over at least 15 minutes with a second dose 7-8 days after Dose 1, for a total cumulative dose of 1.500 g.

In previous studies, ferumoxytol was administered as a rapid injection (which was associated with an increased risk of hypersensitivity reactions and lead to the change to the Prescribing Information as of March 2015). This study was intended to provide the first prospective data on the administration of ferumoxytol via a method other than rapid injection (i.e., two diluted infusions over at least 15 minutes each). The dose delivered in this study remained 1.020 g, as in previous studies.

Objectives

Primary Safety Objective

- To assess the incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, and of moderate to severe hypotension with ferumoxytol as compared to FCM

The null and alternative hypotheses are expressed as:

H0: P1≥P0+0.0264 versus Ha: P1<P0+0.0264

Where P1 and P0 are the true primary endpoint rates in the ferumoxytol group and the FCM group, respectively, and 0.0264 is the NI margin. This margin has been calculated based on the AE rate of the primary endpoint (3.3%) in IDA sNDA studies (IDA301 and IDA302). Details on how the NI margin has been derived from the AE rates are provided in the 'sample size' section.

NI was to be concluded if the upper limit of the 95% CI of the treatment difference of ferumoxytol minus FCM does not exceed the non-inferiority margin of 0.0264 (or 2.64%) for the primary safety endpoint.

Secondary Safety Objective

- To assess the incidence of the composite safety endpoint of moderate to severe hypersensitivity reactions, serious cardiovascular events, and death for ferumoxytol as compared to FCM

The null and alternative hypotheses are expressed as:

H0: P1≥P0+0.036 versus Ha: P1<P0+0.036

Where P1 and P0 are the secondary endpoint rates in the ferumoxytol group and the FCM group, respectively, and 0.036 is the non-inferiority margin. This margin has been calculated based on the AE rate of the secondary endpoint (4.5%) in IDA sNDA studies (IDA301 and IDA302). Details on how the NI margin has been derived from the AE rates are provided in the 'sample size' section.

Non-inferiority was to be concluded if the upper limit of 95% CI of the treatment difference of ferumoxytol minus FCM does not exceed the NI margin of 0.036 (or 3.6%).

Outcomes/endpoints

Primary Endpoint

- the incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, and of moderate to severe hypotension.

The primary endpoint will be the composite of the above events adjudicated as cases by the Clinical Events Committee (CEC).

Signs and symptoms potentially representing hypersensitivity, including erythema, pruritus, urticaria (hives, welts, wheals), flushing, dyspnea, wheezing, bronchospasm, tachypnea, chest tightness, stridor, rapid onset edema (facial, laryngeal, pharyngeal), chest pain, syncope, dizziness, abdominal or back pain and anxiety, will be recorded and adjudicated by a blinded Clinical Events Committee (CEC).

Anaphylaxis will be categorized based on the criteria of Sampson et al, 2006.

Secondary Endpoints

- incidence of the composite safety endpoint of moderate to severe hypersensitivity reactions, including anaphylaxis, serious cardiovascular events, and death.

Sample size

The sample size determination was based on the NI test on the primary safety endpoint assuming a 0.0264 (or 2.64%) NI margin in rate difference. The null and alternative hypotheses can be stated as follows:

H0: P1≥P0+D versus Ha: P1<P0+D

Where P1 and P0 are the primary AE rates (primary safety endpoint) in the ferumoxytol group and the FCM group, respectively, and D is the NI margin. Based on the IDA sNDA studies (IDA301 and IDA302) of ferumoxytol, the AE rate of the primary endpoint is about 3.3%.

Given an assumed 3.3% rate for the primary safety endpoint in both treatment groups, a sample of 2000 subjects in the study will provide approximately 90% power for the non-inferiority test at significance level of 0.025 with a 2.64% NI margin in rate difference (RR=1.8). The sample size calculation was based on large sample assumptions.

For the analysis of mechanisms of hypophosphatemia, due to its exploratory nature, no formal sample size calculation was performed. A sample size of up to 180 was considered sufficient for the study based on previous FCM studies as described in the study protocol.

Non-inferiority margin justification

The Food and Drug Administration (FDA) Guidance on NI trials suggests two key approaches to calculate a NI margin by using either the Rate Difference or the Rate Ratio. Because the estimated event rate for this trial is low (3.3% for the primary safety endpoint and 4.5% for the secondary safety endpoint) it is more appropriate to use the Rate Difference as a basis for the calculation of the NI margin. Rate Ratios become unstable and less informative for low event rates and cannot be used in comparisons where no events are reported in the control group.

In summary, the analyses of the primary and secondary safety endpoints will be based on NI tests between ferumoxytol and FCM. Given the expected overall low rate of events, the NI margin of 4%-5% deemed appropriate in prior studies (e.g., FCM REPAIR-IDA trial), may be too wide for this trial. Therefore a conservative NI margin of 2.64% (which is 1.8 on relative risk) is proposed for the primary safety endpoint and 3.6% (which is 1.8 on relative risk) for the secondary safety endpoint.

For the efficacy NI margin 0.5 g/dL is used.

Interim Analyses

No formal interim statistical analysis was planned.

Randomisation

Eligible subjects were randomized in a 1:1 ratio to receive either ferumoxytol (n=1000) or FCM (n=1000).

Blinding (masking)

This study was double-blind with respect to treatment assignment; all study participants (ie, subject, study staff including the physician, and all non-study individuals) with the exception of the test article preparer (TAP) and the unblinded monitor were blinded to the treatment assigned to each subject.

Statistical methods

Analysis populations

The Safety Population included any randomized subject who received any amount of study drug. All safety analyses were performed on the Safety Population; the treatment group was based on actual treatment.

Adjustment for Multiple Comparisons

To control the familywise type-I error rate, the hypothesis tests will be performed at two-sided 0.05 level of significance sequentially in the following order:

1) NI test on the primary safety endpoint (incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, or moderate to severe hypotension)

2) NI test on the second efficacy endpoint (Hemoglobin change per gram of iron administered from baseline to Week 5).

3) NI test on the first efficacy endpoint (Hemoglobin change from baseline to Week 5).

4) Superiority test on the second efficacy endpoint (Hemoglobin change per mg of iron administered from baseline to Week 5).

5) Superiority test on the first efficacy endpoint (Hemoglobin change from baseline to Week 5).

6) NI test on the second safety endpoint.

Once a hypothesis test was non-significant, the remaining analyses were to be viewed as descriptive.

Based on data from the literature and post marketing experience, the event rate for the second safety endpoint is likely to be very low leading to underpowered comparison. For these reasons, the sequential order of the hypothesis tests listed in protocol have been adjusted here for the order of the hypothesis tests.

Participant flow

This was a multicenter global study conducted at 129 study sites in the US (101 sites), Canada (3 sites) and Europe including Latvia (9 sites), Lithuania (7 sites), Hungary (5 sites), Poland (4 sites) between 29 February 2016 and 16 January 2017.

Table 105: Overall Subject Disposition- Safety Population

Subject Disposition	Treatment Group		Total N=1997
	Ferumoxytol N=997	FCM N=1000	
	n (%)	n (%)	n (%)
Safety Population	997 (100.0)	1000 (100.0)	1997 (100.0)
Early Discontinuation from Study	30 (3.0)	36	66 (3.3)
Reason for discontinuation:			
Adverse event	16 (1.6)	23 (2.3)	39 (2.0)
Pregnancy	1 (0.1)	0	1 (0.1)
Investigator Discretion	1 (0.1)	0	1 (0.1)
Subject request	12 (1.2)	13 (1.3)	25 (1.3)
Completed Study	935 (93.8)	948 (94.8)	1883 (94.3)
Early Withdrawal from Study	62 (6.2)	52 (5.2)	114 (5.7)
Reason for Withdrawal:			
Adverse event	10 (1.0)	9 (0.9)	19 (1.0)
Withdrawal of consent	22 (2.2)	19 (1.9)	41 (2.1)
Lost to follow-up	14 (1.4)	17 (1.7)	31 (1.6)
Death**	4 (0.4)	1 (0.1)	5 (0.3)*
Others	12 (1.2)	6 (0.6)	18 (0.9)

A subject completed the study if the subject had a Week 5 End of Study visit.

*There were a total of six deaths, one subject assigned to Ferric Carboxymaltose experienced an adverse event which lead to death. This subject was withdrawn from study prior to date of death and not included in this table. All six deaths are accounted for in safety analyses.

**All deaths were assessed as non-related to study drug by the Investigator. Data Source: Table 14.1.2.2

Baseline data

Table 6: Summary of Baseline Characteristics (Safety Population)

Baseline Characteristics	Treatment Group		Total N=1997
	Ferumoxytol N=997	FCM N=1000	
Age (years)			
Mean ± SD	55.6 (17.30)	54.8 (17.02)	55.2 (17.16)
Median (range)	53.0 (19, 95)	53.0 (18, 96)	53.0 (18, 96)
Age Group (years) [n (%)]			
age <45	297 (29.8)	308 (30.8)	605 (30.3)
45<= age <55	222 (22.3)	215 (21.5)	437 (21.9)
55<= age <65	138 (13.8)	163 (16.3)	301 (15.1)
65<= age <75	173 (17.4)	173 (17.3)	346 (17.3)
age >=75	167 (16.8)	141 (14.1)	308 (15.4)
Gender, n (%)			
Male	254 (25.5)	224 (22.4)	478 (23.9)
Female	743 (74.5)	776 (77.6)	1519 (76.1)
Race, n (%)			
White	711 (71.3)	715 (71.5)	1426 (71.4)
Black	237 (23.8)	232 (23.2)	469 (23.5)
Others	49 (4.9)	53 (5.3)	102 (5.1)
Asian	32 (3.2)	29 (2.9)	61 (3.1)
American Indian or Alaska Native	6 (0.6)	3 (0.3)	9 (0.5)
Native Hawaiian or Other Pacific Islander	0	2 (0.2)	2 (0.1)
Not Reported	3 (0.3)	4 (0.4)	7 (0.4)
Other	8 (0.8)	15 (1.5)	23 (1.2)
Ethnicity, n (%)			
Hispanic and/or Latino	150 (15.0)	187 (18.7)	337 (16.9)
Not Hispanic and/or Latino	833 (83.6)	800 (80.0)	1633 (81.8)
Not Reported	14 (1.4)	13 (1.3)	27 (1.4)
Weight (kg)			
Mean ± SD	84.26 (24.863)	85.84 (26.045)	85.05 (25.467)
Median (range)	79.30 (44.0, 250.0)	80.40 (50.0, 252.0)	79.95 (44.0, 252.0)
Weight (kg) Group n [%]			
< 60	125 (12.5)	126 (12.6)	251 (12.6)
60 to < 75	265 (26.6)	276 (27.6)	541 (27.1)
75 to < 95	350 (35.1)	297 (29.7)	647 (32.4)
>= 95	257 (25.8)	300 (30.0)	557 (27.9)
Country [n (%)]			
Canada	20 (2.0)	15 (1.5)	35 (1.8)
Hungary	19 (1.9)	15 (1.5)	34 (1.7)
Latvia	57 (5.7)	65 (6.5)	122 (6.1)
Lithuania	60 (6.0)	51 (5.1)	111 (5.6)
Poland	17 (1.7)	17 (1.7)	34 (1.7)
United States	824 (82.6)	837 (83.7)	1661 (83.2)
Baseline Hemoglobin [g/dL]			
n	997	1000	1997
Mean (SD)	10.42 (1.478)	10.39 (1.458)	10.40 (1.468)
Median	10.40	10.50	10.40
Q1, Q3	9.50, 11.40	9.45, 11.30	9.50, 11.40
Min, Max	6.3, 14.2	5.2, 20.0	5.2, 20.0

Data Source: Table 14.1.3.2, Listing 16.2.4.1

Table 14.1.4.3
Distribution of Investigator Identified Subject Underlying Conditions
Safety Population

Underlying Condition	Ferumoxytol (N=997) n (%)	Ferric Carboxymaltose (N=1000) n (%)	Overall (N=1997) n (%)
Chronic Kidney Disease	267 (26.8%)	265 (26.5%)	532 (26.6%)
Abnormal Uterine Bleeding	248 (24.9%)	243 (24.3%)	491 (24.6%)
Gastrointestinal Disorders	284 (28.5%)	298 (29.8%)	582 (29.1%)
Cancer	24 (2.4%)	21 (2.1%)	45 (2.3%)
Others	90 (9.0%)	92 (9.2%)	182 (9.1%)
Unknown	84 (8.4%)	81 (8.1%)	165 (8.3%)

Numbers analysed

Table 5: Subject Population (All Randomized Subjects)

Subject Population	Treatment Group		Total (N=2014)
	Ferumoxytol N=1006	FCM N=1008	
	n (%)	n (%)	n (%)
Randomized	1006 (100.0)	1008 (100.0)	2014 (100.0)
Safety Population	997 (99.1)	1000 (99.2)	1997 (99.2)
ITT Population	997 (99.1)	1000 (99.2)	1997 (99.2)
Excluded Subjects from ITT and Safety population (not treated)	9 (0.9%)	8 (0.8%)	17 (0.8%)
Evaluable Population	843 (84.6)	883 (88.3)	1726 (86.4)
Excluded from Evaluable Population*	154 (15.4)	117 (11.7)	271 (13.6)
Reason for Exclusion:			
No valid Baseline/Week 5 Hgb data*	121 (12.1)	85 (8.5)	206 (10.3)
Did not take two full doses or received study drug not as randomized *±	52 (5.2)	55 (5.5)	107 (5.4)
Not met all incl/excl criteria	12 (1.2)	10 (1.0)	22 (1.1)
Significant protocol violations/deviations	53 (5.3)	44 (4.4)	97 (4.9)
Evaluation of the Mechanisms of Hypophosphatemia Sub-Study Evaluable Population	87 (8.6)	98 (9.7)	185 (9.2)
Withdrawal from Study Prior to Study Drug Dosing	9 (0.9)	8 (0.8)	17 (0.8)
Reasons for Withdrawal Prior to Study Drug Dosing:			
Lost To Follow-Up	1 (0.1)	0	1 (0.0)
Withdrawal Of Consent	1 (0.1)	0	1 (0.0)
Other	7 (0.7)	8 (0.8)	15 (0.7)

* Percentage calculated for the ITT population. Regarding dosing, 16 subjects did not receive full Dose 1 and 100 subjects did not receive full Dose 2 (Table 8).

3.2.7.8. Patient exposure

Table 10 Overall Cumulative Subject Exposure in Completed IDA Clinical Trials

Treatment	Number of Subjects
Ferumoxytol	2162
Ferric Carboxymaltose (FCM)	1000
Iron sucrose	199
Placebo	200

All-cause IDA studies included: IDA-301, IDA-302, IDA-303, IDA-304.
Note: Subjects may be counted more than once across treatment groups due to subjects randomised to placebo in study AMAG-FER-IDA-301 who then received ferumoxytol in the open-label extension study AMAG-FER-IDA-303.

The number of subjects who received more than 1 course (2 doses) of ferumoxytol is following:

- Ferumoxytol Treatment Course 2 (N=244).
- Ferumoxytol Treatment Course 3 (N=69).
- Ferumoxytol Treatment Course 4 (N=18).
- Ferumoxytol Treatment Course 5 (N=4).

3.2.7.9. Adverse events

Initial IDA studies (301, 302, 303)

Integrated Analysis Initial treatment pool (301 and 302)

This analysis included a total of 1413 subjects who received study drug across the 3 treatment groups:

- Total ferumoxytol treatment group (N=1014).
- Iron sucrose treatment group (N=199).
- Placebo treatment group (N=200).

Overview of TEAEs

Table 52 Overview of TEAEs:IDA-301, IDA-302, and Initial Treatment Pool (IDA-301 and IDA-302)

AE category	IDA-301 Ferumoxytol N=608		IDA-302 Ferumoxytol N=406		Total Ferumoxytol N=1014		Placebo N=200		Iron Sucrose N=199	
	Events N	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
All AEs	718	299 (49.2)	360	168 (41.4)	1078	467 (46.1)	206	86 (43.0)	224	88 (44.2)
Related AEs (a)	176	89 (14.6)	115	58 (14.3)	291	147 (14.5)	25	15 (7.5)	73	32 (16.1)
SAEs	23	16 (2.6)	24	17 (4.2)	47	33 (3.3)	6	6 (3.0)	6	5 (2.5)
Related SAEs (a)	4	4 (0.7)	5	2 (0.5)	9	6 (0.6)	0	0	0	0
AESI					11	10 (1.0)	0	0	1	1 (0.5)
Hypotension (b)	--	--	--	--	6	6 (0.6)	0	0	1	1 (0.5)
Hypersensitivity reactions (c)	--	--	--	--	5	4 (0.4)	0	0	0	0
Composite cardiovascular endpoint AE (d)	6	5 (0.8)	5	4 (1.0)	11	9 (0.9)	0	0	4	2 (1.0)
AEs resulting in study drug withdrawal	17	12 (2.0)	11	6 (1.5)	28	18 (1.8)	2	1 (0.5)	8	5 (2.5)
Deaths	2	2 (0.3)	1	1 (0.2)	3	3 (0.3)	1	1 (0.5)	0	0

Source: IAS Table 2.1.1.1, IAS Table 2.1.14.1, and IDA-301 Table 14.3.1.1.2.1, IDA-302 Table 14.3.1.1.2.1.
(a) Per investigator.
(b) Includes moderate to severe hypotension occurring on the day of dosing. Hypotension is based on a TMQ, only applicable for pooled analysis.
(c) Includes moderate to severe hypersensitivity reactions occurring within 48 hours postdose. Hypersensitivity reactions are based on severe cutaneous adverse reactions SMQ, angioedema SMQ, and anaphylactic reaction SMQ. This was only applicable for the pooled analysis.
(d) Include nonfatal myocardial infarction, heart failure, moderate-to-severe hypertension, and hospitalization due to any cardiovascular cause.

When analysed by SOC, the highest occurrence of TEAEs in the ferumoxytol group for this pool was in the SOC GI disorders (11.8%), followed by nervous system disorders (11.0%), and infections /infestations (9.1%). The PTs with the highest incidence in the GI-SOC were nausea (39 subjects, 3.8%), diarrhoea (21 subjects, 2.1%), vomiting (16 subjects, 1.6%), and abdominal pain (15 subject, 1.5%), and for the nervous system headache (54 subjects, 5.3%), dizziness (33 subjects, 3.3%), and dysgeusia (18 subjects, 1.8%). For infections/infestations SOC the most frequent PTs were urinary tract infection (19 subjects, 1.9%) and nasopharyngitis (18 subjects, 1.8%). Hepatobiliary disorders were only recorded in the ferumoxytol group (in 0.6% of subjects 8/1014).

The most common related TEAEs occurring in ≥1% of subjects treated with ferumoxytol (vs. placebo vs. iron sucrose) were: headache (2.1%; 0.5%; 1.0%), nausea (2.0%; 1.0%; 2.0%), dysgeusia (1.4%; 0.5%; 6.5%), dizziness (1.3%; 1.5%; 1.0%), and chest discomfort (1.0%; 0.0%; 1.0% respectively).

By severity

Table 55 **Number and Percent of Subjects with Mild, Moderate, and Severe TEAEs: Initial Treatment Pool (IDA-301 and IDA-302)**

TEAE Severity	Treatment Group: Ferumoxytol (N=1014)		Placebo (N=200)		Iron Sucrose (N=199)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
ALL TEAEs	**1078**	**467 (46.1)**	**206**	**86 (43.0)**	**224**	**88 (44.2)**
Mild	729	256 (25.2)	127	37 (18.5)	174	58 (29.1)
Moderate	322	188 (18.5)	62	38 (19.0)	42	24 (12.1)
Severe	27	23 (2.3)	17	11 (5.5)	8	6 (3.0)

Source: IAS Table 2.1.8.1, IAS Table 2.1.1.1.

Integrated analysis Repeat Treatment Pool (Studies 301 and 303)

The proportion of subjects with TEAEs within 42 days of the first injection for each treatment course was higher in Treatment Course 1 (46.6%, 354 of 759 subjects) compared with subsequent courses, i.e. 29.1% for Course 2, 29.0% for Course 3, 16.7% for Course 4, and 25.0% for Course 5.

Table 64 **Overview of TEAEs Within 42 Days of the First Injection of Each Treatment Course: Pooled Data From IDA-301 and IDA-303 (Safety Population)**

TEAE Category	Ferumoxytol Treatment Group: Course 1 (N=759)		Course 2 (N=244)		Course 3 (N=69)		Course 4 (N=18)		Course 5 (N=4)	
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
All AEs	836	354 (46.6)	162	71 (29.1)	44	20 (29.0)	9	3 (16.7)	1	1 (25.0)
Related AEs (a)	204	107 (14.1)	26	13 (5.3)	3	2 (2.9)	0	0	0	0
Serious AEs	30	21 (2.8)	9	7 (2.9)	3	3 (4.3)	1	1 (5.6)	1	1 (25.0)
Related SAEs (a)	4	4 (0.5)	0	0	0	0	0	0	0	0
AESI										
Hypotension (b)	7	7 (0.9)	0	0	0	0	0	0	0	0
Hypersensitivity reactions (c)	3	3 (0.4)	0	0	0	0	0	0	0	0
Composite cardiovascular endpoint AE (d)	5	5 (0.7)	1	1 (0.4)	1	1 (1.4)	1	1 (5.6)	0	0
AEs resulting in study drug withdrawal	19	14 (1.8)	0	0	2	2 (2.9)	0	0	1	1 (25.0)
Deaths	1	1 (0.1)	0	0	0	0	0	0	0	0

Source: IAS Table 2.2.1.1.2.
Note: Percentages are based on the number of subjects in each treatment group.
Note: Only treatment emergent AEs with onset date and time on or after the first dose date and time and within 42 days of the first dose in each course are included.
Note: For subjects who had a hypotension event and an SBP drop of ≥30%, only the hypotension event is included in this table.
Note: Related AEs are those events with relationship classified by investigator as related to study drug.

(a) Per investigator.
(b) Includes moderate to severe hypotension occurring on the day of dosing. Hypotension is based on a TMQ, only applicable for pooled analysis.
(c) Includes moderate to severe hypersensitivity reactions occurring within 48 hours postdose. Hypersensitivity reactions are based on severe cutaneous adverse reactions SMQ, angioedema SMQ, and anaphylactic reaction SMQ, only applicable for pooled analysis.
(d) Include nonfatal myocardial infarction, heart failure, moderate-to-severe hypertension, and hospitalization due to any cardiovascular cause.

Study 304

Summary of treatment emergent adverse events (TEAEs)

A TEAE was defined as an event with an onset or worsening date and time on or after the first dosing start date and time, or on or after the first dosing start date if the onset time was missing.

The proportion of subjects reporting TEAEs and related TEAEs was numerically lower in the ferumoxytol group compared to FCM (TEAEs- ferumoxytol 32.3% vs. FCM 37.6%; related TEAEs- ferumoxytol 11.6% vs. FCM 16.7%).

Serious adverse events (SAEs) occurred in similar proportions of each group (ferumoxytol 3.6% vs. FCM 3.5%). Related SAEs were reported in 1 ferumoxytol subject and 5 FCM subjects. One ferumoxytol subject had a reported Anaphylactic Reaction that was assessed to be related to the study drug by the Investigator; this event was adjudicated by the CEC as not meeting the prespecified definition for anaphylaxis but did represent a severe hypersensitivity reaction. The 5 FCM subjects and their respective related SAEs included Hypertensive Emergency, Atrial Fibrillation, Chest pain, Hypotension and Syncope.

The incidence of TEAEs in ferumoxytol-treated subjects relative to FCM-treated subjects was similar or lower in all SOCs. Overall, the most frequently affected SOCs were GI Disorders (11.2%), Nervous System Disorders (10.2%), General Disorders and Administration Site Conditions (7.8%), and Respiratory, Thoracic and Mediastinal Disorders (5.3%).

In the GI Disorders SOC, the most common TEAEs in both groups were nausea and diarrhea, which are known to be associated with IV iron products. The incidence of nausea was 3.5% for ferumoxytol and 6.0% for FCM. The incidence of diarrhea was 2.9% for ferumoxytol and 3.3% for FCM.

In the Nervous System Disorders SOC, the most common AEs in both groups were headache and dizziness, which also are known to be associated with IV iron products. The incidence of Headache was 6.0% for ferumoxytol and 8.2% for FCM. The incidence of Dizziness was 2.5% for ferumoxytol and 4.0% for FCM.

In the General Disorders and Administration Site Conditions SOC, the most common TEAE was fatigue (ferumoxytol 3.0%, FCM 3.6%), which is a known potential consequence of IDA. The next most common TEAE in this SOC was Pyrexia (ferumoxytol 0.7%, FCM 2.2%).

In the Respiratory, Thoracic and Mediastinal Disorders SOC, the most common TEAEs were cough (ferumoxytol 1.5%, FCM 1.3%) and dyspnoea (ferumoxytol 1.1%, FCM 1.8%).

For TEAEs that occurred with incidence ≥1% higher in the FCM group, the incidence in ferumoxytol vs. FCM, respectively, was: headache (6.0% vs. 8.2%), nausea (3.5% vs. 6.0%), dizziness (2.5% vs. 4.0%), pyrexia (0.7% vs. 2.2%), urticaria (0.3% vs. 1.3%) and hypophosphatemia (0 % vs. 1.8%). No individual TEAEs occurred with an incidence ≥1% higher in the ferumoxytol group vs. FCM.

Adverse Events Related to Study Drug

Treatment-related TEAEs were reported in 11.6% ferumoxytol subjects and 16.7% FCM subjects. Overall, the most frequently affected SOCs with related TEAEs were Nervous System Disorders (ferumoxytol 4.6%, FCM 4.8%), GI Disorders (ferumoxytol 3.9%, FCM 5.0%) and General Disorders and Administrative Site Conditions (ferumoxytol 3.1%, FCM 4.0%). Overall, the most frequent treatment-related TEAEs were headache (ferumoxytol 3.4%, FCM 3.1%), nausea (ferumoxytol 1.8%, FCM 3.4%), dizziness (ferumoxytol 1.5%, FCM 1.6%), and fatigue (ferumoxytol 1.5%, FCM 1.2%).

Within the Immune System Disorders SOC, related TEAEs were reported in both groups (ferumoxytol, 3 events in 3 subjects, 0.3%; FCM, 1 event in 1 subject, 0.1%). For ferumoxytol this included 2 subjects with related TEAEs of Hypersensitivity and 1 with Anaphylactic Reaction. The latter event was adjudicated

by the CEC as not meeting the prespecified definition for anaphylaxis but did represent a severe hypersensitivity reaction. The 1 FCM subject had a related TEAE of Drug hypersensitivity.

Within the Vascular Disorders SOC, related TEAES were reported in 1.5% of ferumoxytol subjects and 2.0% FCM subjects. The most frequent related TEAE was Flushing (ferumoxytol, 8 events in 8 subjects, 0.8%; FCM, 11 events in 11 subjects, 1.1%). Hypotension was a related TEAE as follows: ferumoxytol, 1 event in 1 subject, 0.1%; FCM, 3 events in 3 subjects, 0.3%.

No unexpected treatment-related AEs were reported, and the incidence of treatment-related AEs did not suggest any adverse safety trend or signal.

Adverse events by intensity

The majority of TEAEs reported in both Treatment Groups were mild (ferumoxytol, 499 events in 199 [20.0%] subjects; FCM, 634 events in 232 [23.2%] subjects) followed by moderate intensity events (ferumoxytol, 157 events in 86 [8.6%] subjects; FCM, 208 events in 110 [11.0%] subjects). Only 37 (3.7%) subjects in the ferumoxytol group and 34 (3.4%) subjects in the FCM group had severe TEAEs.

There were 44 severe TEAEs reported in 37 (3.7%) subjects in the ferumoxytol Treatment Group, each of which was reported in single subjects, except Syncope reported in 3 subjects (0.3%) and in Pneumonia, Seizure, Haemorrhagic anaemia and Acute Kidney Injury in 2 subjects (0.2%). The following severe TEAEs were considered related: Fatigue, Anaphylactic Reaction, and Back Pain. All these TEAEs resolved.

There were 51 severe TEAEs reported in 34 (3.4%) subjects in the FCM Treatment Group. These occurred in single subjects, except for Cardiac Failure Congestive, Acute Kidney Injury, Dyspnoea and Hypotension in 2 subjects (0.2%) each. The following severe TEAEs were considered related: Chest Discomfort, Hypertensive Emergency, Chest Pain, Nausea, Dyspnoea, Hypotension, and Hypophosphataemia. All these TEAEs resolved.

3.2.7.10. Serious adverse events, deaths, and other significant events

Initial IDA studies

Integrated Analysis Initial treatment pool (301 and 302)

Deaths

Four posttreatment deaths were reported in the pooled IDA-301 and IDA-302 safety data, 3 in ferumoxytol-treated subjects (0.3%) and 1 in a placebo-treated subject (0.5%; malignant lung neoplasm). All of the reported deaths were assessed as not related to study drug and could be attributed to comorbid disease and/or disease progression. None of these deaths were temporally related to dosing as they occurred >14 to 53 days post–last dose of study drug (ferumoxytol: disease progression of a pancreatic neoplasm; septic shock; and GI obstruction). None of these deaths were temporally related to dosing as they occurred >14 to 53 days post–last dose of study drug. No mortality signal was identified.

Serious Adverse Events

SAEs were recorded in 33 subjects of the ferumoxytol group (3.3%, versus iron sucrose 5 [2.5%] and placebo 6 [3.0%]). The types of SAEs reported in the total ferumoxytol treatment group were very heterogeneous with most events occurring in only single subjects; many of the reported SAEs were attributable to subjects' comorbid disease and most reported SAEs in the ferumoxytol treatment group

were assessed as not related to study drug by the investigators. With the exception of 1 event (worsening of IDA), all SAEs resolved with treatment and the subjects recovered.

The only SAEs reported in more than 1 ferumoxytol-treated subject (0.1%) were: hypersensitivity (0.3%, 3 out 1014 subjects), anaphylactic reaction (0.2%, 2 out 1014 subjects), anaemia (0.2%, 2 out 1014 subjects), and uterine hemorrhage (0.2%, 2 out of 1014 subjects); no SAEs of hypotension were reported; all events/subjects resolved/recovered. The 2 reported anaphylactic reactions were of severe intensity, resolved with treatment and the subjects recovered.

SAEs in the placebo treatment group (3.0%) occurred in single subjects except for anaemia, which was reported in 1.5% of subjects. All of the SAEs in the iron sucrose treatment group (2.5%) were reported in single subjects (0.5%), and none was assessed as related to study drug.

Treatment related SAEs

SAEs considered related by the investigators were reported in 6 subjects (0.6%) in the ferumoxytol treatment group and included 2 subjects (0.2%) with an anaphylactic reaction, 3 subjects (0.3%) with hypersensitivity, and 1 subject (0.1%) with hypertension, angioedema, urticaria, and tachycardia. The 2 related SAEs of anaphylactic reaction reported in ferumoxytol-treated subjects were severe in intensity and resolved with treatment.

Integrated analysis Repeat Treatment Pool (301 and 303)

Deaths

There were 2 deaths (0.3%, of 759 subjects exposed to at least 1 dose of ferumoxytol) after the first course in the Repeat Treatment Pool. Both of these occurred in IDA-301. There were no deaths in the Extension Study, IDA-303.

Serious Adverse Events and their relation to study drug

SAEs were reported in 2.8% of ferumoxytol-treated subjects in Treatment Course 1, 2.9% of subjects in Treatment Course 2, and 4.3% of subjects in Treatment Course 3, 5.6% of subjects in Treatment Course 4, and in 25.0% of subjects in Treatment Course 5.

Hypersensitivity (0.4%, 3 subjects of 759) was the only SAE reported in more than a single ferumoxytol-treated subject in Treatment Course 1. All other SAEs were reported in only single subjects (0.1%), and were very heterogeneous with many events attributable to subjects' comorbid disease or procedural complications; no SAEs of hypotension were reported. Except for hypersensitivity and anaphylactic reaction, all other SAEs were assessed as not related to study drug by the investigators.

The 9 SAEs reported in 7 subjects (2.9%) in Treatment Course 2 were considered not related to ferumoxytol. The overall incidence of SAEs in Treatment Course 2 was similar to Treatment Course 1, and would suggest no new safety concern is observed with repeat dosing compared with initial treatment.

In Treatment Course 3, 3 unrelated SAEs (of colon cancer metastatic and colon cancer stage III, and Cirrhosis alcoholic) were reported, each occurring in a unique ferumoxytol-treated subject.

In the 18 subjects who received Treatment Course 4 or Treatment Course 5 of ferumoxytol, 1 SAE was reported in Treatment Course 4 (osteomyelitis) and Treatment Course 5 (cellulits), which occurred in the same subject, who had a relevant previous history. The investigator assessed the event of osteomyelitis not related to the study drug.

Study 304

Outcomes of the primary and secondary endpoint

Primary safety endpoint

Table 106: Primary Safety Endpoint: Incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, or moderate to severe hypotension (Safety Population)

	Proportion of Subjects		**Treatment Difference (95% CI)**	**Relative Risk (95% CI)**	**Non-inferiority[1], P value**
	Treatment Group				
	Ferumoxytol (N=997) **n (%)**	**FCM** (N=1000) **n (%)**			
Safety Population					
Moderate Hypersensitivity Reaction	3 (0.30)	6 (0.60)			
Severe Hypersensitivity Reaction	1 (0.10)	0			
Anaphylaxis	0	0			
Moderate Hypotension	2 (0.20)	1 (0.10)			
Severe Hypotension	0	0			
Composite of the above	6 (0.60)	7 (0.70)	-0.10 (-0.80, 0.61)	0.8597 (0.2900, 2.5491)	Yes, p<0.0001

Note: All cases presented on this table were adjudicated by CEC. The rate difference is (Ferumoxytol-FCM), relative risk is Ferumoxytol/FCM. The 95% confidence intervals were calculated using the large sample assumption (Wald confidence interval).

[1] p-value from non-inferiority test using large sample assumption (Wald) with margin = 2.64% at alpha=0.025 level for the rate difference.

Secondary safety endpoint

The proportion of subjects with incidence of the composite safety endpoint of moderate to severe hypersensitivity reactions, including anaphylaxis, serious cardiovascular events, or death for ferumoxytol as compared to FCM is presented for the Safety Population in Table 107.

Based on the pre-specified hierarchal testing scheme, the secondary safety endpoint was not formally tested. However as planned, the test was performed for descriptive purposes and it indicated that ferumoxytol was non-inferior to FCM based on a margin of 3.6% in the proportion of subjects with composite incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, serious cardiovascular events, or death, at any time from Baseline up to Week 5 (ferumoxytol incidence 1.3%, FCM incidence 2.0%, treatment difference: -0.70, 95% CI [1.81, 0.42] (Non-inferiority p<0.0001), Risk Ratio: 0.6520 [0.3261, 1.3034)]). None of the serious cardiovascular events in the ferumoxytol group were considered related by the Investigator and 3 serious cardiovascular events in the FCM arm were considered related by the Investigator. None of the deaths in either group were considered related.

Additional detail on serious cardiovascular events is presented in Section 11.4.1.4.3. Additional detail on deaths is presented in Section 11.4.1.1.

Table 107: Secondary Safety Endpoint: Incidence of Moderate to Severe Hypersensitivity Reactions, Including Anaphylaxis, Serious Cardiovascular Events, and Death (Safety Population)

	Proportion of Subjects		**Treatment Difference (95% CI)**	**Relative Risk (95% CI)**	**Non-inferiority[1], P value**
	Treatment Group				
	Ferumoxytol (N=997) **n (%)**	**FCM** (N=1000) **n (%)**			
Safety Population					
Moderate Hypersensitivity Reaction	3 (0.30)	6 (0.60)			
Severe Hypersensitivity Reaction	1 (0.10)	0			
Anaphylaxis	0	0			
Serious Cardiovascular Event	6 (0.60)	13 (1.30)			
Death	4 (0.40)	2 (0.20)			
Composite of the above	13 (1.30)	20 (2.00)	-0.70 (-1.81, 0.42)	0.6520 (0.3261, 1.3034)	Yes, p<0.0001

Note: All cases of hypersensitivity reaction including anaphylaxis and death presented on this table were adjudicated by CEC. The rate difference was (Ferumoxytol-FCM), relative risk was ferumoxytol/FCM. The 95% confidence intervals were calculated using the large sample assumption (Wald confidence interval).

(1) p-value from non-inferiority test using large sample assumption (Wald) with margin = 3.6% at alpha=0.025 level for the rate difference.

Serious cardiovascular events

Table 24: Serious Cardiovascular events- Treatment Emergent Adverse Events (Safety Population)

MedDRA System Organ Class	Treatment Group				Total (n=1997)	
	Ferumoxytol (n=997)		FCM (n=1000)			
	Events n	Subjects n (%)	Events n	Subjects n (%)	Events n	Subjects n (%)
All Cardiovascular SAEs	**7**	**6 (0.6)**	**14**	**13 (1.3)**	**21**	**19 (1.0)**
Cardiac disorders	3	3 (0.3)	10	10 (1.0)	13	13 (0.7)
Acute Myocardial Infarction	0	0	1	1 (0.1)	1	1 (0.1)
Angina Pectoris	0	0	2	2 (0.2)	2	2 (0.1)
Atrial Fibrillation	0	0	2	2 (0.2)	2	2 (0.1)
Cardiac Failure	0	0	1	1 (0.1)	1	1 (0.1)
Cardiac Failure chronic	0	0	1	1 (0.1)	1	1 (0.1)
Cardiac Failure congestive	1	1 (0.1)	3	3 (0.3)	4	4 (0.2
Cardio-respiratory Arrest	1	1 (0.1)	0	0	1	1 (0.1)
Left Ventricular Failure	1	1 (0.1)	0	0	1	1 (0.1)
Metabolism and nutrition disorders	1	1 (0.1)	1	1 (0.1)	2	2 (0.1)
Fluid Overload	1	1 (0.1)	1	1 (0.1)	2	2 (0.1
Nervous system disorders	1	1 (0.1)	0	0	1	1 (0.1)
Cerebrovascular Accident	1	1 (0.1)	0	0	1	1 (0.1)
Vascular disorders	2	2 (0.2)	3	3 (0.3)	5	5 (0.3)
Aortic Aneurysm	0	0	1	1 (0.1)	1	1 (0.1)
Aortic Stenosis	1	1 (0.1)	0	0	1	1 (0.1)
Hypertensive Crisis	1	1 (0.1)	0	0	1	1 (0.1)
Hypertensive Emergency	0	0	1	1 (0.1)	1	1 (0.1)
Hypotension	0	0	1	1 (0.1)	1	1 (0.1)

Note: Subjects were counted once within the same System Organ Class and Preferred Term.
Percentages are based on the number of subjects in each Treatment Group.
Data Source: Table 14.3.1.4.8

Deaths

There were six deaths reported in this study, 4 in ferumoxytol group and 2 in FCM group. None of the deaths was considered related to study drug. As per CEC assessment, none of the deaths was considered related to hypersensitivity.

Table 108: Pre-Treatment and Treatment-Emergent Deaths (Safety Population)

Treatment Group	SAE leading to death	Time from Last Dose	Relationship to Study drug
Ferumoxytol	Respiratory Failure	25 days	Not Related
Ferumoxytol	Completed Suicide, Intentional overdose*	29 days	Not Related
Ferumoxytol	Pancreatitis acute	16 days	Not Related
Ferumoxytol	Cardio-respiratory Arrest	20 days	Not Related

FCM	Mixed Hepatocellular Cholangio-Carcinoma	33 days	Not Related
FCM	Cardiac Failure	29 days	Not Related

* Acute Bupropion Toxicity

Other SAEs

Overall, 71 (3.6%) subjects had treatment-emergent SAEs during the study, 36 (3.6%) subjects in ferumoxytol group and 35 (3.5%) subjects in FCM group.

The SOCs with SAEs in >2 subjects in the ferumoxytol group included Infections and Infestations (12 events in 9 [0.9%] subjects), Nervous System Disorders (7 events in 6 [0.6%] subjects), GI Disorders (4 events in 4 [0.4%] subjects), Cardiac Disorders (3 events in 3 [0.3%] subjects), Blood and Lymphatic System Disorders (3 events in 3 [0.3%] subjects), Respiratory, thoracic and mediastinal Disorders (3 events in 3 [0.3%] subjects), and Metabolism and Nutrition Disorders (3 events in 3 [0.3%] subjects).

In FCM-treated subjects, the SOCs with SAEs in >2 subjects included Cardiac Disorders (10 events in 10 [1.0%] subjects), GI Disorders (6 events in 5 [0.5%] subjects), Neoplasms Benign, Malignant and Unspecified (5 events in 4 [0.4%] subjects), Nervous System Disorders (4 events in 4 [0.4%] subjects), Infections and Infestations (3 events in 3 [0.3%] subjects), Vascular Disorders (3 events in 3 [0.3%] subjects), and Injury, Poisoning and Procedural Complications (3 events in 3 [0.3%] subjects).

Serious Adverse Events Related to Study Drug

One SAE in ferumoxytol-treated subjects (Anaphylactic Reaction) was assessed to be related to study drug by the Investigator; this was adjudicated by the CEC as not meeting the prespecified definition for anaphylaxis but did represent a severe hypersensitivity reaction. Five study drug related-SAEs were reported in 5 subjects treated with FCM in this study (Hypertensive Emergency, Atrial Fibrillation, Chest pain, Hypotension and Syncope). All treatment-related SAEs were reported as resolved on the same day that they occurred.

No new safety trend or signal was identified after careful review of the treatment-related SAEs.

3.2.7.11. Laboratory findings

Initial IDA studies

Integrated Analysis Initial treatment pool (301 and 302)

Indicators of Liver and Kidney Damage

A small percentage of ferumoxytol-treated subjects had elevations in ALT, AST, and total bilirubin, and few subjects had abnormalities in these combined parameters postdose. Although there were 2 cases that potentially met the conditions for Hy's Law in the ferumoxytol treatment group, both cases were explained by concurrent disease/pathology unrelated to ferumoxytol. In one subject the event was deemed to be not related to study drug, by the investigator, and the subject continued in the study. In another subject no pattern of laboratory abnormalities suggested an association of ferumoxytol treatment with liver injury.

At Baseline, 1 subject (<0.1%) in the ferumoxytol treatment group had elevated serum creatinine, and the number/percent remained essentially unchanged during the postdose follow-up period. Only 1 subject, in the iron sucrose treatment group, also had postdose elevations in serum creatinine.

Hematology

In IDA-301, there was a lower percentage of abnormalities among ferumoxytol-treated subjects compared with placebo-treated subjects. In IDA-302, abnormalities in Hgb meeting MAV criteria decreased in frequency from dosing over subsequent weeks in both treatment groups. These changes in laboratory values are consistent with correction of anaemia following IV iron therapy. In both studies, the percentage of subjects with abnormalities in leukocytes, lymphocytes, neutrophils, and platelets was very small in the ferumoxytol, placebo, and iron sucrose treatment groups.

Mean change from Baseline for hematology parameters is provided.

Across the clinical trials, only 4 subjects had an Hgb >15 g/dL: 0.3% of ferumoxytol-treated subjects, and 0.5% of iron sucrose–treated subjects. All values >15 g/dL were postdose.

Integrated analysis Repeat Treatment Pool (301 and 303)

Indicators of Liver and Kidney Damage

A small percentage of ferumoxytol-treated subjects had elevations in ALT, AST, and total bilirubin, and few subjects had abnormalities in these parameters postdose. No subjects for any Treatment Course had abnormalities that met the criteria for drug induced liver injury, most subjects only had isolated abnormalities post-Baseline. Four subjects (0.5%), in Treatment Course 1 only, reported TRAEs of ALT increased and AST increased.

The incidence of elevated serum creatinine in all subjects exposed to ferumoxytol in the Repeat Treatment Pool was low (0.8%, 6 of 738 subjects), and the number/percent remained essentially unchanged during the postdose follow-up period.

The observed changes in liver and kidney chemistries likely reflect subjects' underlying comorbid conditions and/or concomitant medications rather than to treatment with ferumoxytol (or iron sucrose); this is supported by the comparable rate of these abnormalities in the placebo and iron sucrose treatment groups. No pattern of change in laboratory values was identified to suggest an association of ferumoxytol (or iron sucrose) with liver or kidney injury.

Study 304

Haematology

Mean changes from Baseline to Week 2 and 5 showed increases in both Treatment Groups for Hemoglobin, Hematocrit, Erythrocytes, Erythrocyte Mean Corpuscular Volume, Erythrocyte Mean Corpuscular Hemoglobin, and Erythrocyte Mean Corpuscular Hemoglobin Concentration as expected following IV iron administration. The ferumoxytol Treatment Group increases were similar to the increases observed in the FCM Treatment Group at each post-Baseline time point; no clinically meaningful difference was observed (eg, difference in Hgb <0.5 g/dL). No important changes were noted in Leukocyte, Lymphocyte or Neutrophil counts either between or within Treatment Groups. Small decreases were observed in Platelet counts over time in both Treatment Groups, which were comparable in magnitude.

Clinical chemistry

The only noticeable Treatment Group difference was a reduction in blood phosphate in the FCM group from baseline to Week 2 and Week 5 compared to the ferumoxytol group.

Mechanisms of Hypophosphatemia substudy

The proportion of subjects with hypophosphatemia < 0.6 mmol/L Post Baseline Week 2 in the ferumoxytol group was 0.4% (4/954 subjects) compared to 38.7% (361/932 subjects) in the FCM group.

3.2.7.12. In vitro biomarker test for patient selection for safety

N/A

3.2.7.13. Safety in special populations

Initial Treatment Pool-Studies IDA-301 and IDA-302

A comprehensive analysis of subgroups was conducted including by age group, race, sex, geographic region, and baseline Hgb for the Primary IAS for the Initial Treatment Pool (IDA-301 and IDA-302). Overall, these subgroup analyses did not reveal any drug-demographic interactions or new safety concerns in any specific subgroup.

Subgroup analyses (Study 304)

The Applicant has performed subgroup analyses by age, race, gender and weight. The Applicant has not identified any important differences between different categories within respective groups.

Another subgroup analysis was performed for CKD patients. This subgroup was of particular interest considering the large existing safety database and regulatory approval for use of ferumoxytol administered by rapid injection in this population. In this study, the subgroup of subjects with CKD designated by the investigators as the underlying cause for IDA included 532 subjects in the Safety population (267 ferumoxytol, 265 FCM).

Individual TEAEs occurring with incidence ≥2% in either group in ferumoxytol vs. FCM, respectively, included diarrhoea (5.24% vs. 3.77%), headache (1.87% vs. 5.66%), nausea (1.87% vs. 5.28%), fatigue (1.12% vs. 3.02%), and vomiting (1.12% vs. 2.26%).

Pregnancy

In the Registrational IDA clinical programme, there were 15 confirmed pregnancies. Of these confirmed pregnancies, 11 subjects were known to have been treated with ferumoxytol either in the feeder studies, IDA-301/IDA-302, or in the long-term extension study. Information was received on 4 live births, 4 out of the 5 spontaneous abortions, and 1 of the 2 elective abortions. For 4 subjects, pregnancy outcomes are unknown.

3.2.7.14. Immunological events

Hypersensitivity reactions are discussed in other parts of this report.

3.2.7.15. Safety related to drug-drug interactions and other interactions

Please refer to this section discussed under the CKD indication.

3.2.7.16. Discontinuation due to adverse events

Studies IDA-301 and IDA-302: AEs resulting in permanent discontinuation of study drug were reported in all three Treatment Groups (ferumoxytol, 1.8%; placebo, 0.5%; and iron sucrose, 2.5%).

Study 304

Adverse Events Leading to Temporary discontinuation of Study Drug: 15 subjects (1.5%) in ferumoxytol group and 9 subjects (0.9%) in FCM group experienced AEs that led to temporary discontinuation of the drug.

Adverse Events Leading to Permanent Discontinuation of Study Drug: There were 44 TEAEs that led to permanent discontinuation of the study drug in 17 (1.7%) subjects in the ferumoxytol Group and 68 such AEs in 23 (2.3%) subjects in the FCM Group.

The most common SOCs were General Disorders and Administration Site Conditions (ferumoxytol 0.6%; FCM 1.0%), GI Disorders (ferumoxytol 0.3%; FCM 0.7%), Respiratory, thoracic and mediastinal disorders (ferumoxytol 0.5%; FCM 0.6%) and Nervous System Disorders (ferumoxytol 0.5%; FCM 0.5%).

The most common individual TEAEs that led to permanent discontinuation of the study drug (in >5 subjects overall) were dyspnea (ferumoxytol 0.3%, FCM 0.4%), nausea (ferumoxytol 0.2%, FCM 0.5%), dizziness (ferumoxytol 0.2%, FCM 0.5%) and headache (ferumoxytol 0.2%, FCM 0.4%).

Adverse Events Leading to Study Discontinuation: There were 34 AEs that led to study discontinuation in 13 (1.3%) subjects in the ferumoxytol Group and 15 such AEs in 12 (1.2%) subjects in the FCM Group.

The most common SOCs were General Disorders and Administration Site Conditions (ferumoxytol 0.5%; FCM 0.2%), Cardiac Disorders (ferumoxytol: 0.2%; FCM: 0.2%), Gastrointestinal Disorders (ferumoxytol 0.3%; FCM: 0.1%), Musculoskeletal and Connective Tissue Disorders (ferumoxytol 0.4%; FCM 0 AEs), Renal and Urinary Disorders (ferumoxytol 0.2%; FCM 0.2%]), and Respiratory, Thoracic and Mediastinal Disorders (ferumoxytol 0.4%; FCM 0 AEs).

3.2.7.17. Post marketing experience

Ferumoxytol has been sold mainly in the US.

Worldwide 3,648,181 vials have been sold between 30 June 2009 and 30 June 2021.

After the introduction of the new dosage administration, the rate of anaphylactic reaction/shock, hypersensitivity, cardiac arrest/cardiogenic shock, hypotension and nervous system disorders (syncope, loss of consciousness, unresponsive to stimuli) decreased.

Table 145 Reporting Rates per Single Exposure for Reporting Period (30 June 2012 to 30 June 2021) and Cumulative (30 June 2009 to 30 June 2021) Adverse Events of Interest (AESI)

	Reporting Period									Cumulative (30 June 2009 to 30 June 2021)
	01 July 2020 to 30 June 2021	01 July 2019 to 30 June 2020	01 July 2018 to 30 June 2019	01 July 2017 to 30 June 2018	01 July 2016 to 30 June 2017	01 July 2015 to 30 June 2016	01 July 2014 to 30 June 2015	01 July 2013 to 30 June 2014	30 June 2012 to 30 June 2013	
Immune System Disorders: Anaphylactic Reactions/Shock										
No. of cases	14	13	18	5	7	6	15	23[1]	16	152
Exposure (# of vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0026	0.0027	0.0041	0.0016	0.0024	0.0022	0.0054	0.0085	0.0066	0.0041
Immune System Disorders: Hypersensitivity										
No. of Cases	14 (severe)	18 (severe)	14 (severe)	2 (severe)	3 (severe)	1 (severe)	5 (severe)	8 (severe)	8 (severe)	120
Exposure (# vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0026	0.0037	0.0032	0.0006	0.0010	0.0004	0.0018	0.0030	0.0033	0.0032
Cardiac Disorders: Cardiac Arrest/Cardiogenic Shock										
No. of cases	4	0	3	0	4	2	6	6	7	59
Exposure (# vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0007	0.000	0.0007	0.000	0.0014	0.0007	0.0022	0.0022	0.0029	0.0016
Vascular Disorders: Hypotension (and Related PTs)										
No. of Cases	1	2	1	0	2	0	6	4	7	74
Exposure (# vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0001	0.0004	0.0002	0.000	0.0007	0.000	0.0022	0.0015	0.0029	0.0020

[1] This includes anaphylactic reaction/shock, hypersensitivity (serious)

	Reporting Period									Cumulative (30 June 2009 to 30 June 2021)
	01 July 2020 to 30 June 2021	01 July 2019 to 30 June 2020	01 July 2018 to 30 June 2019	01 July 2017 to 30 June 2018	01 July 2016 to 30 June 2017	01 July 2015 to 30 June 2016	01 July 2014 to 30 June 2015	01 July 2013 to 30 June 2014	30 June 2012 to 30 June 2013	
Nervous System Disorders: Syncope, Loss of Consciousness, Unresponsive to Stimuli										
No. of Cases	5	8	1	2	3	2	7	5	1	57
Exposure (# vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0009	0.0016	0.0002	0.0006	0.0010	0.0007	0.0025	0.0018	0.0004	0.0015

Table 146 Reporting Rates per Single Exposure During Reporting Period (30 June 2012 to 30 June 2021) and Cumulative Reports (30 June 2009 to 30 June 2021) with Fatal Outcomes

	Reporting Period									Cumulative (30 June 2009 to 30 June 2021)
	01 July 2020 to 30 June 2021	01 July 2019 to 30 June 2020	01 July 2018 to 30 June 2019	01 July 2017 to 30 June 2018	01 July 2016 to 30 June 2017	01 July 2015 to 30 June 2016	01 July 2014 to 30 June 2015[1]	01 July 2013 to 30 June 2014	30 June 2012 to 30 June 2013	
Number of cases	4	6	5	0	2	2	8	15	16	71
Exposure (# vials)	530,819	482,911	434,701	299,489	291,956	268,809	274,774	268,658	239,178	3,648,181
Reporting Rate (%)	0.0007	0.0012	0.0012	0.000	0.0007	0.0007	0.0030	0.0056	0.0067	0.0019

[1]First reporting period including data following change in administration to 15-minute infusion.

Following the labelling change to administration by 15-min infusion only, there was a marked drop in fatal outcomes, even when results are presented for only a partial year.

3.2.8. Discussion on clinical safety

The initial development programme supported the IDA-CKD indication that was approved in 2012. The Applicant later applied for a variation to extend the indication to include also all cause-IDA patients, which has been rejected at the time and subsequently the product has been withdrawn from the market. Since then, three additional studies (CKD-201, CKD-401 and IDA-304) were performed that are considered relevant for the currently intended indication. Overall, 4,015 subjects have been exposed to ferumoxytol in one or more treatment courses in completed randomised or open-label IDA-CKD and all-

cause IDA studies. The Applicant presented the safety data separately per indication and separately for the initial applications and the new studies. Therefore, the safety profile of ferumoxytol is also presented in this order. In order to allow comprehensive assessment of the safety profile of ferumoxytol, the Applicant is asked to provide a safety analysis integrating all available data for the intended dose for both indications and for each indication separately, and discuss any differences between the indications (**OC**).

The overall safety database could be regarded as sufficient to characterize the safety profile of ferumoxytol in general, however, any adverse reaction that would occur with incidence of less than 1/1000 would hardly be detected. The sensitivity of the provided safety database is further limited for the CKD population since not all of the patients received the indented dose of 2x510mg, but only about 1/3 of the CKD population (2x510mg: 692; 1.02g in other regimen: 73). Nevertheless, this data is supported by data from another 708 CKD patients who received 1x510mg. In addition, all patients in the all-cause IDA studies received the 2x510mg dose. No concerns are raised.

In order to further support this MAA, the Applicant submitted postmarketing data mainly from the US where Feraheme is approved and marketed. In addition, a review of literature and PI data was also provided but is not of sufficient quality to be considered for further assessment.

IDA due to CKD

The safety data provided for this MAA for the indication for IDA in CKD patients was generated in 11 studies submitted for the initial MAA (7 in CKD patients; 4 in healthy volunteers (mainly pharmacological studies)) and 3 studies in CKD patients performed after the initial marketing authorization (CKD-201, CKD-401 and CKD-304). While study CKD-201 is only supportive (but reassuringly showed overall similar results compared to the initial studies), studies CKD-401 and CKD-304 provide additional data. Study CKD-304 is discussed in the IDA section below. Study CKD-401 provided data on several re-treatment courses over approx. one year. In addition, the dossier includes data for paediatric patients and studies evaluating ferumoxytol as contrast agent. Respective data are only briefly mentioned in the scope of this assessment report, as these indications are not pursued. Nonetheless, available study results for children should briefly be described in the SmPC (**OC**). The Applicant provided a variety of integrated analyses of the initial studies comparing data based on different aspects (study type, treatment, dosing regimen). Data are available for different doses and regimen including lower doses (1 x 125 mg, 1 x 250 mg, 1 x 510 mg), different regimen resulting in the target dose of 1.02g (8 x 128 mg, 4 x 255 mg, 2 x 510 mg) and multiple exploratory dosing regimen (4 x 255 mg followed by 2 x 510 mg and 2 x 510 mg followed by 2 x 510 mg). The assessment in this part of the discussion is focussed on the intended indications (adult CKD patients with IDA) and the intended dose (2x510mg) also used in all post-marketing studies. Important differences are highlighted if applicable. Data from study CKD-401 is discussed separately.

Comparator data is available for placebo (saline), oral iron (both from the initial studies) and iron sucrose (postmarketing studies). Both active comparators are standard treatment options for this patient population.

In the analyses presented for the initial studies, the Applicant distinguished between treatment courses. The available data are mainly for first course treatments (1562 CKD patients with no previous exposure to ferumoxytol) but also limited data is available for 69 patients who were previously exposed to a therapeutic course of ferumoxytol (i.e., any exposure of 1.02 g, regardless of dosing regimen). More data on re-treatment is available from study CKD-401 (see last section of this discussion on CKD patients).

Adverse events

For the intended dose, incidence rates of 44% for AEs (12% related to study medication) were reported. These are lower compared to oral iron but higher compared to placebo. The incidence rates for serious AEs are with 10% (0.3% related to study medication) comparable to oral iron and higher than placebo. Overall, low rates were observed for AEs resulting in temporary or permanent discontinuation of study medication or hospitalization, which were lower compared to oral iron but higher compared to placebo.

The incidences in the 1x510mg treatment group are overall lower and comparable to placebo.

In study CKD-201, similar incidences were observed. Overall, the incidences were lower compared to iron sucrose.

In study CKD-401, much higher incidences were observed for all reported categories but were comparable between ferumoxytol and iron sucrose (TEAEs: ferumoxytol 80.6%, iron sucrose 83.5%; related TEAEs: ferumoxytol 4.6%, iron sucrose, 4.1%). Although the higher incidences might be due to the longer observation period or a population with more co-morbidities and it is reassuring that the incidences are comparable to the iron sucrose group, some aspects require clarification, including also the dropout between treatment periods and AEs that led to discontinuations including SAEs and fatal events (**OC**).

Common Adverse events

In the initial CKD development programme, the most common AEs in CKD patients were diarrhoea, hypotension, nausea, dizziness, headache, constipation and peripheral oedema. These adverse events were consistently observed throughout the seven studies in this population and the postmarketing studies. With the intended dose of 2x 510mg these events occurred with a maximum incidence of 4% (for diarrhoea). Most of these AEs were less frequent compared to oral iron treatment (diarrhoea (4.0% vs. 8.2%), nausea (3.1% vs. 7.5%), constipation (2.1% vs. 5.7%) and oedema peripheral (2.0% vs. 3.2%).

Notably, hypotension was observed with a higher incidence in patients treated with ferumoxytol compared to oral iron (2.5% vs. 0.4%). This was also observed for dizziness (2.6% vs. 1.8%).

Overall, reported AEs are similar between first and second course treatment with similar or lower incidences for the second course. A comparison between both treatment courses is however severely hampered by the very different group sizes (first course: N=1562; second course: N=69) and it can be assumed that patients who experienced severe/serious AEs during the first course did not receive a second course. In this context the validity of the Applicant's reassuring statement that no subjects experienced hypotension following a second course of treatment, is questioned. It has to be clarified whether any of the patients who already experienced hypotension or any cardiovascular adverse events during the first course were treated again (**OC**). Please also refer to the discussion of cardiovascular events below.

Study 401:

Patients receiving ferumoxytol reported most AEs in the categories 'GI disorders' (37.8%), 'Infections and infestations' (32.7%), 'Injury, poisoning and procedural complications' (31.1%), and 'General disorders and administration site conditions' (29.1%) - all comparable to the iron sucrose group.

Although the incidences for the overall category of infections were comparable, the individual adverse events might indicate a higher risk for patients treated with ferumoxytol: pyrexia (15 subjects, 7.7% vs 1 subject, 1%), pneumonia (11 subjects, 5.6% vs. 3 subjects, 3.1%), sepsis (10 subjects, 5.1% vs 2 subjects, 2.1%), urinary tract infection (12 subjects, 6.1% vs 3 subjects, 3.1%). Further, one patient on ferumoxytol died due to sepsis. Since intravenous iron has also been associated with an increased risk of infection in recent publications (Shah et al. 2021), the Applicant is asked to discuss the higher

incidences of the individual AEs compared to iron sucrose and a potential causal relationship between ferumoxytol and death due to sepsis (**OC**).

In the literature, lung oedema was also observed as a consequence of IV iron administration (iron dextran) in dialysis patients (Freter et al., 1997). Respective AEs have been observed with higher incidences in the ferumoxytol group compared to iron sucrose (i.e. pleural effusion (7 subjects, 3.6% vs 0), pulmonary oedema (8 subjects, 4.1% vs 1 subject). The reported cases were also more severe (pulmonary oedema: 3 mild, 3 moderate and 2 severe, iron sucrose: 1 moderate; acute pulmonary oedema: ferumoxytol: 1 moderate and 1 severe; iron sucrose: 2 moderate). The higher incidence and severity require further discussion including plans to investigate this risk (**OC**).

Slightly higher rate of hypertension (7.1% vs 6.2%) and hypotension (8.7% vs 7.2%) was observed with ferumoxytol compared to iron sucrose (please refer to the section on cardiovascular events below).

Severe AEs

Overall, very few severe adverse events were reported in the initial development programme (most common Diarrhoea) and raise no concerns. Only slight differences were observed between treatments which are more likely due to differences in group sizes but difficult to interpret due to the overall low incidences.

In study CKD-401, a higher rate of serious acute respiratory failure was reported with ferumoxytol (7 subjects (3.6%), 6 of which were severe) compared to iron sucrose (2 subjects (2.1%), none severe). The Applicant is asked to discuss these cases (**OC**).

Related AEs

The incidence of related AEs was low. With the intended dose of 2x510mg the most frequently observed related AEs were diarrhoea (1.7%), hypotension (1.6%) and dizziness (1.4%). Similar AEs were also observed in study CKD-201 and CKD-401 (although with higher incidences).

In non-CKD subjects, the most common reported related AEs were changes in laboratory values and all in-line with the mechanism of action of an iron treatment. Other treatment related AEs include pruritus (3.7%), rash (3.7%) and urticaria (1.8%) and do not raise concerns.

The related AEs are currently not appropriately reflected in the SmPC (**OC**, please refer to the respective section at the end of the discussion).

Deaths

In total 53 deaths (initial development: 31; postmarketing study CKD-401: 22) were reported for the CKD population.

In total 35 patients on ferumoxytol treatment died – 26 received the 2x510mg dose. The incidences in the respective studies are lower compared to the oral iron group in the initial studies (1.3% vs 2.8%) and slightly higher compared to the respective iron sucrose group in study CKD-401 (8.2% vs 6.2%). It is however noted that the incidence in study CKD-401 is considerably higher compared to the initial studies, with the majority of fatal events in the initial treatment period (TP1, n=5) or during TP2 (n=9). This should be discussed taking into account different inclusion criteria, comorbidities and concomitant medications (**OC**).

All deaths were considered as unrelated to study drug and no concerns arose from the respective narratives except for one death caused by sepsis with septic shock. Further information is requested (see OC on higher infection rate).

The Applicant reported that the most common adverse events leading to death were cardiovascular in nature and all of the subjects with cardiovascular-related deaths had significant pre-existing cardiovascular disease. Although the pre-existing conditions are acknowledged, this might also indicate an increased risk for such patients to experience potentially fatal events related to treatment with ferumoxytol. Please see below for further discussion of the OC on cardiovascular events.

Serious Adverse Events

Although overall low incidences for SAEs were reported (10.1%, comparable to oral iron and iron sucrose in study CKD-201), concerns are raised regarding the most commonly reported SAEs: infections (2.6%) and SAEs of cardiovascular nature (Cardiac Disorders: 18 patients (2.6%); "Cardiac failure congestive" (5 patients (0.7%)) and "hypotension" (4 patients (0.6%)). Respective OCs are discussed in other sections. The respective OC on infections is discussed above. For a more detailed discussion on the OC regarding cardiovascular events please refer to the separate section below.

Study CKD-401:

The proportion of serious adverse events (SAEs) was high but comparable in both treatment arms [ferumoxytol: 47.4% (259 SAEs in 93 subjects); iron sucrose: 50.5% (174 SAEs in 49 subjects). The higher incidences compared to the initial studies could be explained by the multimorbid population and the long follow-up time. The Applicant is nevertheless asked to comment (**OC**).

Slightly higher incidences of SAEs were observed with ferumoxytol in the SOC 'Infections and infestations' (19.4% vs. 17.5%) and 'Respiratory, thoracic and mediastinal disorders' (10.7% ad 6.2%). As discussed above, respective OCs have been raised regarding these categories in general.

No SAEs were considered related to study drug by the Investigator but no narratives have been presented and are requested (**OC**).

Although the incidence of SAEs with ferumoxytol decreased from TP1 to TP3 including Cardiac disorders, GI disorders, Infections and infestations, these observations have to be interpreted with care in light of the high drop out. A respective OC has already been discussed above.

Treatment Related Serious Adverse Events

A very low incidence of treatment related SAEs was observed in all seven initial studies in CKD-patients. Only three subjects receiving ferumoxytol treatment experienced treatment related serious adverse events. All three experienced hypotension; one was additionally classified as anaphylactic reaction. Please refer to the overall discussion of increased risk for cardiac events/hypotension below.

In the postmarketing studies, one event of anaphylactic reaction after treatment with ferumoxytol was reported as related to treatment in study CKD-401.

No other studies reported treatment related SAEs.

Cardiovascular Events

Based on the provided safety data, concerns arise regarding cardiovascular adverse events. The most common SAEs are cardiovascular in nature as well as most common AEs leading to death. According to the narratives, a relation to pre-existing cardiovascular disease or respective risk factors is likely. Additional factors supporting this concern are the overall incidences of cardiovascular adverse events regardless of severity, most related (S)AEs were cardiovascular events, different incidences for Hgb increase (see below) and the results of the thorough QT study (see PD section of this report). An increased (even fatal) risk especially for patients with cardiovascular risk factors can currently not be ruled out and is especially of concern since pre-existing cardiovascular conditions or risk factors are

common among CKD patients. In order to further investigate this potentially increased risk, the Applicant is asked to discuss this thoroughly, including a safety analysis for CKD patients with pre-existing cardiovascular disease. Further, the Applicant is asked to elaborate on the observed benefit in these patients and discuss whether subgroups can be identified with increased risk for serious or even fatal cardiovascular events. Additionally, the Applicant should provide respective data (from literature) for other iron treatment options. A respective warning in the SmPC might be required and the applicant is asked to suggest a wording accordingly (**OC**).

Laboratory Findings

In general, all identified changes are in line with the treatment effect and comparable between ferumoxytol and the respective comparator treatment oral iron and iron sucrose.

Liver function test elevations were observed in more subjects receiving ferumoxytol (6.8%) compared to oral iron (2.8%) and placebo (4.2%). Most of the ferumoxytol cases were GGT abnormalities. As GGT is known to be the most sensitive indicator of liver injury which precedes increase of other liver enzymes this should be addressed by the Applicant (**OC**).

While ferritin increased similarly in treatment groups, the increase in the ferumoxytol group resulted in mean values close to 800ng/mL with maximum values far above that. This might be indicative for iron overload and requires further clarification (**OC**).

Special populations

No differences were identified in subgroup analyses regarding renal impairment (stage of CKD, transplant status), hepatic impairment (very limited data), Age, Gender, Race, Body Weight or baseline ferritin.

Paediatric population: The paediatric population is not part of the intended indication. Nevertheless, the Applicant submitted very limited safety data for 14 patients from four paediatric studies. No detailed assessment was performed. It was noted that two studies (CKD 251/252 and CKD-253) were prematurely terminated. No reasons were provided. The Applicant is asked to clarify (**OC**).

Elderly patients: The Applicant did not provide a separate discussion of elderly patients. Although it is acknowledged that this population is part of the general CKD-population and respective patients were enrolled in all studies, a discussion on patients ≥65 years of age is warranted, especially regarding the uncertainties regarding cardiovascular risk factors (**OC**).

Haemoglobin: Differences in the incidences of (serious) cardiac disorders have been observed at different increases in Hgb (<0.5 g/dL per week, 0.5 to <1.0 g/dL per week). The clinical relevance of these observations is unknown and the limited numbers currently hamper further conclusions but this aspect should also be included in the general discussion of a potentially increased risk for cardiovascular events (**OC**).

Drug-Drug Interactions

No formal interaction studies were performed. Instead, the Applicant provided subgroup analyses, indicating a general increase in AE incidences (mainly cardiovascular events) in patients who received higher doses of ESA per week. A similar pattern was observed for thrombotic events. The Applicant is asked to discuss a potential underlying effects and propose respective wording for the SmPC (**OC**).

Further, a slight increase in thrombotic events was observed in patients who concomitantly received anticoagulants. Interpretation is hampered by the small numbers. This could be further monitored in the postmarketing. The Applicant is invited to comment (**OC**).

Analysis by treatment period – study CKD-401

Data for Treatment period 1 -3 show a decreasing trend in AE rate in both treatment arms, which could be reassuring but this has to be interpreted with caution due to the high dropout. No reliable conclusions can be drawn after TP3 due to the low number of remaining patients, although data for up to eight treatment periods would be available.

This lack of re-treatment and long term data is regarded as uncertainty for this procedure, since respective IDA-CKD patients are very likely to require re-treatment and especially CKD patients undergoing haemodialysis require repetitive iron dosing for extended periods of time. This is especially of concern regarding the potential for iron overload, which can hardly be observed in short term trials. Iron overload is known to promote endothelial dysfunction, cardiovascular disease, and immune dysfunction which are the leading causes of premature mortality in CKD patients. In this context, it has to be noted that, in the non-clinical studies signals of potential iron deposition in various organs have been observed. An additional objective of study CKD-401 was to evaluate the potential for deposition of iron in cardiac, hepatic and pancreatic tissues and changes in the laboratory parameters over a two year period. However, the substudy was terminated early due to low enrollment related to logistical issues for patients. The performed analysis on the limited number of patients (25: 15 ferumoxytol and 10 iron sucrose) did not yield interpretable results. Consequently, these concerns have not been adequately addressed and the uncertainties remain and should be discussed by the Applicant (**OC**).

All-cause IDA

The safety data of ferumoxytol has been generated in about 2100 patients with all-cause IDA in 4 clinical trials:

- 2 short-term (5 weeks), parallel-group, phase 3 randomised, controlled, clinical trials: AMAG-FER-IDA-301 (IDA-301) and AMAG-FER-IDA-302 (IDA-302),
- an open-label phase 3 six-month extension study, AMAG-FER-IDA-303 (IDA-303), for patients previously enrolled in study IDA-301; and
- a phase 3, randomised, active-controlled, safety trial with a focus on hypersensitivity reactions and hypotension.

The former 3 studies (301, 302 and 303) have already been submitted to EMA as a variation to extend the (previously approved indication in CKD patients) to IDA patients in June 2013. Following reports of hypersensitivity reactions with fatal outcome from post-marketing, the extension of indication was rejected and the Applicant was requested to conduct a safety study to further investigate the risk of these events. Study IDA-304 was implemented as a result of this request. These hypersensitivity reactions were assumed to be associated with the rapid injection; consequently, upon request of PRAC the method of administration was changed to slow infusion of diluted ferumoxytol. The only study where the new method of administration was applied is study IDA-304.

Comparator data is available for placebo (saline), IV iron sucrose and IV ferric carboxymaltose (FCM).

Safety data from the earlier IDA studies (301, 302 and 303) have been pooled and presented as 2 integrated analyses i.e. initial treatment pool (301 and 302), and repeat treatment pool (201 and 303). Results from the study 304 have been presented separately by the Applicant, with a justification that a new method of administration was used in this study. While this argumentation can be followed for immediate adverse events, it is not expected that a slow infusion would influence other adverse reactions. A new integrated safety analysis including all studies in the ferumoxytol IDA clinical programme (301, 302, 303 and 304) is therefore requested (**OC**).

Population

The vast majority of patients had IDA due to AUB and GI disorders. There are concerns that some subgroups of the target population, considered to be more vulnerable and potentially more susceptible to serious or severe adverse events have been underrepresented in IDA clinical studies. For instance, the number of patients with cancer was generally low across individual IDA studies and no conclusion on the safety of ferumoxytol in this subgroup can be made at present. In addition, the overall number of patients with relevant medical history such as cardiovascular disease or inflammatory disease, who are an important part of the target population, has not been clearly presented. These aspects should be addressed within the new pooled safety analysis (**OC**). Further, while the majority of subjects in studies IDA-301 and IDA-302 were naïve to IV iron, it is unclear whether any new users were included in study IDA-304. Since the risk of anaphylactic reactions is highest with new users, it is important to know whether the lower incidence of hypersensitivity reactions/hypotension observed in the Study 304 was due to the majority of subjects included being previously exposed to IV iron (**OC**).

Adverse events

The most common adverse events related to ferumoxytol were headache, nausea and dizziness. No new or unexpected safety concerns were observed according to the Applicant and the severity and types of reported adverse events were generally consistent with those seen with other approved IV iron products. However, some adverse events require further considerations. For example, in the initial treatment pool a higher rate of **treatment-related vascular disorders** was reported with ferumoxytol compared to iron sucrose (1.8% vs 0.5%). Additionally, a slightly higher rate of **serious vascular AEs** was reported with ferumoxytol compared to FCM (0.9% vs 0.3%) in study 304. Together, this poses concerns that should be addressed by the Applicant (**OC**).

The overall incidence of SAEs with ferumoxytol was comparable to FCM (3.6% vs 3.5%) in study 304 and slightly higher compared to iron sucrose (3.3% vs 2.5%) in the initial treatment pool (301 and 302). For most of SOC no clustering of serious SAEs was noted to suggest a safety concern. However, in addition to the vascular adverse events, a slightly higher incidence of **SAEs in SOC Infections and Infestations** was reported in ferumoxytol group (0.9% versus 0.3%) compared to FCM. Since intravenous iron administration is associated with an increased risk of infection, this should be further discussed (**OC**).

In study 304 only 1 SAE was considered related to ferumoxytol - 1 anaphylactic reaction (0.1%), and 5 SAEs were related to FCM: Hypertensive Emergency, Atrial Fibrillation, Chest pain, Hypotension and Syncope. All treatment-related SAEs were reported as resolved on the same day that they occurred.

In the initial treatment pool (301, 302), nine events in 6 subjects (0.6%) were considered related to ferumoxytolt: hypersensitivity (3 subjects), anaphylactic reaction (2 subjects) and angioedema, urticarial, hypertension, tachycardia (1 subject each). No treatment-related SAEs were reported for subjects receiving iron sucrose or placebo.

Four deaths were reported in ferumoxytol and 2 in FCM group in study 304, none was considered related to the study drug, nor due to hypersensitivity reaction. Four deaths were reported in the pooled IDA-301 and IDA-302 safety data, 3 in ferumoxytol-treated subjects (0.3%) and 1 in a placebo-treated subject, none was considered related to study drug.

Discontinuations/withdrawals due to AEs

Data for the initial treatment pool have to be clearly presented, as some information is missing (**OC**). In study IDA-304, a higher proportion of patients experienced AEs that led to temporary discontinuation of the drug in ferumoxytol group compared to FCM group (1.5% vs. 0.9%), however no further details are available and should be provided (**OC**). The majority of AEs that led to discontinuation of FCM were mild in severity (48.5%) and they all resolved. The majority of AEs that led to discontinuation of ferumoxytol were moderate (66%), and most of them resolved. While the rate of AEs that led to discontinuation of study drug was slightly lower in ferumoxytol group compared to FCM group (1.7% vs. 2.3%), 88% of AEs that led to drug discontinuation were related to ferumoxytol. In contrast, only 52% of AEs that led to drug discontinuation were related to FCM. In addition, 72% of AEs that led to withdrawal from the study in the ferumoxytol group were drug related, while in the FCM group this rate was 50%.

Iron overload

In Study 304 it was noted that the increase of ferritin resulted in mean values close to 800ng/mL with maximum values far above that. This might be indicative for iron overload and requires further clarification (**OC**).

Indicators of Liver Damage

One event of **hepatitis** in study 301 was considered related to ferumoxytol. In the Initial treatment pool an increase in the proportion of subjects with markedly abnormal GGT values (>3xULN) from baseline (22 subjects, 2.2%) to overall post-BL (48 subjects 4.8%) was observed, which was higher than in placebo (increase from 2.0% to 2.6%). These events require further discussion, especially in light of signals on potential iron deposits in liver and limited data on repeat use with ferumoxytol (**OC**).

Hypersensitivity reactions (HSRs) and hypotension

Moderate to severe hypersensitivity reactions, including anaphylactic reaction and moderate to severe hypotension were adverse events of special interest (AESI) in the initial treatment pool (studies 301 and 302). In the initial treatment pool, AESIs were reported at slightly higher rates with ferumoxytol compared to iron sucrose (1.0% vs. 0.5%). Moderate to severe hypersensitivity reactions were only reported in ferumoxytol group (5 events in 4/1014 subjects, 0.4%). Moderate to severe hypotension was reported in 6 ferumoxytol-treated subjects (0.6%) and 1 iron sucrose–treated subjects (0.5%). In the repeat treatment pool (studies 301 and 303) 10 AESI emerged (hypotension (7) and hypersensitivity (3)). All of them were reported in the first ferumoxytol treatment course. The major concerns regarding severe/serious HSRs that arose during the assessment of the IDA indication in the past arose however from the post-marketing and not from the clinical studies, which is understandable given the low incidence of these events.

The primary objective of the study IDA-304 was to show noninferiority of ferumoxytol to FCM in terms of the incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, and moderate to severe hypotension. In ferumoxytol group there were 3 moderate and 1 severe hypersensitivity reactions; and 2 moderate hypotension events. In FCM group there were 6 moderate hypersensitivity reactions, no severe HSRs and 1 moderate hypotension event. Non-inferiority was demonstrated for Ferumoxytol against FCM based on a margin of 2.64% in the proportion of subjects with composite incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, or moderate to severe hypotension at any time from Baseline up to Week 5 (ferumoxytol incidence 0.6%, FCM incidence 0.7%, treatment difference: -0.10, 95% CI [-0.80, 0.61]) (Non-inferiority $p<0.0001$).

However, several limitations of the study should be highlighted. Assumptions on the effect size, or in this case, AE rate, are not supported by reference to results of previous studies with FCM, but by reference to results on AE rates observed in previous studies with ferumoxytol. Further, the adverse

events taken into calculation for the assumptions of the AE rate do not correspond to the adverse events considered for the primary endpoint. Namely, the estimate of AE rate was based on the cumulative incidence of 'mild', 'moderate' and 'severe' hypersensitivity reactions and hypotension. In contrast, only 'moderate' and 'severe' hypersensitivity reactions and hypotension are considered for the primary endpoint. This leads to an insensitive comparison and inappropriate (over-)estimation of the anticipated AEs rates for the PEP in study 304, on the one hand, which is reflected in the discrepancy between the assumed (3.3%) and observed AE rates (0.6%); and a likely underpowered study, on the other hand. There are also concerns that the severity of some events may have been misclassified, which needs further clarification. Hence, new analyses should be presented by the Applicant (**OC**).

The secondary safety endpoint was the incidence of the composite safety endpoint of moderate to severe hypersensitivity reactions, including anaphylaxis, serious cardiovascular events, and death. The secondary safety endpoint was not formally tested, however the incidence of composite AEs was lower in ferumoxytol group (1.3% vs 2.0%). There were 4 deaths in ferumoxytol and 2 deaths in FCM group, neither was considered related to the study drug, nor due to hypersensitivity reactions. The incidence of serious cardiovascular events was lower in ferumoxytol group (0.6% vs. 1.30%).

Compared to earlier studies in the IDA population where ferumoxytol was administered as rapid injection, results from study IDA-304 with slow infusion show a modest decrease in terms of serious hypersensitivity/anaphylactic reactions (from 0.6% to 0.4%) and moderate to severe hypotension (from 0.6% to 0.2%). Based on the provided results no robust conclusions can be made whether the new method of administration indeed decreases the risk of hypersensitivity reactions, which was to be expected given the disproportionally small sample size compared to the incidence rate. No head-to-head comparison between the two methods of administration is available, which complicates the comparison of incidences of hypersensitivity reactions, but is understandable from an ethical point of view. However, numbers appear to be lower, which is also in line with lower incidences reported in US postmarketing experience since the introduction of the new method of administration, based on data provided by the Applicant.

The Applicant should analyse the incidence of severe hypersensitivity reactions / AEs of special interest across all clinical studies (CKD and all-cause IDA), and additionally severe hypersensitivity reactions by number of administrations (after the 1st dose [in naïve patients] versus after 2nd dose vs. after subsequent doses/treatment courses), and to update the SmPC accordingly, if accplicable (**OC**).

The Applicant should also present and discuss their data on immunogenicity of ferumoxytol and discuss their conclusions with regard to the (established/most likely) mechanism behind anaphylactic reactions following Ferumoxytol administration (and propose possible counter-measures) (**OC**).

Hypersensitivity reactions, with fatal outcome are very rare and represent a known risk with intravenous iron products. To address the above mentioned concerns, the Applicant has proposed to include in the label following information: a contraindication for patients with a history of drug allergy and in the evidence of iron overload; administration only via slow infusion during at least 15 minutes and careful monitoring for signs and symptoms of hypersensitivity reactions including measurements of blood pressure and pulse during and 30 minutes at least after administration, and only in facilities with adequately trained medical staff and resuscitation equipment available. A warning about fatal anaphylactic reactions has also been included, together with potential subgroups who are at higher risk for these events. The wording in the SmPC is considered in principle acceptable (with some amendments); nonetheless additional risk minimization measures (e.g DHPC, educational materials) should be considered to further mitigate these risks.

Long term data/repeat use

Studies IDA-301 and IDA-303 were integrated as if subjects were part of a single continuous study which is represented by the Repeat Treatment Pool. This analysis provides follow-up safety data on patients over approximately 7 months. However, the need for continued treatment was not present in a significant proportion of patients. The number of subjects who received subsequent doses after the first course rapidly decreased; 244 subjects received 2 course, 69 subjects received 3 courses, 18 subjects received 4 courses and only 4 subjects received 5 courses. A higher incidence of TEAEs was reported after the first treatment course (46.6%) compared with subsequent courses (29.1% for Course 2, 29.0% for Course 3, 16.7% for Course 4, and 25.0% for Course 5). However, the number of subjects who received more than 2 courses of ferumoxytol is too low to draw any meaningful conclusions on safety of repeat use of ferumoxytol. In addition, 7 months is a rather short time frame to investigate a therapy that is not chronic but episodic.

The non-clinical data indicate deposition of iron in many tissues including liver, lymph nodes, spleen and choroid plexus with dose-dependent incidence. These concerns have not been adequately addressed in MRI and oxidative stress sub-studies and the uncertainties remain. The Applicant should present a strategy on how to investigate long term safety from repeated exposure to ferumoxytol in IDA patients (**OC**).

Use in pregnancy

In the Registrational IDA clinical programme, there were 15 confirmed pregnancies. Of these confirmed pregnancies, 11 subjects were known to have been treated with ferumoxytol. Information was received on 4 live births, 4 out of the 5 spontaneous abortions, and 1 of the 2 elective abortions. For 4 subjects, pregnancy outcomes are unknown. Studies in animals have shown reproductive toxicity in rat and teratogenicity in rabbit. As these effects were observed after cumulative exposure, the relevance of this data to humans in the context of episodic treatment with 2 single doses is currently unclear. A nonclinical concern is raised on this issue and responses need to be awaited and assessed before a conclusion on adequate wording in the SmPC can be drawn. In addition, the Applicant should provide an update on all reported pregnancy and their outcomes (from all clinical studies and postmarketing) (**OC**).

Post-marketing data

The MAA has marketed the product starting from 2009. The highest exposure numbers have been achieved in the US with 3,594,836 vials, the overall exposure is 3,648,181 vials between 30 June 2009 and 30 June 2021.

In 2015 the dosage administration from rapid IV injection has been changed to a 15-minute IV infusion of diluted ferumoxytol. After the introduction of the new dosage administration, the rate of anaphylactic reaction/shock, hypersensitivity, cardiac arrest/cardiogenic shock, hypotension and nervous system disorders (syncope, loss of consciousness, unresponsive to stimuli) decreased. Anaphylactic reactions/shock decreased from a rate of 0.0066% to 0.0026%, hypersensitivity reactions from a rate of 0.0033% over a minimum of 0.0004% in the period 2015/2016 to a rate of 0.0026% in the last PSUR. Also cardiac arrest/cardiogenic shock, hypotension and syncope, loss of consciousness and unresponsiveness to stimuli showed a significant decrease.

Slight differences of the rates between the years can be attributed to the fact that data are derived from post-marketing data.

Nonetheless, the applicant is asked to clarify and discuss the discrepancy between the reporting rates in the last PSUR (anaphylactic reaction/shock: 14/530,819 (0.002%) = 0,264 per 10,000) versus literature data e.g. from Dave et al. (2022): 4 per 10,000. The applicant should compare and discuss findings from recent US-post marketing studies / sentinel-studies on marketed iv iron preparations (**OC**).

Adverse Event representation in the SmPC

Most of the adverse events are included in the SmPC section 4.8, but not all (e.g. hepatitis, GGT increased, palpitations). All AEs that were considered related to ferumoxytol should be stated in the SmPC. In addition, it appears that the included AEs were wrongly characterised as uncommon (≥ 1/1,000 to < 1/100), while they were reported with incidences >1%. This has to be corrected (**OC, SmPC comment**).

Further, section 4.8 seems to be based solely on the data from the initial studies. For a comprehensive representation of the safety profile of ferumoxytol, the Applicant is asked to provide a safety analysis integrating all available data for the intended dose for both indications and for each indication separately. Should the integrated analysis lead to different incidences, these shall be updated in the SmPC accordingly. Differences between population should be discussed and a respective wording to highlight these differences in the SmPC should be proposed (**OC, SmPC comment**).

Apart from the presentation of adverse events in the SmPC, safety aspects of the drug administration should be justified. Although the warnings regarding the mitigation of the risk of hypersensitivity reactions appear broadly acceptable, it is unclear why ferrumoxytol should be administered in smaller volume of 0.9% NaCl solution for injection (50-250 ml) compared to the volume used in study 304 (only study where ferumoxytol was administered diluted as slow infusion) i.e. 233 ml (**OC, SmPC comment**).

The proposed wording on the use of ferumoxytol in case of infection currently reads the following: "Parenteral iron should be used *with caution* in cases of immunologic disease or acute or chronic infection." Patients with an ongoing infection have not been systematically evaluated. Patients with active, clinically significant infection were excluded from some studies e.g. CKD-401, IDA-301 and IDA-302; but not explicitly from other studies e.g. CKD-201 and IDA-304. The Applicant is asked to present all available safety data for patients with an ongoing infection who were included in clinical studies and discuss safety findings compared to patients without an ongoing infection at the time of enrollment. Depending on the responses, the wording in the SmPC might have to be strengthened (**OC**, **SmPC**).

In the Mechanisms of Hypophosphatemia sub-study (part of study -304), hypophosphatemia was reported with incidence of 0.4% however, hypophosphatemia is not mentioned in section 4.8 of the SmPC. The incidence of Hypophosphatemia should be analysed across all clinical studies; and the SmPC updated accordingly (**OC**, **SmPC**).

3.2.9. Conclusions on clinical safety

In conclusion, the safety profile of ferumoxytol is considered overall comparable with that of iron sucrose and FCM. Severe hypersensitivity reactions, hypotension, increased risk for infections and risk of iron deposit are known risks for all IV iron products.

No exact incidence for hypersensitivity reactions/anaphylaxis can be calculated, due to the disproportionally small study 304 compared to the low incidence of these events and limitations of postmarketing data. Nonetheless, altogether there is sufficient reassurance that the new mode of administration i.e. slow infusion of diluted ferumoxytol leads to lower and acceptable rates. In order to mitigate these risks, they have to be clearly communicated to the treating physicians via an adequate wording in the SmPC, and probably additional risk minimization measures such as DHPC or educational materials. This is of utmost importance as this product was used to be administered as rapid infusion before it was withdrawn from the market.

Ferumoxytol is considered approvable from a safety point of view, provided the Applicant satisfactorily addresses the open concerns in the LoQ.

3.3. Risk management plan

3.3.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity reactions Hypotension
Important potential risks	Iron overload Cardiac disorders
Missing information	Safety in pregnant women Safety in breastfeeding Safety in children Long term safety Safety in patients with liver disorders Safety in patients with immunologic disease or active infection

3.3.1.1. Discussion on safety specification

Hypersensitivity reactions and hypotension have been considered as important identified risks, iron overload and cardiac disorders as important potential risks.

The Assessor considers, that the summary of safety concerns reflects the most important safety issues both from clinical development and from post-marketing experience.

However, the following should be addressed:

The Applicant should discuss the inclusion of "long-term safety", "safety in patients with immunological disease or active infection", "hypotension" and "cardiovascular disorders".

The Applicant should delete the Safety concern "Safety in children", as the product is not foreseen for children.

The inclusion of "Safety in patients with liver disorders" should be in accordance with the data provided in the response regarding subjects with impaired liver function treated so far with ferumoxytol in all clinical studies as requested in the clinical part.

In addition minor issues ("treatment of international birth date") should be clarified or corrected.
There occurred (serious) cases of *foetal bradycardia* following hypersensitivity reactions of pregnant patients under ferumoxytol treatment and also with other iv iron products.

Therefore this risk should be added as important **potential** risk.

3.3.1.2. Conclusions on the safety specification

Having considered the data in the safety specification it is considered that the following issues should be addressed as important **potential** risk: **foetal bradycardia.**

The Applicant should discuss the inclusion of "long-term safety", "safety in patients with immunological disease or active infection", "hypotension" and "cardiovascular disorders".

The Applicant should delete the Safety concern "Safety in children", as the product is not foreseen for children.

Based on the requested non-clinical and clinical analyses of the product's hepatotoxicity (1) and harms in hepatopathic patients (2), the applicant should discuss the need for (a) respective safety concern(s) beyond the hepatotoxicity related to iron overload. If such safety concern(s) in line with GVP are warranted, the applicant should classify them according to GVP and submit an accordingly updated RMP, including appropriate additional risk minimisation measure(s), routine pharmacovigilance activities beyond adverse reactions reporting and signal detection, and/or additional pharmacovigilance activities."

In addition minor issues ("treatment of international birth date") should be clarified or corrected.

3.3.2. Pharmacovigilance plan

The MAA proposes to address all RMP safety concern with routine pharmacovigilance activities.

Covis Pharma Europe B.V. has no specific adverse reaction follow-up questionnaires implemented, planned or ongoing for ferumoxytol.

As a part of routine pharmacovigilance activity, the MAA will monitor the following Adverse Events of Special Interest (AESI):

- Immune system disorders: Anaphylactic reactions/shock or Hypersensitivity
- Cardiac disorders: Cardiac arrest/Cardiogenic shock
- Vascular disorders: Hypotension
- Nervous system disorders: Syncope/Loss of consciousness/Unresponsive to stimuli

Assessor's comment: The MAA intends to rely on routine pharmacovigilance for all safety concerns. A number of AESI has been selected for further monitoring.

Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
N/A				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
N/A				
Category 3 - Required additional pharmacovigilance activities				
N/A				

Additional pharmacovigilance activities:

Currently there were two ongoing studies, AMAG-FER-CKD-354 and AMAG-FER-IDA-352:

Table Annex II Ongoing studies:

Indication	Protocol #	Phase	Countries	Protocol Title	Study Population	Planned Enrollment	Study Status
CKD (Pediatrics)	AMAG-FER-CKD-354	Phase 3	USA, Mexico, Hungary. Lithuania, Poland	Randomized, Open Label, Multicenter, Study to Evaluate the Safety (Compared to Iron Sucrose), Efficacy and Pharmacokinetics of Ferumoxytol for the Treatment of Iron Deficiency Anemia (IDA) in Pediatric Subjects with Chronic Kidney Disease	Pediatric subjects of IDA with CKD	129	Ongoing (As of 31-Dec-2021, total 42 screened, 28 randomized and 23 completed the study)
IDA (Pediatrics)	AMAG-FER-IDA-352	Phase 3	USA, Lithuania, Poland	A Phase 3, Randomized, Open-Label, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Ferumoxytol for the Treatment of Iron Deficiency Anemia (IDA) in Pediatric Subjects	Pediatric subjects with IDA	75	Ongoing (As of 31-Dec-2021, total 56 screened, 26 randomized and 23 completed the study)

Assessor's comment: The MAA seem to have inconsistently described the two ongoing studies, AMAG-FER-CKD-354 and AMAG-FER-IDA-352. Hence, in a question (Other concern) the clarify the provided information.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.3.3. Risk minimisation measures

3.3.3.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Hypersensitivity reactions	Routine risk communication: Summary of product characteristics (SmPC) sections: Posology and method of administration, Contraindications, Special warnings and precautions for use, and Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Posology and method of administration, the following is recommended: "Ferumoxytol should be administered as an infusion in 50-250 ml of sterile 0.9% sodium chloride or sterile 5% glucose for at least 15 minutes following dilution and must not be administered by direct injection of the undiluted product". In section Special warning and precautions for use, the following is recommended: "Ferumoxytol should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Patients should be carefully monitored for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each infusion of ferumoxytol. In addition, patients should be placed in a reclining or semi-reclining position during infusion and for at least 30 minutes thereafter. If hypersensitivity reactions or signs of intolerance occur during administration, the treatment must be stopped immediately. Facilities for cardiorespiratory resuscitation and equipment for handling acute anaphylactic/anaphylactoid reactions should be available, including an injectable 1:1000 adrenaline solution. Additional treatment with antihistamines and/or corticosteroids should be given as appropriate. Fatal and life-threatening hypersensitivity reactions have been observed with ferumoxytol in the post marketing setting. Clinical presentation has included anaphylactic type reactions presenting with cardiac arrest/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug

Safety concern	Routine risk minimisation activities
Hypotension	Routine risk communication: SmPC sections: Posology and method of administration, Special warnings and precautions for use and Undesirable effects Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Posology and method of administration, the following is recommended: "Ferumoxytol should be administered as an infusion in 50-250 ml of sterile 0.9% sodium chloride or sterile 5% glucose for at least 15 minutes following dilution and must not be administered by direct injection of the undiluted product. In section Special warnings and precautions for use, the following is recommended: "Patients should be monitored for signs and symptoms of hypotension including hypersensitivity during and for at least 30 minutes following each ferumoxytol administration." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Iron overload	Routine risk communication: SmPC sections Contraindications, Special warnings and precautions for use, Undesirable effects and Overdose Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Special warnings and precautions for use, the following is recommended: "Ferumoxytol should not be administered to patients with iron overload. Ferumoxytol must not be given to patients if their haemoglobin is greater than 12 g/dl, serum Transferrin Saturation (TSAT) is greater than 50% or ferritin is greater than 500 ng/ml (see section 4.2). Excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic haemosiderosis. Regularly monitor the haematologic response and iron parameters, such as serum ferritin and transferrin saturation, during parenteral iron therapy." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Cardiac disorders	Routine risk communication: SmPC section Undesirable effects Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug

Safety concern	Routine risk minimisation activities
Safety in pregnant women	Routine risk communication: SmPC section Fertility, pregnancy and lactation Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Fertility, pregnancy and lactation, the following is recommended: "A careful risk/benefit evaluation is therefore required before use during pregnancy and ferumoxytol should not be used during pregnancy unless clearly necessary (see section 4.4). If pregnancy occurs, the patients should be informed of the potential risk. Ferumoxytol should not be used in women of childbearing potential not using adequate contraception. Iron deficiency anaemia occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Treatment with ferumoxytol should be confined to second and third trimester if the benefit is judged to outweigh the potential risk for both the mother and the foetus. Ferumoxytol is not recommended in women of childbearing potential not using adequate contraception." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Safety in breastfeeding	Routine risk communication: SmPC section Fertility, pregnancy and lactation Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Fertility, pregnancy and lactation, the following is recommended: "A decision must be made whether to discontinue breast-feeding or to discontinue ferumoxytol therapy, taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the mother." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Safety in children	Routine risk communication: SmPC sections Posology and method of administration and Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: In sections Posology and method of administration and Special warnings and precautions for use, the following is recommended: "Ferumoxytol is not recommended in patients less than 18 years since the efficacy and safety have not been established in this age group." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug

Safety concern	Routine risk minimisation activities
Long term safety	Routine risk communication: SmPC section Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Special warnings and precautions for use, the following is recommended: "Ferumoxytol has been used to maintain haemoglobin levels for 6 months. Patients should be monitored (Haemoglobin, TSAT, Ferritin) to confirm that they are iron deficient and anaemic before repeated treatment (please see the guidance in Section 4.2 to avoid iron overload). Dosage recommendations of National Guidelines for the treatment of anaemia should be followed." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Safety in patients with liver disorders	Routine risk communication: SmPC section Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Special warnings and precautions for use, the following is recommended: "In patients with liver dysfunction or a history of liver disease, parenteral iron should only be administered after careful risk/benefit assessment." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug
Safety in patients with immunologic disease or active infection	Routine risk communication: SmPC section Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: In section Special warnings and precautions for use, the following is recommended: "Parenteral iron should be used with caution in cases of immunologic disease or acute or chronic infection. (…) It is not recommended to administer ferumoxytol to patients with ongoing bacteraemia. Patients with active infections requiring ongoing treatment were excluded from clinical studies with ferumoxytol. Clinicians should consider the potential risk of using ferumoxytol in patients with active systemic infections." Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription drug

Assessor's comment: Routine risk management relies on information in the SmPC and the legal status (Prescription drug) and this approach will be applied to all safety concerns. In addition, as an additional risk minimisation measure, the MAA intends to issue a DHPC for "Hypersensitivity reactions" and "Hypotension". However, little information is provided on these DHPCs and a question (Other concern) is raised.

3.3.3.2. Additional risk minimisation measures

The MAA proposes a "Direct healthcare professional communication" for Hypersensitivity reactions and Hypotension. The objective of this DHPC letter is to reduce the risk of hypersensitivity reactions and hypotension due to ferumoxytol and inform healthcare professionals on the important changes on the use of ferumoxytol related to method and duration of administration as well as on monitoring for signs and symptoms of hypersensitivity reactions including monitoring of blood pressure and pulse during and for at least 30 minutes following each infusion of ferumoxytol.

Clinical trial and post-marketing data following the change of administration from a rapid IV injection to a 15-minute infusion indicate that this change in administration reduce the risk of serious hypersensitivity reactions including life-threatening and fatal outcomes reported previously and allow healthcare professionals to better intervene at the first signs of prodromal symptoms of hypersensitivity.

The MAA will track the distribution of the DHPC but has no plan to measure the effectiveness of the risk communication.

Assessor's comment: Given the seriousness of hypersensitivity reaction, a DHPC may be reasonable. However, in the RMP on page 36 the MAA provides no information on the target audience or the planned distribution path for the DHPC. In an "Other concern" the MAA is asked to provide more detailed information on these items.

It is noted that Ferumoxytol was centrally authorised in the EU on 15/06/2012 under the brand name Rienso licensed to Takeda Pharma A/S and was indicated for the intravenous treatment of iron-deficiency anaemia in adult patients with chronic kidney disease (CKD). Rienso has since been withdrawn.

In 2015, the procedure EMEA/H/C/2215/PSUV/15 introduced aRMMs (in the form of a Healthcare professional checklist and Patient alert card) covering risks and warnings on hypersensitivity reactions and the monitoring of patients during and after administration.

In this MAA, only routine risk minimisation measures are being proposed by the MAH.

In an "Other concern" the MAA is asked to justify why aRMM are not being proposed to address the important identified risk of hypersensitivity reaction in line with previously mandated aRMM by the PRAC for a similar ferumoxytol containing product (Rienso).

3.3.3.3. Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that: the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.3.4. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.1 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed assessment report and in the list of questions in section 5.

3.4. Pharmacovigilance

3.4.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.4.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The Applicant seeks approval of ferumoxytol for the treatment of iron deficiency anaemia (IDA):

- who have intolerance to oral iron or have had unsatisfactory response to oral iron, or
- in adult patients with chronic kidney disease (CKD).

All patients with iron deficiency anemia should be treated with iron replacement therapy. The rationale is that there is risk for further organ damage/ischemia and progression of anemia unless the underlying cause of the deficiency is addressed and adequate iron stores are replenished.

4.1.2. Available therapies and unmet medical need

Most patients are treated with oral iron because it is generally effective, readily available, inexpensive, and safe. However, up to 70 percent of patients for whom oral iron is prescribed report gastrointestinal side effects. There are a number of settings in which the use of intravenous (IV) iron may be preferable to oral iron such as in case of poor adherence or gastrointestinal side effects of oral iron, preference to replete iron stores in one or two visits rather than over the course of several months, ongoing blood loss that exceeds the capacity of oral iron to meet needs (heavy uterine bleeding, mucosal telangiectasias, anatomic or physiologic condition that interferes with oral iron absorption, or coexisting inflammatory state that interferes with iron homeostasis.

Intravenous iron administration may reduce the use of bloodtransfusion, which in turn avoids transfusion-associated risks.

A number of intravenous (IV) iron formulations are already available, including ferric carboxymaltose (FCM), ferric gluconate (FG), iron sucrose (IS), ferric derisomaltose (also called iron isomaltoside), and low molecular weight iron dextran (LMW ID). All of these formulations have shown largely consistent efficacy and safety results (high molecular weight iron dextran, which had a greater risk of HSRs is noo longer available). Major differences include number of visits/time required to administer the full dose.

IV Iron products that can be administered as a single dose include LMW ID, FCM, and ferric derisomaltose (iron isomaltoside).

Ferumoxytol is proposed to be administered as two single dose 2 to 8 days apart.

4.1.3. Main clinical studies

The clinical efficacy dataset of this marketing authorisation application supporting the first-line IDA indication in CKD patients is based on the results of three pivotal phase 3 studies **FER-CKD-62,745-5**, **FER-CKD-62,745-6** and **FER-CKD-62,745-7**. These formed the pivotal basis for the initial approval in the CKD indication. With this new application, two further clinical trials investigating the IV administration of ferumoxytol against IV iron sucrose are submitted, i.e. phase 2 **FER-CKD-201** and phase 4 **FER—CKD-401**. Clinical safety data was derived from a total of 11 studies previously submitted (pivotal and supportive studies) for the initial MAA and of both new studies.

The clinical efficacy and safety dataset of this marketing authorisation application supporting the second-line **all-cause IDA** indication is based on the results of two pivotal clinical trials investigating the IV administration of ferumoxytol at a dose of 2 × 510mg. Subjects with a history of unsatisfactory oral iron therapy or in whom oral iron could not be used comprised the study population of each trial. Pivotal Phase 3 trial **AMAG-FER-IDA-301** was a randomised, double-blind superiority trial comparing ferumoxytol to placebo, while pivotal trial **AMAG-FER-IDA-302** was a randomised, open-label, non-inferiority trial comparing ferumoxytol with iron sucrose.

4.2. Favourable effects

IDA due to CKD

For the pivotal studies, analysis of the mean change from baseline in Hgb at Day 35 for each study showed superior efficacy compared to oral treatment, supported by secondary analyses on additional markers such as serum ferritin and TSAT levels. Mean increase in Hgb from baseline after ferumoxytol administration ranged from 0.71 to 1.02 g/dL (and 0.5g/dL in study -401; 1.02 g/dL in study -201 [subgroup analysis]) in HD subjects and 0.82 g/dL to 1.22 g/dL in non-dialysis dependent subjects (0.74g/dL in study -201 [subgroup analysis]) . The mean Hgb increase from baseline was much lower in response to oral treatment and ranged from 0.16 g/dL to 0.52g/dL in HD patients and 0.31 to 0.46 g/dL in ND subjects.

For the comparison with IV iron sucrose, non-inferiority could be shown based on a pre-specified NI margin of 0.5 g/dL, with an LS mean difference of ferumoxytol compared to IS of 0.1 g/dL (95%CI: -0.21 to 0.41) in study -201 and 0.13 g/dL (95%CI: -0.11 to 0.36) in study 401 (HD subjects only).

For the pivotal studies, proportion of Hgb responders (IV vs. oral) at day 35 ranged between 39% and 51.8% for ferumoxytol and 18.4% and 19.5% for oral treatment in ND subjects, and from 29.7% and

49.1% for ferumoxytol and 22.7% to 25.0% for oral treatment (pre- and post amendment, respectively) in HD subjects.

Proportions of Hgb responders in study -201 were largely comparable to the pivotal studies (50% and 41.5% for ferumoxytol and IS, respectively), but lower in study -401 (28.1% and 23.7%).

In study 62745-5 (Pre-amendment), another dose regimen of 4x255 mg was additionally investigated. Mean increase from baseline in Hgb was slightly higher compared to 2x510 mg (0.89 vs 0.78g/dL). Hgb responder rates were also higher in the 2x255 mg group (48.3% vs. 32.8%) (with a limited sample size of 60 and 58 subjects, respectively).

In the pivotal studies (-6 and -7), ESA co-treatment enhanced the effect of iron, IV treatment being superior to oral in ESA+ and ESA- subgroups. As per previous analysis in the Rienso application, no differences in the primary efficacy endpoint analyses were observed when adjusted for potential confounders (ESA co-treatment, low baseline ferritin values and history/signs of infection/inflammation) (data not submitted at this stage). In contrast, in study -201, subjects not on ESA therapy showed a lower change from baseline in both treatment groups compared to subjects with concomitant ESA therapy.

Re-treatment: A non-randomised extension phase after completion of the first (randomised) part of the pivotal clinical studies was optional for subjects with persistent IDA. A second treatment course of 2 x 510 mg of Feraheme was administered to a total of 69 patients. Baseline mean Hgb at readmission was 10.42 g/dl. Hgb increase after 5 weeks was 0.5 g/dl and the Hgb responder rate at Week 5 was 26.1%.

Re-treatment was further investigated in study -401. Mean change in Hgb level by month (evaluated over one year) showed an initial increase from baseline (10.4 and 10.3g/dL for ferumoxytol and IS, respectively) to 11.1 and 10.7g/dL at Month 2 and then slightly decreased and remained in a range between 10.9 and 10.7 g/dL (with increasing attrition rates towards the end of the follow-up).

All-cause IDA and IDA due to CKD Ferumoxytol was given at a **fixed dose** of 2 x 510mg regardless of bodyweight in all studies. Instructions for using a lower dose of 1 x 510mg in subjects with low bodyweight and a haemoglobin value >10-≤12 g/dl are included in section 4.2 of the SmPC.

The treatment effect of two doses of 510mg ferumoxytol each could be consistently replicated across four different trials in a study population with IDA that can be considered representative for the intended target population. A beneficial effect on accepted and clinically relevant surrogate laboratory outcomes could be shown in subjects with lower (8.9g/dL in IDA-301 and IDA-302) and relatively higher (10.42g/dL in IDA-304) baseline haemoglobin levels as well as over repeated treatment cycles in IDA-303. Superiority over placebo could be shown with a clinically relevant effect size in terms of Hgb mean increase from baseline of 2.54 g/dL (95%CI: 2.33, 2.75). The mean change of haemoglobin from baseline to week 5 was observed to be 2.7g/dL in IDA-301 and IDA-302, 2.6g/dL in IDA-303 and 1.382g/dL in IDA-304. In addition, non-inferiority to two different iron preparations used as active comparators in trials IDA-302 (iron sucrose) and IDA-304 (ferric carboxymaltose) was demonstrated. After one initial course of treatment, approximately 60% of the subjects who rolled over from IDA-301 into IDA-303 did not require further iron substitution. This effect was replicated in those patients stemming from the placebo arm of IDA-301, who received their first ferumoxytol treatment in the extension study. About 60% of those subjects did not need a further treatment cycle. These data illustrate a satisfactory durability of the treatment effect in subjects with IDA.

4.3. Uncertainties and limitations about favourable effects

IDA due to CKD

Robustness of efficacy results and consistency across studies

Treatment duration for oral iron of three weeks was likely too short to allow maximum response. The low response to oral therapy in study 62745-6 challenges the reported study drug compliance, as higher responses similar to study 62745-7 would have been anticipated. In addition, for study 62745-6 the sensitivity analysis using a worst case imputation for missing data showed a non-statistically significant result. In study 62745-7, the adjusted analyses for co-variates may suggest that the results be driven by one region/certain centres.

The 95%CIs for the primary and secondary analyses were not provided with this submission.

Studies -201 and -401: The robustness of primary endpoint analysis in the ITT and EE population needs further exploration, since the impact of important protocol violations and missing data is not clear at this stage, i.e. the missing data were imputed in a not necessarily conservative way (zero change from baseline was imputed for -401 and LOCF in -201) and the EE Population did not exclude patients with important protocol violations. The numbers of subjects used in the EE population in study -401 can further not be followed. In addition, the margin was not adequately justified, e.g. it remains unclear whether assay sensitivity could be maintained in particular in study -401, which showed an only low mean Hgb increase from baseline in both treatment groups (0.5 and 0.4 g/dL for ferumxytol and IS, respectively). Further evaluation of potential differences between treatment groups in key confounders (ESA use, previous iron use or blood transfusions, history/signs of infection/inflammation) and their potential impact on the results is also awaited.

Subgroup analyses: For the pivotal studies, most subgroup analyses were only discussed in the pooled analysis, except for ESA use (Yes/No), which was pre-specified in the protocol. Of note, adequacy of pooling and use of a modified ITT rather than ITT for the integrated analyses has not been justified. Particular consideration will be given to the subgroup analyses evaluated by study and the consistency across subgroup results. The subgroup analyses by CKD stage and dialysis status suggest that with worsening of the kidney function the response to iron replacement therapy is decreasing in the IV-treatment groups. Even though the highest response in Hgb was observed in subjects with CKD Stage 1 or 2, superiority compared to oral treatment could not be shown, though the numbers of subjects were too low to allow any firm conclusions (7 and 3 subjects in the IV and oral treatment group, respectively).

Patients with peritoneal dialysis were not included in the current studies.

Subgroup results of study -201 do not show non-inferiority of fermumoxytol compared to IS in non-dialysis subjects, subjects with CKD stage 1-3, no ESA use, age 65 to<75 years and <50 years (low sample sizes need to be kept in mind).

Re-treatment: For better interpretability of the data from retreatment periods, additional analyses are requested, as the current data do not allow to conclude on the time course of need of therapy or the effect size after each re-treatment cycle in subjects by total numbers of treatment periods received. No particular treatment recommendations for a long-term treatment can be given based on the currently provided data.

Dose adequacy, risk of iron overload and representativeness of the data for the EEA:

The cut-off values for TSAT and serum ferritin for study eligibility are considered rather high, in particular in subjects not on hemodialysis (HD). It is currently not known in how far the populations included in the studies reflect the target population, considering current European treatment recommendations are generally more cautious with regard to the risk of iron overload and lower cut-off values for treatment

are recommended (in terms of ferritin and TSAT). Proportions of subjects that fulfil *initial* and *re-treatment* criteria according to European treatment guidelines (*Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement*; Nephrol Dial Transplant (2013) 28: 1346–1359 doi: 10.1093/ndt/gft033) as well as proportions of subjects that exceeded the recommended thresholds after initial or re-treatment are not known at this stage.

In the MRI sub-study of study -401, liver iron concentrations were increased at the 6 and 12 month time points in both treatment groups, but were approximately 3-fold higher in the ferumoxytol group compared to the iron sucrose group. While this may be due to overestimation and possible interference of ferumoxytol with the MRI method as suggested by the Applicant, iron deposition in liver and spleen was already reported in animal models and further exploration thereof is needed.

All-cause IDA

For the **all-cause IDA** indication, an underlying condition subgroup analysis in subjects with AUB, cancer, GI disorders, and other underlying conditions was provided for studies IDA-301, IDA-302 and IDA-303. However, the number of subjects in several subgroups is very small, therefore the outcomes should only be interpreted with caution. A positive trend is evident for each subgroup, which is expected due to the pharmacodynamic mechanism of action.

Both indications

As there are no data supporting the recommendation of using a single dose only in patients with body weight below 50 kg and Hgb level of 10-12 g/dL, the Applicant is asked to provide an analysis of all subjects ≤ 50 kg who were treated with one and two doses of Feraheme with regard to mean change from baseline to week 5 in all main studies in tabulated form.

4.4. Unfavourable effects

IDA due to CKD

Treatment-emergent adverse events (TEAEs):

Initial studies: AEs were reported in 44% of patients treated with ferumoxytol, with oral iron and with placebo. In the initial CKD development programme, the most common AEs in CKD patients were diarrhoea, hypotension, nausea, dizziness, headache, constipation and peripheral oedema. These adverse events were consistently observed throughout the seven studies in this population and the postmarketing studies. With the intended dose of 2x 510mg these events occurred with a maximum incidence of 4% (for diarrhoea). Most of these AEs were less frequent compared to oral iron treatment (diarrhoea (4.0% vs. 8.2%), nausea (3.1% vs. 7.5%), constipation (2.1% vs. 5.7%) and oedema peripheral (2.0% vs. 3.2%). Hypotension was observed with a higher incidence in patients treated with ferumoxytol compared to oral iron (2.5% vs. 0.4%). This was also observed for dizziness (2.6% vs. 1.8%).

Study 401: In the ferumoxytol group an incidence of 80.6% was reported and 83.5% for iron sucrose.

Patients receiving ferumoxytol reported most AEs in the categories 'GI disorders' (37.8%), 'Infections and infestations' (32.7%), 'Injury, poisoning and procedural complications' (31.1%), and 'General disorders and administration site conditions' (29.1%) - all comparable to the iron sucrose group. Individual AEs occurred more frequent in the derumoxytol group: pyrexia (15 subjects, 7.7% vs 1 subject, 1%), pneumonia (11 subjects, 5.6% vs. 3 subjects, 3.1%), sepsis (10 subjects, 5.1% vs 2 subjects, 2.1%), %), urinary tract infection (12 subjects, 6.1% vs 3 subjects, 3.1%)

Severe AEs

Overall, very few severe adverse events (0.5%) were reported in the initial development programme (most common Diarrhoea).

In study CKD-401, a higher rate of serious acute respiratory failure was reported with ferumoxytol (7 subjects (3.6%), 6 of which were severe) compared to iron sucrose (2 subjects (2.1%), none severe).

Adverse Events Related to Study Drug

Initial studies: With the intended dose of 2x510mg the most frequently observed related AEs were diarrhoea (1.7%), hypotension (1.6%) and dizziness (1.4%).

Study 401: Fourteen AEs for 9 (4.6%) subjects in the ferumoxytol treatment group and 4 AEs for 4 subjects (4.1%) in the iron sucrose group were reported as related to study drug. None of the AEs was serious and no PT appeared more than once in any treatment group. Related AEs were seen primarily in TP1. Following AEs were reported in ferumoxytol group: hypertension, blood pressure increased, hyperkalaemia, hypocalcaemia, metabolic acidosis, Hypotension, Catheter site pruritus, Pruritus, Urticaria, Nausea.

Serious AEs

Initial studies: SAEs were reported in 10.1% of CKD patients treated with ferumoxytol, which is comparable to oral iron (11.7%) and iron sucrose (7.3) in study CKD-201 where an incidence of SAEs of 8.8% was reported. The most commonly reported SAEs are: infections (2.6%) and SAEs of cardiovascular nature (Cardiac Disorders: 18 patients (2.6%); "Cardiac failure congestive" (5 patients (0.7%)) and "hypotension" (4 patients (0.6%)).

Study 401: Serious adverse events (SAEs) were reported in both treatment arms: ferumoxytol: 47.4% (259 SAEs in 93 subjects); iron sucrose: 50.5% (174 SAEs in 49 subjects.

The most common categories were 'Infections and infestations' (19.4% vs. 17.5%) and 'Respiratory, thoracic and mediastinal disorders' (10.7% ad 6.2%).

The incidence of SAEs with ferumoxytol decreased from TP1 to TP3 including Cardiac disorders, GI disorders, Infections and infestations.

SAEs Related to Study Drug

Initial studies: Three subjects receiving ferumoxytol treatment experienced treatment related serious adverse events in all seven initial studies in CKD-patients.

Study 401: One event of anaphylactic reaction after treatment with ferumoxytol was reported as related to treatment

Death

In total 53 deaths (initial development: 31; postmarketing study CKD-401: 22) were reported for the CKD population. In total 35 patients on ferumoxytol treatment died – 26 received the 2x510mg dose. All deaths were considered as unrelated to study drug. The incidences in the respective studies are lower compared to the oral iron group in the initial studies (1.3% vs 2.8%) and slightly higher compared to the respective iron sucrose group in study CKD-401 (8.2% vs 6.2%).

Discontinuations and Withdrawals due to AEs

The incidence of adverse events that lead to discontinuations was between 1-4% in all CKD studies.

Repeat use

Initial studies: Data from 69 patients showed overall lower incidence of AEs compared to first course treartment in 1562 subjects.

Study 401: Data for Treatment period 1 -3 show a decreasing trend in AE rate in both treatment arms.

Laboratory Findings

Liver function test elevations were observed in more subjects receiving ferumoxytol (6.8%) compared to oral iron (2.8%) and placebo (4.2%). Most of the ferumoxytol cases were GGT abnormalities.

While ferritin increased similarly in treatment groups in all studies, the increase in the ferumoxytol group resulted in mean values close to 800ng/mL with maximum values far above that.

Drug-Drug Interactions

A general increase in AE incidences was observed in patients who received higher doses of ESA per week (no ESA 29.7%, ≥ 40,000 units/week: 64.7%). This was mainly observed for cardiovascular events with an increase from 1.4% up to 17.6%. A similar pattern was observed for thrombotic events (no ESA: 0.2%, ≥ 40,000 units/week: 17.6%).

A slight increase in thrombotic events was observed in patients who concomitantly receive anticoagulants (1.5%, compared to 0.5% for subjects on no anticoagulants).

All-cause IDA

Treatment-emergent adverse events (TEAEs):

***Initial treatment pool (301, 302*)**: TEAE were reported with following rates: ferumoxytol 46.1%, iron sucrose 44.2%, placebo 43.0%. The highest occurrence of TEAEs in the ferumoxytol group was in the SOC GI disorders (11.8%), followed by Nervous system disorders (11.0%), and Infections /infestations (9.1%). For TEAEs that occurred with incidence ≥1% higher in the FCM group, the incidence in ferumoxytol vs. iron sucrose, respectively, was: dizziness (3.3% vs. 1.5%), diarrhoea (2.1% vs 0), back pain (1.7% vs. 0.5%), dyspnoea (1.4% vs. 0), rash (1.4% vs 0.5%), upper respiratory tract infections (1.2% vs. 0.5%), myalgia (1.0% vs. 0). The majority of TEAEs was mild in severity and resolved.

Study 304: The most frequently affected SOCs were GI Disorders (11.2%), Nervous System Disorders (10.2%), General Disorders and Administration Site Conditions (7.8%), and Respiratory, Thoracic and Mediastinal Disorders (5.3%). For TEAEs that occurred with incidence ≥1% higher in the FCM group, the incidence in ferumoxytol vs. FCM, respectively, was: headache (6.0% vs. 8.2%), nausea (3.5% vs. 6.0%), dizziness (2.5% vs. 4.0%), pyrexia (0.7% vs. 2.2%), urticaria (0.3% vs. 1.3%) and hypophosphatemia (0 % vs. 1.8%). The majority of TEAEs was mild and resolved.

Adverse Events Related to Study Drug

Initial treatment pool (301, 302): Related TEAEs were reported at following rates: ferumoxytol 14.5%, iron sucrose 16.1%, placebo group 7.5%. The most common related TEAEs occurring in ≥1% of subjects treated with ferumoxytol (vs. placebo vs. iron sucrose) were: headache (2.1%; 0.5%; 1.0%), nausea (2.0%; 1.0%; 2.0%), dysgeusia (1.4%; 0.5%; 6.5%), dizziness (1.3%; 1.5%; 1.0%), and chest discomfort (1.0%; 0.0%; 1.0% respectively). A higher rate of **treatment-related vascular disorders** was reported with ferumoxytol compared to iron sucrose (1.8% vs 0.5%). TEAEs in the hepatobiliary disorders SOC were only reported in the ferumoxytol treatment group. One event of **hepatitis** in study 301 was considered related to ferumoxytol.

Study 304: The most common related TEAEs with ferumoxytol were headache (3.4%), nausea (1.8%), dizziness (1.5%), fatigue (1.5%), diarrhoea (1%). All other AEs considered related to ferumoxtol were reported at an incidence of <1%. Two events of Hypersensitivity and 1 event of Anaphylactic Reaction were considered related to ferumoxytol.

Serious AEs

Initial treatment pool (301, 302): There was a slightly higher rate of SAE in ferumoxytol group (3.3%) compared to iron sucrose group (2.5%) and placebo group (3.0%). Most of AEs (by PT) were reported in a single patient. Events that were reported in 2 or more subjects in ferumoxytol group were hypersensitivity reaction (3 events in 3 patients), anaphylactic reaction (2 events in 2 patients), anaemia (2 events in 2 patients) and uterine haemorrhage (2 events in 2 patients).

Study 304*:* The overall incidence of SAEs was comparable between ferumoxytol (3.6%) and FCM (3.5%) subjects. The incidence of SAEs in SOC **Infections and Infestations,** was slightly higher in ferumoxytol group (0.9% versus 0.3%) compared to FCM). A slightly higher rate of **serious vascular AEs** was reported with ferumoxytol compared to FCM (0.9% vs 0.3%).

SAEs Related to Study Drug

Initial treatment pool (301, 302): Nine events in 6 subjects (0.6%) were considered related to ferumoxytolt: hypersensitivity (3 subjects), anaphylactic reaction (2 subjects) and angioedema, urticarial, hypertension, tachycardia (1 subject each). All reported SAEs in the ferumoxytol treatment group were assessed as not related to study drug by the investigators except for hypersensitivity (n=3), anaphylactic reaction (n=3), hypertension (1), angioedema (1), urticaria (1), and tachycardia (1). All events resolved with standard medical treatment and all subjects recovered. No treatment-related SAEs were reported for subjects receiving iron sucrose or placebo.

Study 304: One AE of anaphylactic reaction (later re-classified to severe hypersensitivity reaction) was assessed to be related to ferumoxytol. Five related-SAEs were reported with FCM: Hypertensive Emergency, Atrial Fibrillation, Chest pain, Hypotension and Syncope). All treatment-related SAEs were reported as resolved on the same day that they occurred.

Death

Initial treatment pool (301, 302): Four deaths were reported in the pooled IDA-301 and IDA-302 safety data, 3 in ferumoxytol-treated subjects (0.3%) and 1 in a placebo-treated subject. All of the reported deaths were assessed as not related to study drug.

Study 304: Four deaths were reported in ferumoxytol and 2 in FCM group, neither was considered related to the study drug, nor due to hypersensitivity reactions.

Discontinuations and Withdrawals due to AEs

Initial treatment pool (301, 302): AEs resulting in permanent discontinuation of study drug were reported at following rates: ferumoxytol, 1.8%; placebo, 0.5%; and iron sucrose, 2.5%. Withdrawal from the study was reported at following rates: ferumoxytol, 0.6%; placebo, 1.5%; and iron sucrose, 1.0%.

Study 304**:** Temporary discontinuation of the study drug due to AEs was reported in 1.5% and 0.9% of subjects in ferumoxytol and FCM group, respectively. Permanent discontinuation of the study drug due to AEs was reported in 1.7% and 2.3% subjects in ferumoxytol and FCM group, respectively. The majority of AEs that led to discontinuation of ferumoxytol were moderate (66%), and most of them resolved. AEs that led to withdrawal from the study were reported in 1.3% and 1.2% of subjects in ferumoxytol and FCM group, respectively. Drug-related AEs that led to drug discontinuation were reported in 88% and

52% of subjects in ferumoxytol and FCM group, respectively. Drug-related AEs that led to withdrawal from the study were reported in 72% and 50% of subjects in ferumoxytol and FCM group, respectively.

Laboratory findings

Initial treatment pool (301, 302): One event of hepatitis in study 301 was considered related to ferumoxytol. In the Initial treatment pool an increase in the proportion of subjects with markedly abnormal GGT values (>3xULN) from baseline (22 subjects, 2.2%) to overall post-baseline (48 subjects 4.8%) was observed which was higher than in placebo (increase from 2.0% to 2.6%).

***Study 304*:** While ferritin increased similarly in treatment groups in all studies, the increase in the ferumoxytol group resulted in mean values close to 800ng/mL with maximum values far above that.

Hypersensitivity/anaphylactic reactions/hypotension

The incidence of composite of moderate/severe hypotension and hypersensitivity reactions in the initial treatment pool (301, 302) was 1.0% with ferumoxytol and 0.5% with iron sucrose. No AESI were reported with placebo. Moderate to severe hypotension was reported in six subjects in ferumoxytol group (0.6%) vs 1 subjects in iron sucrose group (0.5%). Moderate to severe hypersensitivity reactions occurred only with ferumoxytol (0.4%), no hypersensitivity reactions were reported for iron sucrose. The incidence of serious hypersensitivity/anaphylaxis reactions with ferumoxytol was 0.6%. No serious HSRs were reported with iron sucrose or placebo.

In Study IDA-304, the incidence of composite of moderate/severe hypotension and hypersensitivity reactions was 0.6% for ferumoxytol and 0.7% for FCM. Moderate to severe hypotension was reported in 2 subjects in ferumoxytol group (0.2%) vs 1 subject in FCM group (0.1%). Moderate to severe hypersensitivity reactions occurred only with ferumoxytol (0.4%). The incidence of serious hypersensitivity/anaphylaxis reactions was 0.4% with ferumoxytol and 0.6% with FCM.

In the initial treatment pool (IDA-301 and IDA-302) the rate of **serious hypersensitivity reactions** was higher in the ferumoxytol (6/1014, 0.6%) group as compared to iron sucrose and placebo (0 events in both groups). In addition, the rate of serious HSRs was higher in the IDA subgroup as compared to the CKD subgroup (IDA 0.6%, 6/1014 vs. CKD 0.12%, 2/1642). In Study IDA-304 where ferumoxytol was administered diluted as slow infusion, the incidence of serious hypersensitivity reactions was 0.4%.

In study 304 ferumoxytol was noninferior to FCM based on the pre-specified margin of 2.64% in the proportion of subjects with composite incidence of moderate to severe hypersensitivity reactions, including anaphylaxis, or moderate to severe hypotension at any time from Baseline up to Week 5 (ferumoxytol incidence 0.6%, FCM incidence 0.7%, treatment difference: -0.10, 95% CI [-0.80, 0.61]) (Non-inferiority $p<0.0001$).

No fatal event was associated with hypersensitivity/anaphylactic reactions in either study.

4.5. Uncertainties and limitations about unfavourable effects

Cardiovascular events

The most common SAEs are cardiovascular in nature as well as most common AEs leading to death. According to the narratives, a relation to pre-existing cardiovascular disease or respective risk factors is likely. Additional factors supporting this concern are the overall incidences of cardiovascular adverse events regardless of severity, most related (S)AEs were cardiovascular events, different incidences for Hgb increase and the results of the thorough QT study. In order to further investigate this potentially increased risk, the Applicant is asked to discuss this thoroughly including a safety analysis for patients with pre-existing cardiovascular disease. Further, the Applicant is asked to elaborate on the observed

benefit in these patients and discuss whether subgroups can be identified with increased risk for serious or even fatal cardiovascular events. Additionally, the Applicant should provide respective data (from literature) for other iron treatment options.

Increased risk for infections

Although the incidences for the overall category of infections were comparable between treatment groups, the individual adverse events might indicate a higher risk for patients treated with ferumoxytol. Further one patient on ferumoxytol died due to sepsis. Since intravenous iron has also been associated with an increased risk of infection in recent publications (Shah et al. 2021), the Applicant is asked to discuss the higher incidences of the individual AEs compared to iron sucrose and a potential causal relationship between ferumoxytol and death due to sepsis.

Lung oedema

In the literature, lung oedema was also observed as a consequence of IV iron administration (iron dextran) in dialysis patients (Freter et al., 1997). Respective AEs have been observed with higher incidences in the ferumoxytol group compared to iron sucrose (i.e. pleural effusion (7 subjects, 3.6% vs 0), pulmonary oedema (8 subjects, 4.1% vs 1 subject). The reported cases were also more severe (pulmonary oedema: 3 mild, 3 moderate and 2 severe, iron sucrose: 1 moderate; acute pulmonary oedema: ferumoxytol: 1 moderate and 1 severe; iron sucrose: 2 moderate). The higher incidence and severity require further discussion including plans to investigate this risk.

Death

The incidence of deaths in study CKD-401 is considerably higher compared to the initial studies, with the majority of fatal events in the initial treatment period (TP1, n=5) or during TP2 (n=9). This should be discussed taking into account different inclusion criteria, comorbidities and concomitant medications. Further, the most common adverse events leading to death were cardiovascular in nature and all of the subjects with cardiovascular-related deaths had significant pre-existing cardiovascular disease. Although the pre-existing conditions are acknowledged, this might also indicate an increased risk for such patients to experience potentially fatal events related to treatment with ferumoxytol.

Classification of Hypersensitivity reactions

Adverse events such as erythema, pruritus, urticaria, bronchospasm, dyspnea etc., which are also signs and symptoms of hypersensitivity reactions (preferred term 'hypersensitivity', SOC Immune system disorders) were reported under individual preferred terms (PT) and across different system organ classes (SOCs). Clarification is needed as to which criteria were applied to designate these events as 'hypersensitivity reactions' or 'not-hypersensitivity reactions'.

Iron overload

For both indications, the achieved increase of ferritin resulted in mean values close to 800ng/mL with maximum values far above that, which might be indicative for iron overload. Therefore, additional analyses are needed to understand whether this may be associated with worse safety profile.

Indicators of Liver Damage

GGT is known to be the most sensitive indicator of liver injury which precedes increase of other liver enzymes and in light of signals on potential iron deposits in liver from non-clinical data, this requires further investigation.

Drug-Drug Interactions

No formal interaction studies were performed. The group size in the provided subgroup analyses for CKD patients was limited. The potential underlying effects have not been discussed.

Long-term/repeat use safety data, liver damage

In the initial studies for the CKD indication, limited data from 69 patients are available who received a previous treatment with ferumoxytol. Study CKD-401 was supposed to evaluate efficacy and safety for repeat use with ferumoxytol compared to iron sucrose. Although in total data for up to eight treatment periods are available, the majority of patients only completed the third treatment period. Due to the small numbers of subjects who received more than three courses, no valid conclusions can be made on long-term/repetitive use of ferumoxytol.

The general trend of decreasing AE incidenes with repeat treatment cannot be reliably interpreted, due to decreaing sample sizes. Further, it can be assumed that patients who experienced severe/serious AEs during the first course did not receive a second course.

Study 303 was a rollover study in which subjects who completed IDA-301 could enroll and receive treatment with ferumoxytol if they met criteria for treatment over a 6-month follow-up period. This study provides safety data for repeat (episodic) treatment of ferumoxytol over a course of 7 months in total.However, the number of subjects who received more than 2 courses of ferumoxytol is too low to draw any meaningful conclusions on long-term safety of ferumoxytol. The need for continued treatment was not present in a significant proportion of patients. In addition, 7 months is a rather short time frame to investigate a therapy that is not chronic but episodic.

The non-clinical data indicate deposition of iron in many tissues including liver, lymph nodes spleen and choroid plexus with dose-dependent incidence. A MRI substudy was conducted within study CKD-401 with the aim to assess the potential for deposition of iron in cardiac, hepatic, and pancreatic tissues and changes in laboratory parameters over a two-year period. It was however terminated early (data up to one year) and did not provide conclusive results due a very limited number of patients (25) and limitations of the method itself. Its limitations notwithstanding, an increase in liver iron concentrations at the 6 and 12 month time was observed with ferumoxytol and iron sucrose, but was approximately 3-fold higher in the ferumoxytol group. While this may be due to overestimation and possible interference of ferumoxytol with the MRI method as suggested by the Applicant, iron deposition in liver and spleen has been reported in animal models, therefore further exploration is needed.

Elderly patients

The Applicant did not provide a separate discussion of elderly patients. Although it is acknowledged that this population is part of both populations and were enrolled in the clinical studies, a discussion of patients ≥65 years of age is warranted, especially regarding the uncertainties regarding cardiovascular risk factors and a potential risk of iron overload. This should be performed for each population separately and respective differences should be discussed.

Use in pregnancy

Data on use of ferumoxytol in pregnancy is very limited, however studies in animals have shown reproductive toxicity in rat and teratogenicity in rabbit. In order to decide on the adequate recommendations in the SmPC, additional non-clinical, clinical and post-marketing data are requested.

All-cause IDA Population

All-cause IDA comprises patients with heterogeneous underlying diseases. The vast majority of patients in previous IDA studies (301, 302) and study 304 had IDA due to AUB and GI disorders. There are concerns that some subgroups of the target population, considered to be more vulnerable and potentially more susceptible to serious or severe adverse events, have been underrepresented in IDA clinical studies. For instance, the number of patients with cancer was generally low across individual IDA studies and no conclusion on the safety of ferumoxytol in this subgroup can be made at present. In addition, the overall number of patients with relevant medical history such as cardiovascular disease or inflammatory disease, who are an important part of the target population, has not been clearly presented.

Further, while the majority of subjects in studies IDA-301 and IDA-302 were naïve to IV iron, it is unclear whether any new users were included in study IDA-304.

Hypersensitivity reactions, contribution of study 304

The non-inferiority margin has not been justified from the clinical perspective. Assumptions on the effect size, or in this case, AE rate, are not supported by reference to results of previous studies of FCM, but on AE rates observed in previous studies with ferumoxytol. Further, there is a disproportion between the adverse events taken into calculation for the assumptions of the AE rate and sample size on the one hand, and adverse events considered for the primary endpoint on the other hand. Namely, the estimate of AE rate was based on the cumulative incidence of 'mild', 'moderate' and 'severe' hypersensitivity reactions and hypotension. In contrast, only 'moderate' and 'severe' hypersensitivity reactions and hypotension are considered for the primary endpoint. This leads to an insensitive comparison and inappropriate (over-)estimation of the anticipated AEs rates for the PEP, on the one hand, which is reflected in the discrepancy between the assumed (3.3%) and observed AE rates (0.6%); and a likely underpowered study, on the other hand. There are also concerns that the severity of some events may have been misclassified, which needs further clarification. Hence, new analyses should be presented by the Applicant.

No head-to-head comparison between the two methods of administration is available, which is understandable from an ethical point of view, but it complicates the comparison.

In addition, it is unclear whether severe/serious hypersensitivity reactions occurred in mostly patients naïve to IV iron (after the first administration) or also in patients previously exposed to IV iron (after second or subsequenty administrations). Therefore, a separate analysis in requested based on data from all clinical studies.

Mechanism of hypersensitivity reactions

The root cause/mechanism of the severe hypersensitivity reactions is currently unclear. Any data that might help elucidate this issue should be provided.

4.6. Effects Table

Table Effects Table for Ferumoxytol 2x510 mg for the treatment of IDA in adults with CKD (data cut-off not provided)

Effect	Short Description	Unit	Ferumoxytol 2x510mg	Oral iron 200mg daily (21 days)	Iron sucrose (1000mg)*	Uncertainties/ Strength of evidence	References
Favourable Effects							
Hgb response	Mean change from Baseline in Hgb to Week 5 (ITT)	g/dL	0.82	0.16		Results for the presented ITT population are paralleled for the EE Population 95% CIs not provided for pivotal studies	(1)
			1.22	0.52			(2)
			1.02	0.46			(3)
	Mean change from baseline in Hgb to Week 5 (ITT)		0.71		0.61		(4)

Effect	Short Description	Unit	Ferumoxytol 2x510mg	Oral iron 200mg daily (21 days)	Iron sucrose (1000mg)*	Uncertainties/ Strength of evidence	References
	LS mean difference (95% CI) (ITT)		0.10 (-021 - 0.41)				
	Mean change from baseline in Hgb to Week 5 (ITT)		TP1 0.5		0.4		(5)
			TP2 0.6		0.3		
	LS mean difference (95% CI) (ITT)		TP1	0.13 (-0.11 – 0.36)			
			TP2	0.30 (0.06 – 0.55)			
Unfavourable Effects							
			Subjects (%)	Subjects (%)	Subjects (%)		
Death	Initial studies:	all	19 (1.1)	8 (2.8)		Ferumoxytol: N=1726 Oral iron: N=290	ISS
		2x510 mg dose	10 (1.3)			Ferumoxytol: N=692	ISS
	Study 401:		16 (8.2)		6 (6.2)		CSR 401
SAEs	Initial studies:		7 (12.1)	34 (11.7)			ISS
	Study 401:		93 (47.4)		49 (50.5)		CSR 401

Abbreviations: CKD: Chronic kidney disease; HD: Hemodialysis; ND: non-dialysis dependent; TP: Treatment Period

Notes:*administered as 5x200 mg in ND subjects and 10x100mg in HD subjects; (1) data from pivotal study 62,745-6 in ND subjects (2) data from pivotal study 62,745-7 in ND subjects (3) data from pivotal study 62,745-5 (post-amendment) in HD subjects (4) data from study -201 in HD and ND subjects (5) data from study Long term study -401 in HD subjects

Table: Effects Table for Ferumoxytol 2x510 mg for the treatment of IDA in adults who have intolerance to oral iron or have had unsatisfactory response to oral iron (data cut-off not provided)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects all-cause IDA						
Haemoglobin (Hgb)	Mean change of Hgb from baseline to week 5	g/dL	2.7 (Ferumoxytol 1.02 g)	0.1 (PLB)	Treatment effect could be replicated over 4 studies, NI to 2 different iron preparations used as active comparators; study -303 with methodological limitations	(1)
			2.7 (Ferumoxytol 1.02 g)	2.4 (Iron sucrose 1.0)g		(2)
			2.6 (Ferumoxytol 1.02 g)	(Uncontrolled EXT study)		(3)
			1.382 (Ferumoxytol 1.02 g)	1.623 (FCM 1.5g)		(4)
Unfavourable Effects						
Composite of moderate to severe HSR, anaphylactic reaction and moderate to severe hypotension	Initial treatment pool (301, 302 rapid injection)		Ferumoxytol 10/1014 (1.0%)	Iron sucrose 1/199 (0.5%)	Open label design of study 302, small sample size	(1, 2, 4)
	Study IDA-304 (slow infusion)		Ferumoxytol 6/997 (0.6%)	FCM 7/1000 (0.7%)	small sample size, lack of assay sensitivity for the comparator	
Serious HSRs	Initial treatment pool (301, 302 rapid injection)		Ferumoxytol 6/1014 (1.0%)	Iron sucrose 0	Same as above	(1, 2, 4)
	Study IDA-304 (slow infusion)		Ferumoxytol 4/997 (0.4%)	FCM 6/1000		
Cardiac events	Initial treatment pool (301, 302 rapid injection)		Ferumoxytol 2.2% (0.5% related)	Iron sucrose 1.5% (0.5% related)	Same as above	(1, 2, 4)
	Study IDA-304 (slow infusion)		Ferumoxytol 1.8% (0.7% related)	FCM 2.0% (0.5% related)		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Vascular events	Initial treatment pool (301, 302 rapid injection) Study IDA-304 (slow infusion)		Ferumoxytol 3.3% (1.8% related) Ferumoxytol 2.7% (1.5% related; 0.9% serious)	Iron sucrose 3.0% (0.5% related) FCM 4.6% (2.0% related; 0.3% serious)	Same as above	(1, 2, 4)
Serious TEAEs in SOC Infections and infestations	Initial treatment pool (301, 302 rapid injection) Study IDA-304 (slow infusion)		Ferumoxytol 9/997 (0.9%)	FCM 3/1000 (0.3%)	small sample size, lack of assay sensitivity for the comparator	(4)
GGT increased	Proportion of subjects who had GGT>3xULN		Ferumoxytol at baseline 2.2% Ferumoxytol overall-post baseline 4.8%	Placebo at baseline 2.0% Placebo overall-post baseline 2.6%	Randomized, Double-blind, placebo controlled trial	(1)

Abbreviations: EXT: extension; FCM;: ferric carboxymaltose; IDA: Iron deficiency anemia; NI: non-inferiority ; PLB : Placebo

Notes: (1) data from the pivotal placebo- controlled study (IDA-301) (2) data from the pivotal controlled study compared to iron sucrose (IDA-302) (3) data from the single arm long term extension study (IDA-303); (4) Data from study with Ferric carboxymaltose (IDA-304); Clin Efficacy part of AR 3.3.4

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

A formal major objection is raised on the indication wording, which should be further simplified. The targeted CKD IDA population is considered a subpopulation of IDA patients and clinical findings do not suggest different clinical benefits in CKD patients as compared to patients with IDA due to other causes. In addition, it is considered that ferumoxytol should be reserved for second line treatment, i.e. when the oral route is insufficient or poorly tolerated, based on general safety concerns related to hypersensitivity reactions including anaphylaxis, associated with IV iron products. The following wording is suggested: "Ferumoxytol is indicated for the treatment of iron deficiency anemia in adults when oral iron preparations are ineffective or cannot be used (see section 5.1)". This is considered to cover all IDA subpopulations that were investigated and reflects the available dataset and overall study programme (MO). In addition, the sentence "The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2)" should be deleted as it is not considered necessary and determination if a patient fulfils the indication is expected to be covered by general medicinal state-of-the-art knowledge of the treating physician.

IDA due to CKD

The effect on Hgb as demonstrated in the pivotal studies is considered clinically relevant for the CKD population and the proposed reduced frequency of administrations in particular valuable for Non HD-patients (in a second line indication), where the administration of a reduced frequency of infusions can be considered an advantage to preserve veins for future access. Further sensitivity analyses are however requested in order to further explore the robustness of the treatment effect across all trials. Of note, the concerns that were previously discussed in the Rienso application are repeated within this submission for completeness, as the dossier was not updated with the responses from the previous procedure, but are not considered to have a significant impact on the efficacy conclusion.

It is further noted that, although the adequacy of pooling and use of a modified ITT rather than ITT for the integrated analyses has not been justified, this raises no concern, since the overall pooled efficacy analysis does not contribute in a significant way to the benefit risk balance.

Dose adequacy: A fixed dose regimen of 2x510 mg is proposed for all subjects, except those with body weight below 50 kg and Hgb values 10-12g/dL. The dose has overall not been adequately justified, e.g., reference was made to outdated treatment guidelines and was also not discussed with regard to the broad population, which includes CKD patients with stages 1-5 not on hemodialysis or on hemodialysis or peritoneal dialysis, with or without concomitant ESA therapy, respectively. Distinction between absolute and function IDA might also be necessary in this discussion. It will therefore be important to evaluate whether the thresholds for ferritin and TSAT levels that are recommended by current European treatment guidelines might be exceeded with this fixed dose regimen and if yes, what patients might be particularly at risk for excess iron. Reference is also made to the findings of the MRI sub-study in study -401, where a 3-fold higher liver concentration was observed compared to iron sucrose. Iron deposition in liver and spleen was also reported in animal models. In that respect, it is also important to further evaluate whether the data generated are sufficiently representative for the European target population. While mean serum ferritin and TSAT levels at baseline were lower in the pivotal studies and are likely sufficient to allow a conclusion on the adequacy of the dose after *initial* treatment, mean baseline values particularly for ferritin in the study investigating re-treatment with Ferumoxytol against iron sucrose over one year (study -401) were much higher and may not be sufficient to provide further recommendations for re-treatment with ferumoxytol. This is not raised as a major objection, however, since this can be adequately handled in the SmPC, as was also done in the previous Rienso application. While the data are likely sufficient to support re-treatment with one further cycle, further long term use might not be fully supported by representative data for the EEA. At this stage, the data provided are not fully comprehensive and the additional analyses requested will help to increase interpretability regarding the time course and the number of treatment courses needed and whether the results can be considered representative for the European situation.

Description of study population: The question may arise whether the study population had been previously treated with oral iron therapy, in particular ND or PD subjects. In order to be able to better describe the population under section 5.1 of the SmPC, further information is requested in that regard. It should also be kept in mind that the European treatment recommendations suggest a trial of oral therapy in ND and PD CKD subjects, when tolerated, '*if there is an absolute iron deficiency (TSAT <20% and serum ferritin <100 ng/mL) or an increase in Hb concentration without starting ESA treatment is desired and TSAT is <25% and ferritin is <200 ng/mL in ND-CKD patients and <25% and ferritin is <300 ng/mL in dialysis patients.*' (Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement; 2013).
It is further notable that the data from the pivotal trials suggest a lower response in Hgb with decreasing kidney function, but when particularly looking at the subpopulation with lower disease severity, the

subgroup analysis results from study -201 indicate a lower effect on Hgb compared to iron sucrose in patients with lower CKD stage. In addition, superiority compared to oral treatment was also not shown in the pivotal trials in patients with CKD stage 1-2, but these results must be cautiously interpreted due to low sample sizes. Furthermore, extrapolability of the results to CKD subjects on PD needs further discussion.

All-cause IDA

The dose of 2x510mg is justified for the all-cause IDA target population based on the beneficial treatment effect that could be consistently replicated across four different trials in subjects with IDA.
However, since use of a lower dose of 1x510 mg in patients with body weight<50 kg and Hgb level of 10-12g/dL is suggested and could be considered overall acceptable, as to avoid excess iron accumulation, further analyses are awaited to provide further support for this approach based on the study results. The study populations were comprised of the following subgroups: Abnormal Uterine Bleeding (AUB), Cancer, GI Disorders, Postpartum Anaemia, CKD (-study 304 only) and Other (the latter not being further determined, however) and are considered representative of the broad all-cause IDA target population. These data illustrate a satisfactory durability of the treatment effect in subjects with IDA. Data on repeat use is however limited to a 6 month-period and 244 subjects who received more than one Ferumoxytol treatment course in the all-IDA extension study (IDA-303). Only 69 subjects received more than two courses. Re-assessment of the need of further treatment courses as well as the lack of long term data beyond 6 months will be important to be adequately reflected in the SmPC. Some uncertainties will need to be addressed by providing further sensitivity analyses, but this is not considered to significantly affect the benefit risk balance for this indication.

Even though uncertainties remain with regard to efficacy outcomes in certain subgroups, no subgroup should be excluded from the label as no compelling reason exists for any subgroup to assume that intravenously administered and therefore 100% bioavailable iron would not influence the iron metabolism and in consequence, erythropoiesis in a beneficial way. The underlying mechanism causing anaemia is more complex and difficult to treat in cancer patients and is also influenced by type of chemotherapy etc., therefore, the trend towards lower Hgb increases observed in this subgroup is not surprising.

Overall safety profile

The safety profile of Ferumoxytol is broadly in line with that of other IV iron products that have been used as comparators in the clinical studies such as iron sucrose and FCM and partially oral iron. Most of the reported adverse events were mild in severity and resolved. Severe hypersensitivity reactions, hypotension and increased risk for infections are known risks for all IV iron products and were reported at overall low rates. However, for CKD patients the majority of serious AEs and AEs resulting in death were of cardiovascular nature and occurred in patients with underlying cardiovascular disease or respective risk factors. Given that these are common co-morbidities in this population, it has to be clarified whether subgroups with an increased risk for fatal or serious events exist. This might require further amendments to the SmPC. The overall number of patients with relevant medical history such as cardiovascular disease or inflammatory disease, who are an important part of the target population but are considered more vulnerable, has not been clearly presented. This aspect has partly been covered by the wording in the SmPC which states that the risk of hypersensitivity reactions is greater in subjects with known allergies including drug allergies, and patients with a history of severe asthma, eczema or other atopic allergy immune or inflammatory conditions, however this should be addressed in a more comprehensible manner within the new pooled safety analysis.

Hypersensitivity reactions can occur during infusion of any intravenous iron product; such reactions are rare but can be life-threatening. According to the external data, the risk of anaphylactic reactions is highest with new users. Accordingly, additional analyses are requested for ferumoxytol based on data from all studies. Morevover, additional information on the prior history of IV iron use is also requested for study -304, in order to exlude the possibility that the lower incidence of hypersensitivity reactions/hypotension observed in this study was due to the majority of subjects included being previously exposed to IV iron.
Based on the provided results of study 304 no robust conclusions can be made whether the new method of administration indeed decreases the risk of hypersensitivity reactions compared to the 'old' method of administration i.e. undiluted rapid injection. It was, however, to be expected that this study could not allow for robust conclusions on this matter, given the disproportionaly small sample size compared to the incidence rate. Therefore, the contribution of this study to the overall concerns raised in the past as regards the higher risk for hypersensitivity/anaphylactic reactions cannot be allayed with a high degree of confidence solely based on the results from this study. Nonetheless, the study provided some reassurance that these events are rare and the incidence may be comparable to that of the comparator. Data from the postmarketing in the US are further reassuring that the new method of administration does reduce the risk for hypersensitivity and anaphylaxis to a rate that seems to be comparable to other IV iron products. However, it is considered important that treating physicians are well-informed about that risk and the new method of administration, also considering that the product was previously approved with the "old" method of administration. In addition to adequate SmPC wording, additional risk minimization measures such as DHPC and educational material might be considered.
The data on whether some subgroups of the target population might be at an increased risk for severe hypersensitivity reactions is still incomplete and a new integrated analysis is requested to help further elucidate this issue.
Other uncertainties regarding e.g. drug-drug interactions might require amendments to the SmPC.

4.7.2. Balance of benefits and risks

Despite some uncertainties regarding the interpretation of efficacy results that need to be clarified, Ferumoxytol showed non-inferiority compared to IV iron sucrose in **CKD subjects with IDA** (and superiority compared to oral iron therapy with remaining uncertainty due to short oral iron treatment duration and observed low responses) as per the primary efficacy analysis of mean Hemoglobin change from baseline at week 5 and supported by additional relevant secondary endpoints.

Ferumoxytol at a dose of 2x 510mg showed superiority against placebo and non-inferiority against IV iron sucrose and IV ferric carboxymaltose and showed consistent effects across four different trials in a study population with **all-cause IDA** that can be considered representative for the intended target population.

Although some uncertainties are yet to be resolved, the overall safety profile of ferumoxytol appears similar to other IV iron products. Severe hypersensitivity reactions, hypotension, increased risk for infections and risk iron deposit are known risks for all IV iron products and were reported at low rates. The risk for severe hypersensitivity reactions appears overall low but needs an adequate wording in the SmPC (including contraindications in subgroups known to be at increased risk and additional warnings) and a clear communication to treating physicians.

Taking into consideration demonstrated efficacy in correcting iron-deficiency anaemia and the safety profile largely favourable and broadly in line with other approved IV iron products, the benefit risk ratio of ferumoxytol could be positive from a clinical perspective, provided the uncertainties listed in the LoQ

are resolved and the PI is updated in accordance with the comments made. However, there is a MO on the wording of indication and therefore the overall B/R is currently negative.

4.7.3. Additional considerations on the benefit-risk balance

N/A

4.8. Conclusions

The overall benefit /risk balance of FERAHEME is currently negative.