EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 April 2012
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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Rienso

Common name: **Ferumoxytol**

Procedure No.: **EMEA/H/C/002215**

Note

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

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Product information

Name of the medicinal product:	Rienso
Applicant:	Takeda Global Research and Development Centre (Europe) Ltd. 61 Aldwych London WC2B 4AE United Kingdom
Active substance:	Ferumoxytol
Common Name:	Ferumoxytol
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication:	Rienso is indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2).
Pharmaceutical form:	Solution for injection
Strength:	30 mg/ml
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package sizes:	1 vial, 10 vials

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List of abbreviations

AC	Anticoagulants
ACE	angiotensin converting enzyme
AE	adverse event
ALT	alanine aminotransferase
AIM	Active Ingredient Manufacturer
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APEP	absolute prediction error percent
API	Active Pharmaceutical Ingredient
APTT	activated partial thromboplastin time
AR	Assessment report
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
AV	atrioventricular
bw	body weight
CHF	Chronic heart failure
CHMP	Committee for Medicinal Products for Human Use
CHr	reticulocyte haemoglobin content
CKD	chronic kidney disease
Cl	Clearance
C_{max}	maximum observed concentration in blood/serum
CNS	central nervous system
CSR	clinical study report
DDI	drug-drug interaction
DLS	Dynamic Light Scattering spectroscopy
DSM	DSM Pharmaceuticals, Inc (USA)
ECG	electrocardiogram
EEP	Efficacy Evaluable Population
eGFR	estimated glomerular filtration rate
EMA; EMEA	European Medicines Agency
EPO	erythropoietin
ESA	erythropoiesis stimulating agent(s)
EU	European Union
FDA	Food and Drug Administration
Fe	iron
FTIR	Fourier Transformation Infra Red spectroscopy
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl-transferase
GLP	Good Laboratory Practice
GPC	Gel Permeation Chromatography
h	hour
HD	haemodialysis
HED	human equivalent dose
hERG	human ether-a-go-go related gene
Hgb	haemoglobin
HLN	higher limit of normal
HPLC	High Performance Liquid Chromatography
i.a.	intra-arterial
i.m.	intra-muscular
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
IDA	iron deficiency anaemia
IL	interleukin
ISE	Integrated Summary of Effectiveness
ITT	Intent-to-Treat
IV	intravenous(ly)
IVRS	Interactive Voice Response System

K/DOQI	Kidney Disease Outcomes Quality Initiative
kDa	kilo Dalton
kg	kilogram
K_m	Michaelis-Menten constant
λz	apparent elimination rate constant
LLN	lower limit of normal
LLOQ	lower limit of quantification
LSC	Liquid scintillation counting
MAA	marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µg	microgram
MHRA	National authority of the United Kingdom
min	minute
ml	millilitre
MPA	National authority of Sweden
MR	magnetic resonance
MRA	magnetic resonance angiography
MRI	Magnetic Resonance Imaging
N, n	number of subjects
nm	nanometer
NMR	Nuclear Magnetic Resonance Spectroscopy (prefix: ^{1}H-, ^{13}C-)
NOAEL	No observed adverse effect level
NOEL	No observed effect level
p.v.	para-venous
PBMC	peripheral blood mononuclear cells
PD	peritoneal dialysis
PD	pharmacodynamic
PEP	Prediction Error Percent
pH	power of Hydrogen
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PK	pharmacokinetic(s)
ppm	parts per million
PR	Interval measured from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex (onset of ventricular depolarization)
PSC	Polyglucose Sorbitol Carboxymethylether
PT	prothrombin time
p-value	probability value
Q	distribution clearance
QA	quality assurance
QRS	Interval measured from beginning of the Q wave to the end of the S wave; time it takes for ventricular depolarization to occur
QT	interval measured from the beginning of the QRS complex to the end of the T wave; represents total duration of ventricular systole
QTc	corrected QT interval
QTcB	QT Interval using the Bazett Correction Formula
QTcF	QT Interval using the Fridericia Correction Formula
QTcI	corrected QT interval using an individual correction method
R	readmission phase
RBC(s)	red blood cell(s)
s.c.	sub-cutaneous
SAE(s)	serious adverse event(s)
SBP	systolic blood pressure
SD	standard deviation
SEC	Size Exclusion Chromatography
SmPC	Summary of product characteristics
T_1	spin-lattice relaxation time
$t_{1/2}$	serum elimination half-life
T_2	spin-spin relaxation time
TCT	thrombin clotting time
TD-NMR	time domain nuclear magnetic resonance

TEAE	treatment--emergent adverse event
TIBC	total iron binding capacity
TSAT	transferrin saturation
UK	United Kingdom
USA	United States of America
USAN	United States Approved Names
V1	central volume of distribution
V2	peripheral volume of distribution
Vd	volume of distribution
VE-MRI	vascular-enhanced magnetic resonance imaging
V_{max}	maximum elimination rate
V_{ss}	volume of distribution at steady state
WBC	white blood cell(s)
WNL	within normal limits
w/v	Weight / Volume
w/w	Weight / Weight
XRD	X-Ray Diffraction spectroscopy
XRF	X-Ray Fluorescence spectroscopy

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AMAG Europe Limited submitted on 31 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rienso, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 2 June 2008. The applicant was changed to Takeda Global Research and Development Centre (Europe) Ltd during the procedure.

The applicant applied for the following indication: *treatment of iron deficiency in adult patients with chronic kidney disease (CKD). The diagnosis of iro*n deficiency *must be based on appropriate laboratory tests.*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/38/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/38/2010 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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.

New active Substance status

The applicant requested the active substance ferumoxytol contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

Rienso (Feraheme) has been given a Marketing Authorisation in the United States on 30 June 2009 and in Canada on 8 December 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Dr Harald Enzmann Co-Rapporteur: Dr Romaldas Maciulaitis

- The application was received by the EMA on 31 May 2010.
- The procedure started on 23 June 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 September 2010 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 September 2010 .
- During the meeting on 21 October 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 October 2010 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2011 .
- During the CHMP meeting on 23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed by the applicant .
- The summary report of the inspection was issued on 19 December 2011.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 March 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 April 2011 .
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 April 2011 .
- During the meeting on 16-19 April 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rienso on 19 April 2012.

2. Scientific discussion

2.1. Introduction

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, and increased iron utilization for red blood cell (RBC) production in response to erythropoiesis stimulating agents (ESA).

The correction of iron deficiency and 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.

Intravenous (IV) administration is considered the optimum route for the delivery of iron to patients with CKD, as oral iron is poorly absorbed in uraemic individuals. Most CKD patients initially require a cumulative dose of 600 – 1000 mg of iron to restore Hgb levels and to replete iron stores in the correction phase, followed by regular lower doses to maintain the target Hgb level as specified by the relevant therapy guidelines (2004 EBPG Anaemia Guidelines and 2006 KDOQI Guidelines).

The currently available parenteral iron preparations are generally considered equally efficacious but vary in their safety profiles. Anaphylactic/anaphylactoid reactions, hypotension, risk of sensitisation, peripheral oedema, infections, iron overload and pigmentation changes are adverse effects of special concern as are possible acute and long term toxic effects. To prevent adverse effects, the currently used standard preparations should be administered slowly and in small single doses after dilution.

Rienso is a new iron preparation for intravenous treatment of iron deficiency states in adult patients with chronic kidney disease (CKD). The active substance is an aqueous colloidal suspension of ferric superparamagnetic iron oxide particles surrounded by a polyglucose sorbitol carboxymethylether (PSC) carbohydrate shell for isolation and a molecular weight of approximately 750 kDa. The solution contains 30 mg/ml of elemental iron and mannitolit is isotonic with an osmolality of 270 - 330 mOsm/kg and has a pH of 6 to 8.

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 (RES) 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. The precise cellular events of iron loading onto transferrin, however, and the export of iron-transferrin complexes from RES macrophages into the blood remain unknown.

Ferumoxytol has been designed to enable the administration of high dose regimens without dilution at rapid injection rates, thus requiring shorter infusion times and fewer injections compared to conventional IV iron replacement therapies currently available in Europe.

The applicant applied for the following indication: *treatment of iron deficiency in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests.*

The final indication agreed by the CHMP is for *the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2).*

2.2. Quality aspects

2.2.1. Introduction

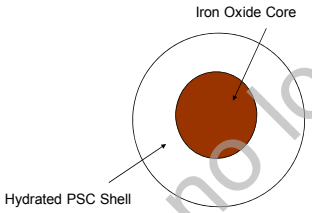
Rienso is presented as solution for injection containing 30 mg of iron as ferumoxytol (active substance) in each ml of solution. Each vial contains 17 ml of solution equivalent of 510 mg of iron. The solution is black to reddish brown, isotonic with osmolality of 270 – 330 mOsm/kg and pH of 6.5 – 8.0.
Excipients used to formulate Rienso include polyglucose-sorbitol carboxymethylether (PSC), mannitol, water for injections, sodium hydroxide and hydrochloric acid for pH adjustment as well as nitrogen.

Rienso is supplied in vials made of type I glass with a chlorobutyl rubber stoppers and aluminium crimp-on seals.

2.2.2. Active Substance

Ferumoxytol (USAN) is a dark-brown substance, which consists of nano-sized super paramagnetic iron (III)-oxide-cores coated with a small-sized carbohydrate shell of polyglucose sorbitol carboxymethylether (PSC).

Schematic structure of ferumoxytol is presented below:



The proposed molecular formula of Ferumoxytol is:

$$Fe_{5874}O_{8752}C_{11719}H_{18682}O_{9933}Na_{414}$$.

The iron crystals are a mixture of non-stoichiometric iron oxides. The general formula for the superparamagnetic iron oxide which is covered with PSC is:

$$(Fe_2O_3)_m(FeO)_n$$

The backbone of PSC consists of α-1,6 glycosidic linkages between glucose molecules. The general formula for the polysaccharide PSC that forms a coating around the iron oxide is: $C_6H_{11}O_5$ - $(C_6H_{10}O_5)_{60}$ - $C_6H_{13}O_6$ with 14 $(C_2H_2O_2Na)$ carboxylate groups.

The structure of the active substance was analysed by XRD as a constitution of mostly oxidised magnetite. The crystals have an inverse spinal structure, a cubic shape. Its molecular weight is approximately 750 kDa.

Manufacture

The active substance manufacturing process is part of a continuous manufacturing process with the in-situ formation of the purified iron oxide-complex immediately followed by the preparation of the

finished product intermediate, which is formulated from the aqueous colloidal active substance, PSC and water for injections with the pH adjusted.

Ferumoxytol is obtained in a chemical reaction between iron salts and ammonium hydroxide in presence of polyglucose sorbitol carboxymethylether (PSC). It is a semi-synthetic polyglucose polymer made from the reduction and carboxymethylation of dextran.

In general, sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described. The manufacturing process has been shown to be robust and reproducible over several reaction parameters changes.

The active substance and the finished product (solution) have been characterized using:

- magnetic susceptibility and MR relaxivity to describe the magnetic properties of the colloid,
- transmission electron microscopy, diffuse reflectance and Fourier transformed infrared spectroscopy (FTIR) to describe the bulk properties of the iron oxide crystal,
- size exclusion chromatography and dynamic light scattering to describe the colloidal particle size in solution,
- X-ray diffraction (XRD) to obtain information on crystallinity, including crystal size

Potential impurities have been well discussed in relation to the method of synthesis and the raw materials utilized in the process, permitted daily exposure limits and forced degradation studies.

Specification

The active substance manufacturing process is part of a continuous manufacturing process with the in-situ formation of the iron oxide-complex (ferumoxytol) immediately followed by the preparation of the finished product intermediate and ferumoxytol is not isolated. The quality of the active substance and subsequent intermediate is assured via appropriate in-process control specification. This specification includes tests for appearance, conductivity, iron content, PSC content, ratio of PSC to iron.

A non-routine testing was proposed for the PSC content. The approach was accepted, however the Committee recommended further monitoring of the ratio total PSC / free PSC during long term stability testing in order to demonstrate that this ratio will be a constant over a long time.

A detailed description for all analytical methods was provided. Complete and satisfactory method validation data was provided for the non compendial (*in-house*) analytical methods.

In general specification limits and analytical methods proposed are suitable to control the quality of the active substance and the finished product intermediate.

Batch analysis results have been presented. All batches were manufactured by the proposed commercial manufacturer according to the proposed processes. It can be concluded that the batch analysis results indicate that the processes are reproducible and under control.

Stability

The active substance manufacturing process is part of a continuous manufacturing process of the finished product in which active substance is not isolated.

The intermediate used in manufacturing process of the finished product can be stored therefore studies have been performed to validate the proposed maximum holding time. These data were found acceptable, however the Committee recommended continuation of the stability program (nominal and

accelerated storage conditions) Based on the available stability data the finished product intermediate was shown to be stable when stored under the proposed conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to obtain an iron containing injectable product with lower hypersensitivity reactions (anaphylaxis) than conventional iron dextran/sucrose/glucose injections. Only one formulation was developed and used throughout the development. This is the same formulation which was used in all clinical trials and which is intended for commercialisation.

Properties of the active substance that were explored during development included: stability, particle size, robustness of manufacturing and low activity in animal models of carbohydrate anaphylaxis. The ease with which the complex is eliminated from the body and its stability were also considered.

The PSC coating was selected to minimise the risk of anaphylactic potential. Alternative coatings to PSC were also considered during development. The compounds were screened for anaphylactic reactions and ease of manufacture, and stability of resultant complex. PSC was selected as the most suitable.

The influence of the number of carboxymethyl groups on the PSC chain was investigated. This series of tests allowed optimise the substitution pattern.

PSC is considered a novel excipient and it is used in the product also as a free molecule. PSC was part of the toxicity studies provided and the results were considered sufficient to prove safety of PSC. During the course of the marketing authorisation application procedure additional results from 14-day repeated dose *iv* toxicity studies with PSC in rats and dogs were provided. Taking into account the amount of PSC administered to animals and the intended therapeutic dosage schedule, the results of these studies do not raise concerns regarding the intended use of the product in humans.

Mannitol is used in the formulation to raise the tonicity of the drug product to 270 – 330 mOsm/kg, to ensure that the solution is isoosmotic as this is a critical factor for intravenous formulations.

In addition, studies were performed to evaluate the biodegradability of ferumoxytol by following the fate of the carbohydrate coating with ^{14}C labeled product. The studies demonstrated that the carbohydrate coating is released intracellularly and predominately renally excreted with some faecal excretion. The iron oxide crystals are dissolved and the iron is incorporated into the normal body iron stores, appearing in red blood cells.

Studies were conducted to investigate the compatibility of the product with administration devices. One study tested the compatibility of the drug product with several devices used in the dialysis unit or other medical settings. Another study tested the compatibility and maximum dwell time for the product in syringes. The product was found compatible with the administration devices investigated.

More than one manufacturing site was proposed for the finished product. A comparability exercise was performed to prove that products from the proposed manufacturing sites are comparable. The applicant provided sufficient evidence demonstrating that products manufactured at different sites are comparable.

It can be concluded that the formulation development of the product was satisfactorily described. The key critical parameters were identified and successfully evaluated. The formulation choice and optimisation were considered acceptable. Furthermore, the CHMP recommended further investigation

of the structure of the active substance and comparability of the product manufactured at different manufacturing sites. The applicant should investigate the possibility that the PSC coating is multi-layered and possibility that particles exist as agglomerates/aggregates. Further evidence of the structure should be obtained using imaging techniques such as Transmission Electron Microscopy (TEM).

Adventitious agents

None of the excipients used in the product are of animal origin.

Manufacture of the product

The manufacturing process is sufficiently described as well as a process flow diagram provided.

The manufacturing process of the finished product is sufficiently described.

The proposed manufacturing process was successfully validated on 3 commercial scale batches. The validation report of three cycles verified that the terminal sterilization cycle is sufficient to produce a sterile product. Critical steps of the manufacturing process have been identified and are sufficiently controlled by in-process control testing.

Batch analysis data on three production scale batches manufactured at the proposed manufacturing site indicate satisfactory uniformity and compliance with the proposed specifications.

Product specification

The finished product specifications include tests for appearance, identity of PSC, (FTIR), identity of ferric ion (UV-Vis/AA), identification of mannitol (HPLC), total PSC content (UV-Vis), ionic iron content (AA), ferrous ion content (UV-Vis/AA), mannitol content (HPLC), content heavy metals (ICP-MS), extractable volume, solution density, pH, magnetic susceptibility, iron core size, particle size (laser light scattering), osmolality (freezing point depression), particulates (microscopic particle count), uniformity of dosage units, sterility, bacterial endotoxins.

The proposed specification was justified based on the batch and stability results and are generally adequate for assuring the product quality and therefore were accepted.

A detailed description for all analytical methods was provided. Full method validation data was provided for the non compendial (in-house) analytical methods.

With regards to the reference standard which is used in analytical testing, the CHMP recommended that the content of this substance is evaluated by two independent testing methods as this reference standard is only appropriate for identity and not for assay testing (content not assigned). Alternatively, different reference standard appropriate for assay testing should be selected.

Stability of the product

Stability studies of the finished product were performed in accordance with ICH stability guidelines. Results were obtained on three commercial scale batches of the finished product. The stability data indicate that the product is stable. The studies for the storage conditions of 30ºC/65% RH and 40ºC/75% RH have been completed with data through 12 and 6 months respectively.

Batch analysis results demonstrated compliance with the proposed specifications and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance, ferumoxytol, was of acceptable quality. In general sufficient evidence regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided. The synthesis and process parameters have been well characterised and described.

Specification limits and analytical methods are suitable to control the quality of the active substance.

The finished product which is a sterile formulation intended for intravenous administration was well characterised. The product contains a novel excipient - PSC. Sufficient evidence supporting the safety of this excipient was provided. The formulation is considered appropriately justified.

The method of manufacture is considered standard and has been satisfactorily described, including holding times and in-process tests. The validation data shows consistent manufacture and is considered sufficient for this manufacturing process.

The proposed specifications were justified based on the batch and stability results, and are in general adequate for assuring the product quality and therefore were accepted.

The stability program is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance (ferumoxytol) and the finished product (solution for injection) have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that ferumoxytol as well as the solution for injection can be reproducibly manufactured. Therefore the product should have a satisfactory and uniform performance in the clinic.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The CHMP agrees with non-routine testing for free PSC and recommends collection of further data on the ratio Total PSC / Free PSC during long term stability testing in order to confirm that this ratio is constant over a long time.
2. The CHMP recommends that the content of the reference standard is performed by two independent testing methods as this reference standard is only appropriate for identity and not for assay testing (content not assigned). Alternatively, the applicant should use different reference standard appropriate for assay testing.
3. The CHMP recommends continuation of the ongoing stability program for the Drug Product Intermediate over the intended period. Any out of specification result should be reported.

4. The CHMP recommends further investigation of structure of the active substance and comparability of the product manufactured at different manufacturing sites. The applicant should investigate the possibility that the coating is multi-layered and possibility that particles exist as agglomerates/aggregates. Further evidence of the structure should be obtained using imaging techniques such as Transmission Electron Microscopy (TEM).

2.3. Non-clinical aspects

2.3.1. Introduction

The pharmacological evaluation of Ferumoxytol included studies to determine the rate and extent of incorporation of Ferumoxytol-derived iron into RBCs, and to assess the efficacy of Ferumoxytol in reversing signs of iron deficiency and anaemia in an animal model. Safety pharmacology studies assessed the effect of intravenously administered Ferumoxytol on vital organ systems and function, and included in vitro and in vivo studies in mice, rats, guinea pigs and dogs.

Pharmacodynamic studies were not conducted under GLP conditions. Safety pharmacology studies were conducted according to GLP with exception of two cardiovascular pilot studies and the pivotal cardiovascular, renal and pulmonary safety study in anaesthetised dogs.

All PK studies were non-GLP, except the toxicokinetics evaluation of the repeated dose toxicity studies in rats and dogs and a study investigating lacteal transfer in rats.

Most of the non-clinical toxicology studies were performed according to GLP requirements. Studies which do not fulfil GLP requirements are indicated.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The pharmacological evaluation of Ferumoxytol determined the rate and extent of incorporation of Ferumoxytol-derived iron into RBCs, and to assess the efficacy of Ferumoxytol in reversing signs of IDA in an animal model. Given that the primary objective of Ferumoxytol therapy is to treat IDA, the use of animals with IDA, albeit without renal insufficiency, was considered to be an appropriate choice of animal model.

A comparative assessment of iron-related parameters in Ferumoxytol-treated and untreated animals on a low iron diet, as well as in normal diet control rats demonstrated that a single i.v. bolus of Ferumoxytol at a dose of 30 mg Fe/kg partially reversed the effects of IDA within 3 weeks of treatment. Values of Hgb, haematocrit, RBC count, MCHC, serum iron concentration, serum total iron binding capacity (TIBC) and transferrin saturation (TSAT) were significantly greater than those for untreated animals on a low iron diet; within 3 weeks of Ferumoxytol administration, values of RBC count and MCHC were similar to those for animals on a normal diet (data not shown).

Similar improvements in iron-related blood parameters have been demonstrated following the administration of parenteral iron dextran to newborn pigs [Dilov, 1984; Egeli, 1998; Egeli, 1999], lambs [Dilov, 1984; Tait, 1979] with IDA, and to calves [Reece, 1985]. The intraperitoneal (i.p.) administration of iron dextran has been reported to increase liver ferritin in iron-deficient rats [Tran, 2002] and stimulate erythropoiesis in hereditarily anaemic rats [Zaric, 1998]. These data indicate that various forms of iron deficiency anaemia respond to iron therapy and thus support the use of animals without renal impairment in the pharmacological study with Ferumoxytol.

Secondary pharmacodynamic studies

The potential of Ferumoxytol as a contrast agent for MRI was assessed in preliminary studies in rats because of its ability to reduce magnetic relaxivity enabling the creation of MR images with enhanced contrast. Imaging studies measured the changes of signal intensity in a variety of tissues including the liver, spleen, aorta and hepatic vein following IV administration of Ferumoxytol.

Safety pharmacology programme

Two GLP-compliant safety pharmacology studies were presented. One study investigated possible effects on the CNS. Intravenous administration of up to 1000 mg Fe/kg Ferumoxytol did not produce behavioural or physiological changes in mice when compared to vehicle control group in the Irwin observation test. The other GLP compliant test explored the effects of Ferumoxytol on the hERG potassium channels in human embryonic kidney cells. The study showed that Ferumoxytol may induce a shortening of the QT-interval (data not shown, see discussion on non-clinical aspects).

Additionally, the Applicant provided two studies on the haemodynamic response in the rat and in the guinea pig on intravenous injections of Ferumoxytol. Both studies show, that Ferumoxytol does not reduce the blood pressure significantly (data not shown, see discussion on non-clinical aspects).

In one non-GLP compliant pivotal study to assess effects on cardiovascular, pulmonary and renal system, no effects of Ferumoxytol on cardiovascular and respiratory parameters have been observed. Variable changes on urinary flow and sodium, potassium and chloride excretion in verum as well as in placebo group animals were shown (data not shown, see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No studies on pharmacodynamic drug interactions were conducted.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetics programme consisted of multiple *in vivo* studies (including toxicokinetic studies) and one *in vitro* study in order to characterize the absorption (in rats, guinea pigs, rabbits and dogs), distribution (in rats and rabbits), metabolism (in rats) and excretion (in rats and rabbits) of Ferumoxytol. In all *in vivo* pharmacokinetics studies Ferumoxytol, either unlabelled or radiolabelled (^{59}Fe-Ferumoxytol or ^{14}C-Ferumoxytol) was administered IV, the clinically intended route for Ferumoxytol. The fate of Ferumoxytol and/or of degradation products thereof was monitored using time-domain nuclear magnetic resonance (TD-NMR; for unlabelled Ferumoxytol) or liquid scintillation counting (for ^{59}Fe-Ferumoxytol: gamma counting; for ^{14}C-Ferumoxytol: beta counting). The TD-NMR measurements were based on determination of T1 (spin-latice) and T2 (spin-spin) relaxation rates.

In the course of a study in rats with administration of ^{14}C-Ferumoxytol, gel-permeation-chromatography was used in addition to determine the size of ^{14}C labelled material excreted in urine and faeces.

Investigations of early phase half-lives ($t_{1/2}$) of Ferumoxytol after IV administration focused on the iron component of Ferumoxytol using TD-NMR for detection of unlabelled Ferumoxytol and LSC for detection ^{59}Fe-Ferumoxytol. In all species investigated, serum half-lives were significantly longer at higher doses. Using unlabelled Ferumoxytol, in the rat serum half-lives were shown to increase from 6770 min at a dose of 2.2 mg Fe/kg b.w. to 167 min at 6 mg Fe/kg b.w. and in the dog from 91 min at 2 mg Fe/kg b.w. to 155 min at 12 mg Fe/kg b.w. In another study, a half-life in blood of just half the

duration (86 min) at the same dose (6 mg Fe/kg b.w.) in the same rat strain was calculated, but the experimental conditions of this study (mainly small number of animals per group and shorter sampling period) are likely to have resulted in a less representative value of the true half-life in rats.

Studies using ^{59}Fe radiolabelled Ferumoxytol showed roughly similar half-lives in serum of rats (104 min), guinea pigs (121 min) and rabbits (81 min) at the dose of 2.2 mg Fe/kg b.w. At the high doses of 37 mg Fe/kg b.w. in the rat and 19 mg Fe/kg b.w. in the rabbit, significantly longer half-lives were found (234 min in the rat, 264 min in the rabbit). At a mid dose of 6 mg Fe/kg b.w. in the rat, the half life was 122 min.

Exposure to Ferumoxytol was investigated using TD-NMR as part of the 13 week repeated dose toxicity studies in rats and in dogs at Ferumoxytol doses of 2, 6 and 12 mg Fe/kg b.w. Values of C_{max} and AUC increased in both species with the dose. In the rat, values of systemic clearance (Cl) and volume of distribution at steady state (V_{ss}) decreased at higher doses and increases in exposure were generally greater than dose proportional. In the dog, Cl and V_{ss} did not markedly change as a function of dose and exposure increased generally in a dose-related manner. In the rat at 6 and 12 mg Fe/kg b.w./day, drug accumulation was observed over the study interval of 13 weeks whereas in the dog, drug exposure at the end of the study was just less than 20% at all dose levels higher compared to Day 1. Values of V_{ss} in rats and dogs were higher than the plasma volume but lower than the volume of the extracellular fluid.

Using ^{59}Fe-labelled Ferumoxytol and investigating distribution in whole blood, plasma and red blood cells (RBC), it was shown that Ferumoxytol initially distributes to the plasma, from which it is rapidly cleared. After 24 hrs ^{59}Fe-derived radioactivity slowly rises again in whole blood with practically the entire measured radioactivity present in the RBC fraction.

Most of the ^{59}Fe-Ferumoxytol derived radioactivity was found 48 hrs after injection of 37 mg Fe/kg b.w. to rats and 19 mg Fe/kg b.w. to rabbits mainly in the liver (58% in rats; 22% in rabbits).

Unlabelled Ferumoxytol, followed using TD-NMR and expressed as elevations of relaxation rate above baseline, distributed at Day 1 after IV injection to rats at doses of 2.2 and 6 mg Fe/kg b.w. mainly to spleen, liver, central lymph nodes (and peripheral at the higher dose) and bone marrow with baseline values reached at the latest at the end of studies. Following the administration of 2.2 mg Fe/kg to rats, tissue $t_{1/2}$ values were 3.45, 17.7, and 23.8 days for the liver, spleen and central lymph glands, respectively. Tissue $t_{1/2}$ values for liver, spleen and central lymph calculated from the later phase of the elimination profile after administration of 6 mg Fe/kg b.w. were 30.3, 23.8 and 30.5 days, respectively. Due to physical characteristics, relaxometric measurements of supraparamagnetic iron in tissues are just semi-quantitative and serve to provide only relative comparisons of elimination rates across the range of tissues.

The fate of the carbohydrate coating of Ferumoxytol was investigated using ^{14}C-labelled Ferumoxytol in rats at IV doses of 2.2 and 6 mg Fe/kg b.w. The detected ^{14}C levels were highest in the liver, spleen and central lymph glands at Day 1, and declined by first-order kinetics over the 84 day study period with mean elimination half-lives ranging from 10 to 15 days. The half-life of intact ^{14}C-Ferumoxytol in blood was not determined experimentally (see discussion on non-clinical aspects).

In the course of single dose toxicity studies in rats and dogs employing Ferumoxytol in doses of up to 450 mg Fe/kg b.w., the histological investigation of sections of several organs of groups sacrificed at Day 4 and 16 post administration included Perls´ stain for detection of iron. Brown pigment, primarily intracytoplasmic in macrophages or Kupffer cells, found in the liver, spleen, lung, lymph nodes, thymus, testes, epididymides, and ovaries of rats and dogs stained strongly positive for iron and was dose-related in both incidence and intensity. In the rat, but not in the dog, there was evidence for limited

reduction in the amount of pigment between Day 4 and Day 16 post administration, but the interval is considered rather short in order to enable detection of reversal of iron accumulation.

Lacteal transfer of Ferumoxytol was investigated in rats given a single dose of either unlabelled Ferumoxytol, ^{59}Fe-Ferumoxytol or ^{14}C-Ferumoxytol at doses of 100 mg Fe/kg b.w. at Day 10 or Day 11 after they had given birth to pups. Peak concentrations in milk were found at 8 or 24 hrs post administration and the maximum concentration determined was 14 µg Ferumoxytol/g of milk. Comparison of the concentration over time values for ^{59}Fe-Ferumoxytol, ^{14}C-Ferumoxytol, and unlabelled Ferumoxytol indicate that excretion of Ferumoxytol 10 to 11 days after birth in the milk of rats is minimal and that the iron excreted in milk does not appear to have dissociated from Ferumoxytol.

Conventional investigations on the formation of metabolites of the components of Ferumoxytol have not been performed, but some information on the fate of the carbohydrate coating (PSC) and on the iron core of Ferumoxytol has been obtained in studies investigating the distribution and excretion of Ferumoxytol.

The excretion of iron, PSC coating and its byproducts was evaluated using ^{59}Fe-Ferumoxytol (rats and rabbits) and ^{14}C-Ferumoxytol (rats only). In rats, given a single dose of ^{59}Fe-Ferumoxytol 37 mg Fe/kg b.w., and in rabbits given a single dose of ^{59}Fe-Ferumoxytol 19 mg Fe/kg b.w, negligible amounts of ^{59}Fe were excreted in the urine and less than 2 % were recovered in the faeces at 48 hrs post dose. The minimal excretion of iron from Ferumoxytol within 48 hrs is considered consistent with the highly conserved nature of physiological iron.

PSC is considered a novel excipient and it is used in the product as a free molecule. PSC (bound and free) were part of the toxicity studies provided, therefore the available data, especially from single dose toxicity study are seen to be sufficient to prove safety of PSC for single treatment (2 separated injections as early as 2 to 8 days later). During the course of the marketing authorisation application procedure the Applicant submitted the results of 14-day repeated dose IV toxicity studies with PSC (free) in rats and dogs. Taking into account the amount of free PSC administered to the animals and the intended therapeutic dosage schedule, the results of these studies do not raise concerns regarding the intended therapeutic use of Ferumoxytol in humans.

In rats receiving ^{14}C Ferumoxytol as single doses of 2.2 mg Fe/kg b.w. or 6 mg Fe/kg b.w., after one day, 15 or 42% of injected ^{14}C was excreted with the urine, respectively, and less than 3% were excreted in the faeces. At the end of the studies, total recovery of the label was about 90% with cumulative recoveries of 72 to 78% in the urine and 10 to 19% in the faeces.

Gel-permeation-chromatography (GPC) investigations of urine and faeces from animals receiving the higher dosage indicate that in urine 81 % of the excreted PSC was intact, while 19% was recovered as structures <4,300 Da molecular weight, and in the faeces 24% of the excreted PSC was intact, while 76% had a molecular weight calculated by the Applicant to be <3,300 Da. No structural identification of the metabolites has been performed. Even though the main route of PSC excretion is as intact molecule via the kidneys the non-clinical data obtained using kidney-healthy animals do not raise concern regarding accumulation of PSC with single use of ferumoxytol and renal events observed in patients under IV ferumoxytol are less or equal those seen under oral iron treatment. The Applicant demonstrated that PSC has the ability to cross high-flux kidney dialysis membranes while PSC passage through low-flux dialysis membranes was demonstrated to occur slowly. Nevertheless, due to in vivo metabolism and faecal excretion and due to the intended therapeutic schedule of ferumoxytol administration, accumulation in patients on dialysis using low-flux membranes is not considered likely.

2.3.4. Toxicology

Single dose toxicity

Two single-dose IV toxicity studies were conducted with the product in the rat and dog at doses of up to 450 mg Fe/kg, followed by a 15 day recovery period. The high dose was at least 100-fold above the anticipated human dose.

No effects on mortality, body weight, food consumption or ophthalmologic findings were noted in either species. In rats, treatment-related effects were observed at the highest dose of 450 mg Fe/kg which included transient limb swelling, dose-related accumulation of brown pigment in multiple tissues, increase in liver weight, associated with iron uptake in the Kupffer cells and hepatic sinusoidal distention, changes in coagulation parameters (slightly prolonged prothrombin time (PTT) and activated partial thromboplastin time (APTT) with a concomitant marked decrease in fibrinogen concentration) and increased mean values for neutrophil and monocyte counts at day 4 (significantly for monocytes in females). Effects on the liver included slightly lower activities of AST and LDH in males and increase in GGT in females at day 4. Similar findings were observed in the high dosage group dogs with the exception of the changes in leukocyte counts.

Repeat dose toxicity

An overview with major findings of repeated-dose studies performed in rats and dogs is presented in the table below.

Table 1 – Overview on repeated-dose studies performed in rats

Study ID/ GLP Status	Species	Dose (mg Fe/kg)/ Route	Duration	Major findings
A No	rats;	0, 30, 90, 180, 360 i.v.	2 weeks	0, 30, 90 mg/kg: piloerection and lacrimation 180, 360 mg/kg: paw swelling; discoloration of ears, snout and paws; piloerection; paw swelling and piloerection absent in recovery period concentration depending body weight gain - recoveries were incomplete (weight gains:126, 120, 59 and 24 g for the iron groups, respectively, and 191 g for the mannitol group), recoveries were incomplete
B Yes	rats	0, 6, 18, 37 i.v.	4 weeks	<u>all dosages:</u> ↑serum iron values; yellowish-brown discolouration in the cytoplasm of reticuloendothelial cells of almost all organs and injection site; ↑liver and spleen weight <u>37 mg/kg:</u> dark coloration of the injection site; ↓body weight + food consumption; ↓glucose concentration; ↑cholesterol + globulin; ↓UIBC; ↑leukocytes, neutrophils, monocytes m: ↑total protein+ albumin <u>18 mg/kg:</u> ↑cholesterol m: ↓body weight + food consumption, ↓glucose concentration; ↑total protein + globulin recovery: <u>all groups:</u> yellowish-brown discolouration in the cytoplasm of reticuloendothelial cells of almost all organs and injection site <u>f 18 and all 37 mg/kg/day:</u> ↓body weight f <u>18 and f 37 mg/kg/day:</u> hepatic changes (haemorrhage + haemorrhagic necrosis + chronic inflammation, bile duct hyperplasia m 18 and 37 mg/kg/day: ↓body weight + food consumption; ↑leukocytes, neutrophils, monocytes (week 9) 18 and 37 mg/kg/day: ↑serum iron values; ↓UIBC; ↑cholesterol

Study ID/ GLP Status	Species	Dose (mg Fe/kg)/ Route	Duration	Major findings
C Yes	rats	0, 2, 6, 12 i.v.	13 weeks	<u>all dosages:</u> ↓body weight gain; ↑iron levels; ↓UIBC; ↑cholesterol level m: ↑HGB; ↓mean glucose values; accumulations of iron-positive pigment (liver, kidneys, gastrointestinal tract, spleen, lungs, lymph nodes, pancreas, prostate, testes, uterus, ovaries, eyes) <u>12 mg/kg:</u> brown coloration of the injection site; ↓body weight; ↓food consumption; ↓RBC; ↑WBC counts + neutrophils, monocytes; ↑ALT, AST, ALP; ↑weight liver + spleen m: thin appearance; rough coat; ↑GGT, ↑basophiles f: ↑TIBC; ↑lymphocytes <u>6 mg/kg:</u> brown coloration of the injection site; ↓RBC; ↑weight liver + spleen m: ↓food consumption; ↓TIBC f: ↑ALP; ↑neutrophils, monocytes <u>2 mg/kg</u> m: ↓TIBC f: ↑liver weight
D Yes	Beagle dog	0, 6, 18, 37 i.v.	4 weeks	<u>all groups:</u> ↑iron concentration; ↓UIBC; accumulations of yellowish-brown iron-positive pigment in the reticuloendothelial cells of many organs; ↑liver and spleen weight <u>37 mg/kg:</u> brown sclera of the eye + skin/pelage; ↑leukocyte count; <u>18 mg/kg:</u> brown sclera of the eye + skin/pelage; ↑neutrophils 6 mg/kg: m: ↑neutrophils recovery: <u>all groups:</u> ↑leukocyte and neutrophil counts; accumulations of yellowish-brown iron-positive pigment in the reticuloendothelial cells of many organs; ↑liver and spleen weight <u>18 and 37 mg/kg:</u> brown sclera of the eye + skin/pelag
E yes	Beagle dog	0, 2, 6, 12 i.v.	13 weeks	<u>all groups:</u> ↑iron concentration; ↓UIBC; ↑liver + spleen weight; brown iron-positive pigment in many organs and injection sites <u>12 mg/kg:</u> yellow conjunctiva and gums <u>6 mg/kg:</u> yellow gums

m=male; f=female; ↓=decrease; ↑=increase

No mortality was observed until 37 mg Fe/kg for 4 weeks and 12 mg Fe/kg for 13 weeks in rats and dogs.

Multiples for safety comparison to Human Cumulative Dose (17 mg Fe/kg for a 60 kg Human) were calculated with up to ~10 (rats) and ~39 (dogs) from the 4- and 13-weeks repeated dose toxicity studies.

Genotoxicity

All genotoxicity studies were conducted according to current OECD protocols and met GLP requirements. Results were negative as summarised below.

Table 2 – Overview on genotoxicity studies conducted with Ferumoxytol

Type of testGLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative /equivocal
AMES test yes	Salmonella strains	+/- S9; Concentrations from 0 - 5000 µg/plate	negative
Chromosomal aberrations in mammalian cellsyes	CHO-cells	+/-S9; 3 h treatment; Concentration from 0 - 5100 µg/ml +/-S9, 17.8 h treatment, Doses from 0 - 5100 µg/ml	negative
Micronucleus *assay in vivoyes*	Mouse, micronuclei in bone marrow in Crl:CD-1 (ICR) BR mice	Doses from 0- 1500 mg/kg i.v. single dose	negative

Carcinogenicity

No carcinogenicity studies were conducted, which is accceptable as Ferumoxytol replenishes endogenous iron at physiological levels and is only intended for a short duration of treatment.

Reproduction Toxicity

Studies concerning fertility and early embryonic development conducted with Ferumoxytol are summarised below.

Table 3 – Overview of studies concerning fertility and early embryonic development conducted with Ferumoxytol

Study Number / GLP Compliance / Species	Duration /	Dose and Route of Administra -tion	Major Findings	NOAEL
FERTILITY AND EARLY EMBRYONIC DEVELOPMENT				
STUDY A yes Rats	m: 4 wks prior to mating, throughout the mating period (≥ 7 wks total) f: 2 wks prior to mating-GD7	0, 6, 12, 18 mg/kg; i.v. injection	F0: **males**: clinical signs: brown staining of ears, tails and paws starting at D42 in HD + MD; brown staining around eyes starting at D70 in HD body weights: ↓↓ in MD + HD starting on D32 organ weights: relative testes weights ↑↑ in MD + HD necropsy: brown lumbar, renal + iliac Lnn in LD, MD + HD; enlarged renal Lnn in MD + HD; enlarged spleens in HD sperm motility/epididymal count: no effects **females**: clinical signs: none body weights: no effect organ weights: no effect necropsy: brown lumbar, renal + iliac Lnn in LD, MD + HD; enlarged Lnn in 1/20 MD + 2/20 HD; brown pancreatic Lnn in 3/20 HD precoital interval: no effects pregnancy rate: no effect	F0: m: 6 mg/kg f: 18 mg/kg F0 reproduction: m + f: 18 mg/kg F1 early embryonic development: 18 mg/kg
EMBRYO-FOETAL DEVELOPMENT				

Study Number / GLP Compliance / Species	Duration /	Dose and Route of Administra -tion	Major Findings	NOAEL
FERTILITY AND EARLY EMBRYONIC DEVELOPMENT				
STUDY B yes rats	GD6-GD17; during organogensis	0, 10, 31.6, 100 mg/kg; i.v. injection	F0: clinical signs: dark staining of ears, tails and paws starting in 1/25 MD on GD20 and all HD starting on GD14 body weights: ↓↓ in HD starting at GD8 food consumption: ↓↓ in all treatment groups necropsy: dark livers and spleens, yellow adipose tissues in HD F1: foetal body weights: HD ↓↓ malformations: HD: 1 x umbilical hernia, 1 x diaphragma hernia, 1 x forked/fused ribs; MD: 1 x acaudate + anal atresia, 2/1 agenesis of lung lobes, 1 x vertebral anomaly + absent ischium; LD: 1 x situs inversus, 1 x agenesis of lung lobes variations: wavy ribs + incomplete ossification ↑↑ in HD	F0: 31.6 mg/kg F1: 31.6 mg/kg
STUDY C) yes rabbits	GD7-GD20; during organogensis	0, 6, 16.5, 45.3 mg/kg; i.v. injection	F0: clinical signs: MD + HD: hyper-pigmentation (dark ears, nose/mouth), HD: additionally dark eyes body weight gain, food consumption: HD↓ necropsy: dark/brown spleens, livers, dark yellow adipose tissues in MD + HD; dark ovaries, amniotic sacs, and uteri in HD F1: foetal body weights HD ↓↓ malformations HD: malrotated or flexed fore- and malrotated hindlimbs, internal hydrocephalies, absent brains, cleft palate and microglossia	F0: 45.3 mg/kg F1: 16.5 mg/kg
PRENATAL AND POSTNATAL DEVELOPMENT				
STUDY D yes rats	GD6 – LaD20 25 f	0, 10, 30, 60 mg/kg; i.v. injection	F0: clinical signs: none body weights: ↓↓ in HD during gestation at some time points and during whole lactation period necropsy: no effects duration of gestation: no effect parturition: no effect F1: pup birth weights: ↓↓ in HD f pup weights ↓↓ in MD + HD from day 4 until day 21 in both sexes pup survival: no effect reflex development: no effect activity: no effects learning + memory (water maze): no effect reproduction: m: delayed preputial separation, decreased reproductive competence in initial (paired with treated f) and subsequent breedings (paired with naive f) in HD f: delayed vaginal opening, disruption of estrus cycle in some animals and decreased reproductive competence in initial (paired with treated m) and subsequent breedings (paired with naive m) in MD + HD	F0: 30 mg/kg F1: m: 30 mg/kg f: 10 mg/kg

GD=gestation day; LaD= Lactation Day; m=male; f=female; LD=low dose; MD=mid dose; HD=high dose; ↓=non significant decrease; ↓↓=significant decrease; ↑=non significant increase; ↑↑=significant increase

Toxicokinetic data

Toxicokinetic studies were conducted as part of the repeated dose toxicity studies. The systemic exposure to Ferumoxytol was monitored by NMR spectroscopy.

Ferumoxytol seems to be rapidly distributed into the plasma compartment and is then quickly removed from the plasma by phagocytic reticuloendothelial cells of the liver, spleen and bone marrow. Iron is then released from the iron-carbohydrate complex to enter the normal iron cycle. Thus, the evaluation of toxicological data in terms of initial systemic exposure (Cmax, AUC) in the toxicology species relative to human exposure at the maximum recommended dose is not very informative, particularly in view of the observed nonlinear PK. For this reason and since iron is highly conserved, cumulative doses provide a better estimation of exposure.

In the toxicology studies, single doses of Ferumoxytol ranged from 2 to 1500 mg Fe/kg and cumulative doses ranged from 72 to 2142 mg Fe/kg. The proposed clinical dose of Ferumoxytol and that examined in the pivotal Phase III studies, is 2 x 510 mg Fe, i.e. 17 mg Fe/kg for a 60 kg patient. The highest dose tested in single dose toxicity studies was 450 mg Fe/kg. The highest daily doses tested in repeated dose toxicity studies were 37 mg Fe/kg (4 week studies) and 12 mg Fe/kg (13 weeks studies), corresponding to cumulative doses of 1100-1200 mg Fe/kg.

Comparing rat and dog, at a dose level of 6 and 12 mg Fe/kg rats had a higher exposure to Fe than dogs. In both species findings are linked with accumulation in some specific tissues/organs. Accumulation was clearly demonstrated in the rat (adrenals, spleen, ovaries, liver, kidneys). Thus it is possible to understand and explain the increase of organ weight and macrophage accumulation. Accumulation in specific tissue cells, in some cases resulting in necrosis, abscesses or haemorrhages. In the dog this kind of accumulation is also recorded, but without the degenerative lesions observed in the rat.

Local Tolerance

A local tolerance study was conducted to assess local tissue tolerance to Ferumoxytol (30 mg Fe/ml) when administered as a single i.v. (marginal ear vein), p.v. (adjacent to the marginal ear vein) or i.a. (central ear artery) injection to rabbits.

The IV and intra-arterial doses of Ferumoxytol were thought to be corresponding to the anticipated clinical dose. The paravenous injection dose volume was considered to be the maximum amount injectable into the surrounding perivascular tissue without causing physical tissue trauma. All animals in all groups appeared clinically normal throughout the study. For all three methods of administration, no erythema or oedema reactions were observed. Individual haematomas observed at the injection sites were considered incidental, since they did not occur at any significantly greater frequency with Ferumoxytol than with the control/vehicle. At necropsy, there were no macroscopic or microscopic findings at the injection sites, except for a low incidence of residual Ferumoxytol that was observed microscopically at some of the injection sites. This was not associated with any inflammatory response. Even though the tested dosage was only 1.5 of the human dosage the concentration used in tolerance testing is acceptable. According to the NfG on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00), parenteral tolerance testing includes also intramuscular, intrathecal and subcutaneous routes as well as a repeated administration according to clinical usage. The applicant did

not justify the test strategy chosen, but in the context of the tested routes and the findings of the repeated toxicity studies the local tolerance study is acceptable.

Other toxicity studies

Blood comparability was tested with pooled human plasma (influence on APTT, TCT) and in an in-vivo rat study (influence on APTT, PT and TCT). The potential to cause haemolysis as well as visible flocculation, precipitation, or sedimentation in human plasma and serum was also examined with human whole blood. Ferumoxytol caused dose-dependent haemolysis of human erythrocytes, therefore Ferumoxytol is expected to have a minimal potential for inducing haemolysis in human subjects at the dose to be used clinically. It did not cause any visible flocculation, precipitation or sedimentation. The single human dosage is given with 510 mg elemental iron. Assuming a person with body plasma of ~3 l, a concentration of 0.17 mg/ml could be assumed in humans. In-vitro testing took place with concentrations up to 15 mg Fe/ml which is far above the concentrations reached in clinics. Therefore the in-vitro testing should provide a moderate safety assessment. The dosage in the in-vivo testing was 50 mg/kg (HED = 8 mg/kg) and therefore near the human dosage (8.5 mg/kg) and can be accepted.

The immunotoxic potential of Ferumoxytol was evaluated in a series of in-vitro and in-vivo tests for immunomodulatory and anaphylactic effects, as Ferumoxytol is taken up by macrophages, the PSC coating is derived from dextran and certain forms have antigenic potential. Limb swelling was observed in certain standard toxicity studies in rats and slightly increased leukocyte counts were reported in rats and dogs receiving cumulative doses of 1.1 g Fe/kg. The immunologic safety assessment of Ferumoxytol can be regarded as in accordance with all tenets of the ICH S8 Guidance and the conduct of a 'data-driven' safety assessment for human pharmaceuticals. Based on the data obtained from multiple studies and from clinical experience, no further testing is considered necessary or justifiable.

Concentration- and time-depending effects on immunological system were seen in concentrations comparable to human dosages. In the Listeria monocytogenes host resistance immunosuppression assay, a dose-related increase in mortality was observed following Listeria monocytogenes challenge among the Ferumoxytol-treated animals. Overall, mortality across all time groups was 69% in the 60 mg Fe/kg dose group, 44% in the 6 mg Fe/kg dose group and 31% in the 0.6 mg Fe/kg dose group, compared to 30% in the vehicle control group. As a consequence, a warning was included in section 4.4, ('Special Warnings and Precautions for Use') of the SmPC indicating that parenteral iron should be used with caution in cases of immunologic disease or acute or chronic infection and that it is not recommended in patients with ongoing bacteraemia. Furthermore, Ferumoxytol increased the production of IL-1β and IL-6 in a concentration-related manner in non-stimulated cells. Within the SmPC, it is pointed out that intravenously administered iron products can cause hypersensitivity reactions including serious and life-threatening anaphylactic/anaphylactoid reactions and that patients have to be observed for signs and symptoms of hypersensitivity for at least 30 minutes following the injection and the drug is only to be administered when personnel and therapies are readily available for the treatment of hypersensitivity reactions. If at any time during the intravenous administration any signs of hypersensitivity reaction or intolerance are detected, administration must be stopped immediately.

The phototoxic potential of Ferumoxytol was measured with and without ultraviolet radiation (± UVR) in incubated Balb/c 3T3 mouse fibroblasts. The study results indicated that Ferumoxytol (when incubated with 3T3 cells in Dulbecco's Phosphate Buffered Saline at up to the highest OECD 432 Guidance-defined test concentration of 1000 mg/l) demonstrated no phototoxic or cytotoxic potential.

Impurity analysis of commercial scale batches was conducted. It was indicated that the relevant impurities were below the reporting, identification and qualification thresholds specified in the ICH Q3A (R2) guideline. The stability testing programme for the drug substance did not identify any degradation products, with commercial scale batches of the drug substance remaining well within the acceptance criteria for all attributes. No additional investigation was made of impurities and degradation products.

2.3.5. Ecotoxicity/environmental risk assessment

The exposure of the environment to ferumoxytol was considered in terms of exposure to the two principal components of the drug substance: a) the PSC coating, and b) the iron oxide core.

The PSC coating, which is carbohydrate in nature, constitutes approximately 42% (w/w) of the iron oxide-carbohydrate complex, and is exempt from the requirement for ERA (CPMP/SWP/4447/00). The iron oxide core constitutes approximately 58% (w/w) of the iron oxide-carbohydrate complex. Predicted Environmental Concentration (PEC) has been calculated for the iron oxide component of ferumoxytol DS. The calculation for PEC was restricted to the aquatic compartment and uses assumptions and default values [with the exception of the *market penetration factor (Fpen)*] as stated in CHMP/SWP/4447/00. Results are summarised in the following table.

Table 4 – Summary of main study results

Substance (INN/Invented Name): Ferumoxytol			
CAS-number (if available): 722492-56-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	The active ingredient is a carbohydrate coated iron oxide nanoparticle. Bioaccumulation potential cannot be determined using standard methods for small molecules.		Potential PBT: no conclusion possible
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	no data availbale	
	BCF	no data available	
Persistence	DT50 or ready biodegradability	no data available	
Toxicity	NOEC or CMR	no data available	
PBT-statement :	A PBT assessment has not been conducted		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0009	µg/l	>0.01 threshold (N)
Other concerns (e.g. chemical class)	nanoparticle		(Y)

2.3.6. Discussion on non-clinical aspects

The Applicant provided a single non-GLP pharmacodynamic study to prove the suitability of Ferumoxytol in iron replacement therapy. It should be noted that the design of the study is questionable in details, since only male rats were included and no placebo control was included. In the pre treatment period the laboratory results of the iron deficient groups were pooled for further statistical analysis. Unfortunately, the housing conditions differ between the groups. The iron deficient

animals were placed into individual metabolism cages and were fed a powdered low iron diet, whereas the control group animals were placed into regular cages and fed with regular commercial rat chow (pellets are assumed). Therefore, differences in weight gain and other laboratory parameters due to the differences in the holding conditions can not be completely excluded. However, the study shows clearly that ferumoxytol reverses the symptoms of iron deficiency in juvenile rats. The Applicant therefore provided an adequate proof of concept.

In secondary pharmacology studies, ferumoxytol reduced the relaxivity of surrounding nuclei due to its paramagnetic properties, which should enable the imaging software to calculate high contrast images. However, no conclusion can be drawn due to insufficient quality of the images presented in the reports.

Safety pharmacology studies (partly non-GLP compliant) were conducted investigating the effect on CNS, cardiovascular, pulmonary and renal system. No specific hazard could be identified. One GLP compliant study showed that Ferumoxytol may induce a shortening of the QT-interval. However, in clinical studies no relevant effects have been observed. In other non-GLP compliant haemodynamic studies blood pressure was not reduced significantly by ferumoxytol. However, the interpretation of these studies is limited, since the blood pressure within the first 10 min after application is not presented. Moreover, since short and transient changes in blood pressure are easily recognised and reported by the participants in the clinical studies no further action is required regarding this question.

In the non-GLP compliant pivotal study to assess effects on cardiovascular, pulmonary and renal system did not achieve the adequate scientific standard, since information on the data acquisition set up/instruments used, validation of instruments, processing and archiving of data were not provided. Nevertheless, no effects of Ferumoxytol on cardiovascular and respiratory parameters have been observed. Irrespective of the identified deficiencies, the study showed variable changes on urinary flow and sodium, potassium and chloride excretion in verum as well as in placebo group animals, most likely due to the mannitol used in the formulation applied.

The nonclinical pharmacokinetics programme consisted of multiple in vivo studies (including toxicokinetic studies) and in vitro study in order to characterize the absorption (in rats, guinea pigs, rabbits and dogs), distribution (in rats and rabbits), metabolism (in rats) and excretion (in rats and rabbits) of Ferumoxytol.

Exposure in humans in terms of AUC appears to be roughly 10 times higher than in the animal species investigated at the same dosage level. Whereas the C_{max} of Ferumoxytol is rather comparable between different species, half-life in plasma of humans is much longer than in rats and dogs. Ferumoxytol is assumed to be taken up by cells of the reticuloendothelial system (RES). The Applicant was asked to discuss, whether species differences (human vs. rat/dog) could be due to differing pool sizes of cells of the RES. Due to the obvious lack of information in the public domain a literature search performed by the Applicant did not retrieve information on pool sizes of cells of the RES. As the liver accumulates the highest total amount of the administered Ferumoxytol dose, a lower hepatic blood flow/per kg b.w. in humans compared to dogs and rats could partially contribute to the observed differences in half-lives.

The fate of Ferumoxytol was investigated using unlabelled and radiolabelled ^{59}Fe-Ferumoxytol and ^{14}C-labelled PSC. The half-life of ^{14}C-labelled free PSC in blood was not determined experimentally, but it is concluded that Ferumoxytol is taken up by cells of the reticuloendiothelial system (in liver, spleen lymph nodes, bone marrow) as intact Ferumoxytol, and that, therefore, the half-life of ^{14}C-labelled PSCshould be similar to the half-life in blood determined using either unlabelled Ferumoxytol (detection with TD-NMR) or ^{59}Fe-Ferumoxytol (detection with LSC).

Taken together the non-clinical toxicokinetics data are in agreement with the concept that after IV injection Ferumoxytol is at first distributed from plasma to phagocytotic cells in different tissues, and

that the iron of Ferumoxytol appears with a delay of several hours incorporated into red blood cells where it can be detected for several weeks (most likely for the physiologic life-time of erythrocytes).

The non-clinical toxicology program included single- and repeated-dose toxicity studies (up to 13 weeks in rats and dogs), genotoxicity and reproductive toxicity studies, immunotoxicity studies, studies concerning local tolerance and blood biocompatibility. Toxicokinetic studies were conducted as part of the repeated-dose toxicity studies.

In single dose toxicity studies in rats, treatment-related effects were observed at the highest dose of 450 mg Fe/kg which included transient limb swelling, dose-related accumulation of brown pigment in multiple tissues, increase in liver weight, changes in coagulation parameters (slightly prolonged prothrombin time (PTT) and activated partial thromboplastin time (APTT) with a concomitant marked decrease in fibrinogen concentration) and increased mean values for neutrophil and monocyte counts. Effects on the liver (possibly due to the increased pigment material) included slightly lower activities of AST and LDH in males and increase in GGT in females. Similar findings were observed in the high dosage group dogs with the exception of the changes in leukocyte counts. The significantly higher mean cell haemoglobin concentration values at day 3 were attributed to the erythrocyte uptake of the test material. The applicant claimed that the observations were generally related to iron uptake and not associated with any histopathological changes that could indicate drug toxicity. Although the increases of neutrophil and monocyte counts were thought to be an indirect effect of the administration of the iron, they may represent a slight increase in circulating leukocytes due to displacement by siderophages, noted histologically at the second interim sacrifice in the liver, spleen and lymphoid tissues.

Thus, the no observable adverse effect level (NOAEL) of Ferumoxytol 15 days after a single i.v. injection in rats and dogs was estimated to be at least 450 mg Fe/kg in both species.

In repeat-dose toxicity studies, no mortality was observed until 37 mg Fe/kg for 4 weeks and 12 mg Fe/kg for 13 weeks in rats and dogs.

The most important non-clinical safety findings in the 4-week repeated dose toxicity studies were the decrease of body weight, increase of organ weights and iron-positive pigmentation that was dose-related in intensity and incidence (liver, spleen, heart, and lymph nodes and secondarily in the alimentary and gastrointestinal tracts, bone marrow, larynx, injection site and other organs). The dose-related incidence and intensity of pigmentation observed in phagocytic reticuloendothelial cells in tissues/organs are assumed to be the result of iron storage and/or phagocytosis of the test article.

The Applicant discussed most of the effects detected in single and repeated dose toxicity studies and could show that these were mostly connected to the treatment with iron. The only remaining peculiarity concerns the hepatic changes seen in female rats of the 4 week repeated dose study with 26 weeks recovery. After 26 weeks of recovery, the degree of pigmentation in the liver of the female animals did not decrease. Additionally, the 18 and 37 mg Fe/kg/day-treated females had hepatic changes consisting of focal or multifocal haemorrhage, hemorrhagic necrosis, chronic inflammation, and/or bile duct hyperplasia in three of five and four of five females, respectively. The hyperplastic biliary epithelium was prominent and, in two 37 mg Fe/kg/day-treated females, approached atypical hyperplasia. The cumulative HED of the 18 and 37 mg Fe/kg/day dose in rats compares to a safety multiple of 5.1 and 10.5 to the cumulative human therapeutic dose (2 x 510 mg Fe) in a 60 kg human. The 18 and 37 mg Fe/kg/day-treated males had moderate to moderately severe hepatic pigmentation without haemorrhage, necrosis or bile duct hyperplasia. In the dog, the same kind of accumulation was also recorded, but without degenerative lesions observed in the female rat.

Based on an ICH compliant standard battery of studies for genotoxicity Ferumoxytol in the tested formulation is considered to be devoid of any relevant genotoxic potential. Studies on the carcinogenic potential have not been performed with Ferumoxytol which is considered acceptable.

Ferumoxytol did not induce adverse effects on male and female fertility. Relative testes weights were significantly increased in mid and high dose males reflecting the significantly decreased body weights rather than an increase in actual testes weights in these dose groups.

When pregnant rats were treated with Ferumoxytol during the period of organogenesis food consumption was significantly decreased in all treatment groups but only body weights of the high dose group were significantly affected. Fetal body weights were also significantly decreased in the high dose group. As only single instances of different malformations were observed in all treatment groups these malformations were not interpreted as drug induced. In pregnant rabbits Ferumoxytol induced clear teratogenic and fetotoxic effects without any overt maternal toxicity. In rats, exposure to Ferumoxytol from implantation to weaning induced maternal toxicity (significantly decreased body weight) in the high dose group but had no effect on the duration of pregnancy and parturition.

The Applicant has provided studies on local tolerance, blood comparability and immunotoxicity. Within the phototoxicity testing (3T3 NRU test) no phototoxic or cytotoxic potential with and without simultaneous exposure to ultraviolet irradiation was seen. Based on the study results, ferumoxytol is not considered to have phototoxic potential in humans.

2.3.7. Conclusion on the non-clinical aspects

The Applicant has provided a set of pharmacodynamic, pharmacokinetic and toxicological studies to characterise the non-clinical aspects of the product. The non-clinical toxicology program included repeated-dose toxicity studies (up to 13 weeks in rats and dogs), genotoxicity and reproductive toxicity studies, immunotoxicity studies, studies concerning phototoxicity, local tolerance and blood biocompatibility. Toxicokinetic studies were conducted as part of the repeated-dose toxicity studies. Most of the studies were conducted according to the requirements of Good Laboratory Practice (GLP) as discussed above. All preclinical studies have been performed with the active substance.

The likely overall safety of the product has been adequately evaluated and potential adverse effects identified.

2.4. Clinical aspects

2.4.1. Introduction

The applicant applied for the following indication: *treatment of iron deficiency in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests.*

The final indication agreed by the CHMP is for *the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2).*

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 5 – Summary of PK studies

Study number	Lot Number	Study Objective	Study Design	Number of Subjects Entered/Completed	Subject status Mean Age (Range)	Ferumoxytol Treatment*
7228-01	98080401	Evaluate effect of increasing dose and administration rate	Randomised, double-blind, placebo-controlled	41/41 (of those, 33/33 in Ferumoxytol PK analysis)	Healthy subjects 33 (20-58)	1, 2, and 4 mg Fe/kg at 2 mL/min; 4 mg Fe/kg at 3, 6, and 60 mL/min
62,745-2	98080401	Evaluate Ferumoxytol PK in CKD 5D patients on HD	Open-label, randomised	20/20	CKD 125 mg dose group: 57 (39-69) 250 mg dose group: 65 (34-77)	Either 125 or 250 mg
62,745-9	05091301	Evaluate effect of Ferumoxytol on QTc and PK evaluation	Double-blind, randomised, parallel group	174/172 (58 on Ferumoxytol, all received first dose per protocol, 57 second dose)	Healthy subjects 30 (18-45)	2 x 510 mg at 24 h interval

Abbreviations: CKD=Chronic kidney disease, PK=Pharmacokinetics
*All studies were conducted with the same formulation of Ferumoxytol, 30 mg Fe/mL IV.

Table 6 – Summary of Clinical Efficacy studies

Study No	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design / Control/ Study Population	Route and Regimen	No. Subjects Enrolled/ Completed/ Withdrawn	Primary Efficacy Endpoint Efficacy Parameters of Interest
PIVOTAL EFFICACY STUDIES						
62,745-6	10 May 04/ 25 Sep 06	20 USA	**Randomised:** Phase III Open-label multicentre active controlled CKD stages 1-5	2 x 510 mg Rienso IV 200 mg/day oral iron for 21 days	304 randomised; Rienso, N=228; oral iron, N=76 271 completed; Rienso, N=208; oral iron, N=63 33 withdrawn; Rienso, N=20; oral iron, N=13	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days pre-dose and 21 and 35 days post-dose
			Readmission[a]: Optional Phase III Open-label, multicentre, uncontrolled CKD stages 1-5	2 x 510 mg Rienso IV	62 entered Readmission 58 completed 4 withdrawn	Efficacy analyzed 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)

Study No	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design / Control/ Study Population	Route and Regimen	No. Subjects Enrolled/ Completed/ Withdrawn	Primary Efficacy Endpoint Efficacy Parameters of Interest
62,745-7	02 Jun 04/ 20 Dec 06	31 USA	**Randomised:** Phase III Open-label, multicentre, active controlled CKD stages 1-5	2 x 510 mg Rienso IV 200 mg/day oral iron for 21 days	304 randomised [b]; Rienso, N=227; oral iron, N=77 282 completed; Rienso, N=215; oral iron, N=67 22 withdrawn; Rienso, N=12; oral iron, N=10	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days pre-dose and 21 and 35 days post-dose
			Readmission[a]: Optional Phase III Open-label, multicentre, uncontrolled CKD stages 1-5	2 x 510 mg Rienso IV	51 entered Readmission 50 completed 1 withdrawn	Efficacy analyzed 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)
62,745-5[c]	09 Aug 04/ 24 Apr 07	Posta. 44 USA	**Post-amendm. (primary efficacy analysis):** Phase III Open-label, multicentre, randomised, active controlled CKD stage 5D on HD	2 x 510 mg Rienso IV 200 mg/day oral iron for 21 days Random. 1:1	230 randomised; 2 x 510 Rienso, N=114; oral iron, N=116 201 completed; 2 x 510 Rienso, N=102; oral iron, N=99 29 withdrawn; 2 x 510 Rienso, N=12; oral iron, N=17	Mean change from Baseline in Hgb at five weeks (Day 35) Haematology and iron indices drawn at 10 and five days pre-dose and 21 and 35 days post-dose
		Prea. 22 USA	**Pre-amendm.:** Phase III Open-label, multicentre, randomised, active controlled CKD stage 5D on HD	2 x 510 mg Rienso IV 4 x 255 mg Rienso IV 200 mg/day oral iron for 21 days Random. 3:3:1	148 randomised; 2 x 510 Rienso, N=64; 4 x 255 Rienso, N=62; oral iron, N=22 125 completed; 2 x 510 Rienso, N=54; 4 x 255 Rienso, N=55; oral iron, N=16 23 withdrawn; 2 x 510 Rienso, N=10; 4 x 255 Rienso, N=7; oral iron, N=6	Efficacy analyzed separately Haematology and iron indices drawn at 10 and five days pre-dose and 21 and 35 days post-dose
			Readmission[a]: Optional Phase III Open-label, multicenter, uncontrolled CKD stage 5D on haemodialysis	2 x 510 mg Rienso IV	75 entered Readmission (total from post- and pre-amendment populations) 73 completed 2 withdrawn	Efficacy analyzed 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

Study No	1st Subject Entered/ Last Subject Completed	No. Ctrs	Design / Control/ Study Population	Route and Regimen	No. Subjects Enrolled/ Completed/ Withdrawn	Primary Efficacy Endpoint Efficacy Parameters of Interest
						Phase (Day 0R)
SUPPORTING STUDIES, NONRANDOMISED						
62,745-3	20 Jan 03/ 19 June 03[d]	5	Phase II Open-label, multicentre, active controlled CKD stage 5D	8 x 128 mg Rienso IV 2 x 510 mg Rienso IV 325 mg/day oral iron	36 enrolled; 8 x 128 Rienso, N=15; 2 x 510 Rienso, N=11; oral iron, N=10 31 completed; 8 x 128 Rienso, N=10; 2 x 510 Rienso, N=11; oral iron, N=10 6 withdrawn; 8 x 128 Rienso, N=6; 2 x 510 Rienso, N=0; oral iron, N=0	Mean changes from Baseline in Hgb and TSAT for eight weeks following the initial dose of study medication Haematology and iron indices drawn at three days pre-dose and weekly for eight weeks post-dose
62,745-4	07 Oct 02/ 27 Dec 02[d]	3	Phase II Open-label, multicentre, uncontrolled CKD stages 1-5 (not on haemodialysis) or stage 5D on peritoneal dialysis	4 x 255 mg Rienso IV 2 x 510 mg Rienso IV	21 enrolled; 2 x 510 Rienso, N=11; 4 x 255 Rienso, N=10 20 completed; 2 x 510 Rienso, N=10; 4 x 255 Rienso, N=10 1 withdrawn; 2 x 510 Rienso, N=1; 4 x 255 Rienso, N=0	Mean changes from Baseline in Hgb and TSAT for eight weeks following the initial dose of study medication Haematology and iron indices drawn at three days pre-dose and weekly for eight weeks post-dose

a. In Protocols 62,745-6; 62,745-7; and 62,745-5, there was an optional Readmission Phase with open-label IV Rienso in eligible subjects from any of the treatment groups in the Randomised Phase of the study to obtain data on the safety and efficacy on a second course of IV iron therapy or a first course of IV iron therapy for subjects previously treated with oral iron. Subjects in the oral iron or Rienso treatment groups in the Randomised Phase of the study were eligible to enter if they continued to meet the study entry criteria, including a Hgb measurement (performed by the central laboratory) on Day 35. Protocol 62,745-5 readmitted subjects from the 4 x 255 Rienso, pre- or post-amendment 2 x 510 Rienso, and oral iron treatment groups.

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

c. Protocol 62,745-5 initially randomised subjects with Hgb ≤12.0 g/dl to either one of two dosing regimens of Rienso (4 x 255 mg or 2 x 510 mg) or oral iron in a 3:3:1 treatment allocation. After 148 subjects had been enrolled and randomised, the protocol was amended, and the Hgb entry criterion was changed from ≤12.0 g/dl to ≤11.5 g/dl. The 4 x 255 mg Rienso treatment group was removed, and the randomisation was changed to allocate subjects in a 1:1 ratio to Rienso or oral iron.

d. In Protocols 62,745-3 and 62,745-4, this date is the date of last dose of study medication.

e. Mean age is presented. Abbreviations: B=Black or African-American; C=Caucasian or white; Ctrs=centres; F=female; Fer=Rienso; M=male; No.=number; O=Other races.

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of Ferumoxytol was assessed in 3 Phase I studies examining doses from single 1 mg/kg to two doses of 510 mg in healthy subjects and single doses of 125 mg to 250 mg in subjects with CKD 5D as described in Table 5 and are summarised below.

Table 7 – Summary of PK results

Parameter	Study 7228-01			Study 62,745-9			Study 62,745-2	
Subjects	**Healthy subjects**			**Healthy subjects**			**CKD 5D on HD**	
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**
Analysis Method	**NCA**	**NCA**	**NCA**	**NCA (individual data)**	**NCA (population-model simulated data)**	**NONMEM[c]**	**NCA**	**NCA**
N	8	8	17	58	1	58	10	10
$AUC_{0-\infty}$ (µg·hr/mL)	365 (128)	996 (313)	2930(685)	15400 (3750)[d]	14800[d]	--	--	--
C_{max} (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]
$t_{½}$ (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]	--	--
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]	--	--
V_d (L)	3.45 (0.81)	2.62 (0.67)	2.36 (0.55)	3.16 (0.48)	3.26 (V_1)	2.71 (V_1), 0.443 (V_2)[j]	3.44 (1.08)	3.20 (1.06)
V_d/weight (mL/kg)	41.5 (11.8)	34.8 (7.9)	30.8 (7.8)	41.8 (6.6)	42.5[i]	--	--	--
V_{max} (mg/hr)	--	--	--	--	--	14.3	--	--
K_m (mg/L)	--	--	--	--	--	77.49	--	--
Q (mL/hr)	--	--	--	--	--	22.1	--	--

Abbreviations: CKD=Chronic kidney disease, NCA=Noncompartmental analysis
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 C_{max}, Dose 2 C_{max}
g. Represents time-averaged values
h. Calculated at two plasma ferumoxytol concentrations: (i) 300 µg/mL and (ii) much less than K_m (<<77.49 µg/mL)
i. Calculated using mean subject weight (76.6 kg)
j. V_1 and V_2 represent the volumes of distribution of the central and peripheral compartments, respectively.

Absorption

Bioavailability studies were not conducted as ferumoxytol has been developed for IV administration only. Information on comparability of different drug products used in the development and intended for

marketing has been provided. As Ferumoxytol is administered IV, no studies were performed to evaluate the effect of food on the PK of Ferumoxytol.

Distribution

In Study 7228-01 the volume of distribution decreased with increasing dose, Vd (SD) values were calculated to be 3.45 (0.81), 2.62 (0.67), and 2.38 (0.44) L for the 1, 2, and 4 mg Fe/kg dose, respectively. The effect was less pronounced with weight-normalised Vd; values (SD) were 41.5 (11.8), 34.8 (7.9), and 31.1 (8.4) mL/kg, respectively. Different infusion rates had no statistically significant influence on the volume of distribution.

For Study 62,745-9 volumes of distribution of the central and peripheral compartments V1 and V2 were calculated from the population PK analysis to be 2.71 and 0.443 L, respectively. The exploratory noncompartmental analysis showed a Vd (SD) of 3.16 (0.48) L, and the population-model simulated results were 3.26 L for Vd and 42.5 mL/kg for weight-normalised Vd using the mean subject weight of 76.6 kg.

These estimates for the volume of distribution are consistent with plasma volume, indicating that like other IV iron products Ferumoxytol initially distributes only into the plasma compartment.

Protein binding has not been determined which is considered acceptable.

Pharmacokinetics in the target population has only been investigated in CKD patients on haemodialysis up to a dose of 250 mg and with insufficient sampling time points. The limited data indicate that the volume of distribution is similar to values observed in healthy subjects and consistent with plasma volume. The mean plasma concentrations did not change significantly during this first 3 hours of PK sampling suggesting that ferumoxytol is not removed from the plasma by the dialysis process.

Elimination

In Study 7228-01 both CL and weight-normalised CL of Ferumoxytol from plasma decreased more than 50% with increasing dose; values (SD) were 265 (118), 164 (56), and 114 (15) mL/h and 3.15 (1.52), 2.18 (0.66), and 1.49 (0.32) mL/h/kg for the 1, 2 and 4 mg doses, respectively. The calculated apparent elimination rate constant λz for the 4 mg Fe/kg dose, 0.049 ± 0.006 hr-1, was about 35% slower than for the 1 mg Fe/kg dose, 0.074 ± 0.017 hr-1; t1/2 was about 48% longer with 14.4 ± 1.7 h and 9.72 ± 2.01 h for the 4 and 1 mg dose, respectively.

For the different infusion rates with the 4 mg dose PK parameters differed minimally; differences were less than 12% in λz and t1/2 between groups. A difference of up to 31% between groups was found for CL, but with weight normalization CL differences were less than 13%.

In Study 62,745-9 the final estimate of the population mean maximum elimination rate from plasma (Vmax) was 14.3 mg/h (SEM 1.3%), the Michaelis-Menten Constant (Km) 77.49 mg/L, and the distribution clearance (Q) 0.0221 L/h (16.6%).

Simulated noncompartmental parameters (SD) for 2 x 510 mg Fe based on final parameter estimates from the NONMEM analysis are 69.1 mL/h for CL and 0.901 mL/h/kg for weight normalised CL, respectively, 15.8 h for t½, and for λz.

Data derived by noncompartmental analysis using WinNonlin are 69.1 (13.9) mL/h and 0.901 (0.156) mL/h/kg for CL and weight normalised CL, respectively, and 19.0 (4.6) h for t½.

Overall, elimination of Ferumoxytol from plasma was dose dependent; plasma clearance decreased with increasing dose, indicating a capacity-limited elimination.

Exploratory data in the target population also suggested that the rate of elimination was not affected by renal insufficiency.

Dose proportionality and time dependencies

Data on dose proportionality are limited to Study 7228-01 investigating weight-based IV doses of 1, 2, and 4 mg Fe/kg bw. Mean plasma concentrations of ferumoxytol increased with dose and the rate of decline appeared to follow first-order kinetics. In this dose range Cmax and weight-normalised Vd demonstrated linear kinetics. Cmax increased proportionally with dose and although Vd decreased with increasing dose, Vd/weight revealed a statistically insignificant effect of dose. All remaining parameters demonstrated non-linear kinetics. AUC0-∞, dose-normalised AUC0-∞, and t1/2 increased significantly with increasing dose while the terminal elimination rate constant λz, CL, and weight-normalised CL decreased significantly with increasing dose. The data suggest a dose-dependent, capacity-limited elimination mechanism.

Special populations

Impaired renal function: All patients in the Phase III studies had renal impairment and PK of Ferumoxytol has been investigated in patients with CKD stage 5D on HD in Study 62,745-2. However data from Study 62,745-2 are limited and no PK data from Phase III studies have been provided.

Impaired hepatic function: Ferumoxytol is metabolised intracellularly in lysosomes of phagocytic cells of the RES system and not in the liver; therefore, no additional hepatic studies were conducted. In addition, the active metabolite of Ferumoxytol is iron, which is very highly conserved in the human body and is neither excreted by the kidneys or the liver.

Gender: In Study 7228-01 V_d and CL were higher for male compared to female subjects at the 4 mg Fe/kg dose. No significant differences were seen when V_d and CL were weight-normalised.

Weight: Study 7228-01 indicated an effect of body weight on Ferumoxytol PK parameters. The addition of weight as a covariate in the population PK analysis in Study 62,745-9 indicated a substantial linear relationship between weight and the central volume of distributionV_1 and the addition significantly improved the PK parameter predictions and reduced intersubject variability in V_1 by 26.3%.

Other: The effect of ethnicity and age on PK parameters of Ferumoxytol has not been investigated.

Pharmacokinetic interaction studies

No Drug-drug interaction studies with Ferumoxytol have been conducted. Since Ferumoxytol is not metabolised in the liver, nor substantially excreted via kidney, no interaction with drugs primarily relying on hepatic metabolism or urinary excretion is expected.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical studies addressing the mechanism of action were submitted.

Primary and Secondary pharmacology

The pharmacodynamic effect on haematologic parameters in humans including serum ferritin, serum iron and transferrin saturation (TSAT) were evaluated in the pharmacokinetic studies 7228-01, 62,745-

9 and 62,745-2. However, as these PK-studies were conducted in non-anaemic patients with mostly normal iron status at baseline, PD endpoints to objectively assess the pharmacodynamic effect of Rienso on iron metabolism in the target population were not incorporated.

The pharmacodynamic effect on haematologic parameters including Hgb, serum ferritin and TSAT were assessed as primary and secondary endpoints in the clinical efficacy studies.

The pharmacodynamic effect on cardiac electrophysiology (QT/QTc prolongation) subsequent to the administration of a supratherapeutic dosing regimen to healthy volunteers was investigated in Study 62,745-9, a Phase 1, active- and placebo-controlled, double-blind (with respect to Rienso and placebo), randomised, parallel group, single centre study in healthy volunteers. 174 subjects were randomised to placebo, Rienso, or unblinded moxifloxacin (n = 58 per group).

The pharmacological effect of Rienso on iron indices was shown by an increase particularly in serum ferritin, at Day 7 relative to baseline values.

The heart rate was not affected. Transient changes in T wave morphology were identified in 3/57 subjects (5.3%) receiving Rienso. The observed transient changes were not considered clinically relevant. The Applicant concludes that overall Rienso did not express clinically meaningful ECG effects.

An observed decrease in QT interval (mean change 0 to -4 msec with the lower bound of the 95% CI < 10 msec) is not considered to be of clinical relevance. ECG analyses did not reveal any safety signal.

2.4.4. Discussion on clinical pharmacology

The Applicant has provided only a limited pharmacokinetic characterisation of ferumoxytol. Particularly, data on the pharmacokinetic profile of the proposed dose in the target population are missing, but since PK in the target patient population is not expected to differ from that of normal volunteers this is considered acceptable.

The volume of distribution is roughly in line with plasma volume as expected; protein binding has not been determined. Elimination of ferumoxytol from plasma was dose dependent; clearance decreased with increasing dose, indicating a capacity-limited elimination. Excretion, metabolism, pharmacokinetics of metabolites, and consequences of possible genetic polymorphism have not been studied in clinical trials and no specific clinical data are considered necessary.

No studies in special populations have been performed; effects of weight and gender have been analysed in Study 7228-01. While weight was directly related to the volume of distribution, the limited data suggest that gender had no relevant effect on pharmacokinetic parameters. Effects of impaired renal or hepatic function on pharmacokinetics have not been investigated, but the pivotal clinical studies investigated efficacy and safety in patients with renal impairment. Due to the known pharmacokinetics for IV iron, no relevant influence of renal insufficiency or impaired hepatic functions on PK parameters is expected and information has been adequately included in section 4.2 of the SmPC and the risk management plan. Thus the lack of formal pharmacokinetic data is acceptable. The effect of ethnicity, age, or drug-drug interaction have not been investigated; as no influence is expected, this is acceptable. No adverse events associated with cardiac dysfunction were noted in the thorough ECG trial. Small changes in QT interval (towards shortening), which were observed in the safety pharmacology study, are not considered to be of clinical relevance.

An additional E/R analysis examining the effect of ferumoxytol plasma concentration on the change from baseline in QTcI in this ECG-study revealed that ferumoxytol has no clinically important effect on cardiac repolarisation. The predicted QTcI change at Cmax was -2 ms with an upper confidence interval of 0 ms, and the slopes for QTc effect vs. plasma concentration exposure were near zero.

By virtue of its superparamagnetic properties (using a dosage of ≤ 4 mg/kg of ferumoxytol), administration of Rienso may transiently affect the diagnostic ability of MR imaging. Therefore, as it is advised in section 4.5 of the SmPC that anticipated MR imaging studies should be conducted prior to the administration of Rienso.

2.4.5. Conclusions on clinical pharmacology

The Applicant has provided a limited pharmacokinetic characterisation of ferumoxytol, but since PK in the target patient population is not expected to differ from that of normal volunteers this is considered acceptable.

The basic mechanism of action of the iron component is well established. The precise cellular events of iron loading onto transferrin, however, and the export of iron-transferrin complexes from RES macrophages into the blood remain unknown.

The stability of the iron-PSC-complex at physiologic pH has been demonstrated and the controlled intracellular release in the lysosomes of RES macrophages is supported by degradation studies and pre-clinical biodistribution studies. The pharmacodynamic properties of ferumoxytol have been studied in sufficient detail. No further pharmacodynamic studies are required. No interaction of ferumoxytol particles with dialysis membranes was found. Ferumoxytol particles do not pass through dialysis membranes; minimal amounts of iron are retained in the dialysis system including the membrane. Free PSC with its molecular size of ~ 10 kD is dialyzable through high-flux membranes.

No effect of a supratherapeutic regimen of ferumoxytol was observed on AV conduction, depolarization, or cardiac repolarization as measured by the PR, QRS, or QTc interval durations, and there were no associated clinical cardiac symptoms reported.

In conclusion, the PK/PD profile is acceptable.

2.5. Clinical efficacy

2.5.1. Dose response studies

No true dose-response studies have been submitted, as in all the clinical efficacy trials a total dose of 1.020 mg of Rienso was administered. Different dosing schemes were tested in supportive clinical studies: in one treatment arm of study 62,745-5 (pre-amendment part) 4 x 255 mg of Rienso was administered to 62 IDA patients on HD. Additionally 10 patients (CKD stage 1-5 +/- peritoneal dialysis-treatment) were treated with 4 x 255 mg IV in the supporting clinical study 62,745-4; furthermore 15 patients (CKD stage 5D on HD) received 8 x 128mg in the supporting study 62,745-3.

In the safety study 62,745-8 the adverse events following a single IV-dose of 510 mg versus placebo were evaluated in 750 patients with CKD (stages 1-5 and 5D). The lack of dose response studies is acceptable since the chosen total dose of iron (around 1 g) corresponds to the standard total dose in published clinical trials and is in line with the recommendations for IV iron replacement therapy (in anaemic CKD patients) in relevant clinical treatment guidelines (e.g. Revised European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure). The chosen total dose allows for comparison with published study results of marketed standard IV-iron preparations. Further dose response studies are therefore not required.

2.5.2. Main studies

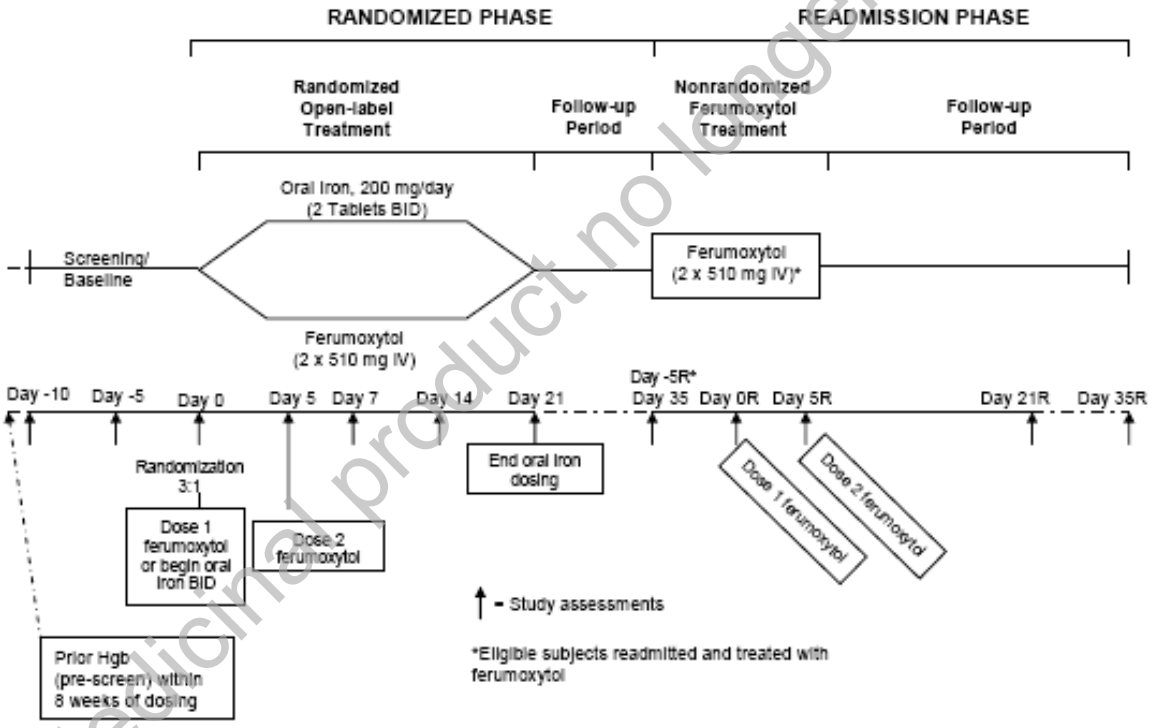
The Applicant submitted three Phase III multicentre open label studies (62,745 6, 62,745 7 and 62,745 5-post amendment part) using oral iron as active control in order to support the application. The main studies included a non-randomised, optional extension Phase for patients, who - after completion of the first study phase - continued to meet the study entry criteria (see below). In this readmission phase all patients were treated with 2 x 510 mg Rienso. In the whole clinical study programme the undiluted iron solution for injection was rapidly administered (up to 30 mg/sec) without a test dose.

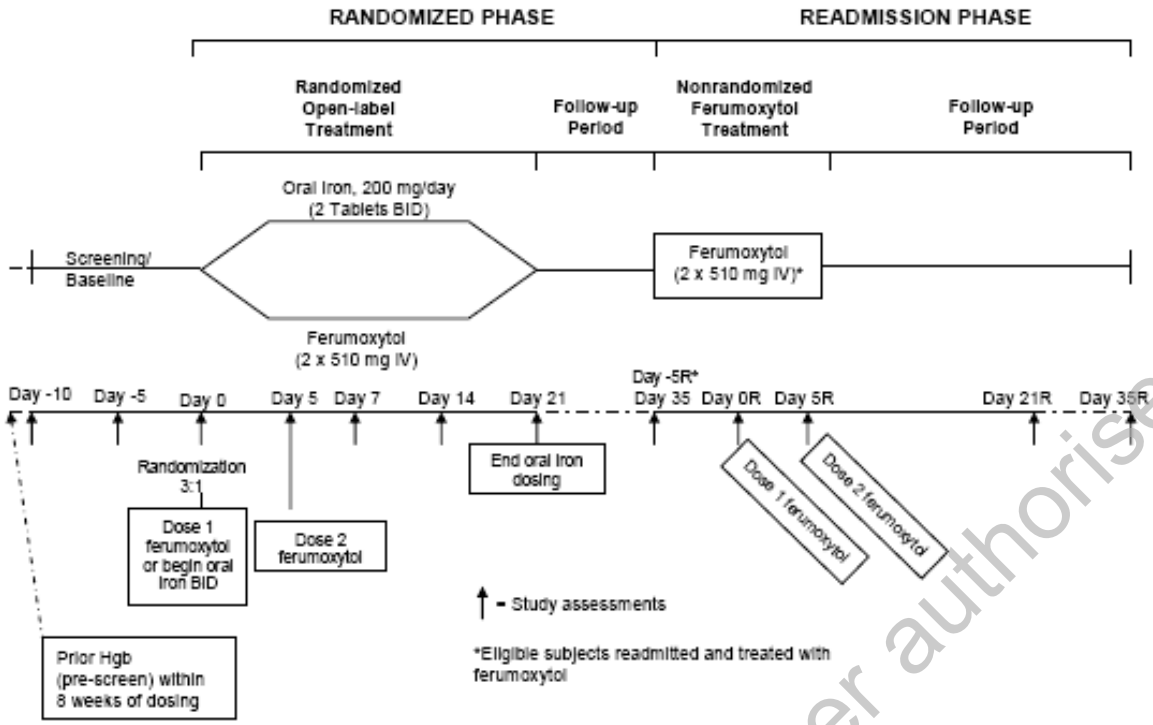
Two of the main studies (62,745-6 and 62,745-7) had identical designs and methodology and were conducted in anaemic patients with CKD stages 1 to 5 not on dialysis with or without concomitant ESA-therapy (> 90% of patients at a stable-dose).

The third study (62,745-5) enrolled CKD-patients (stage 5D) on haemodialysis all of whom were receiving supplemental ESA therapy (76 - 84% of patients at a stable dose).

Methods

The overall study design was similar in all 3 trials and is displayed in the following figure.





Source: Study Protocol 62,745-7, p.37.

Figure 1 - Study Protocol 62,745-6/7 Overall Design

Study Participants

The inclusion criteria for the three pivotal studies as specified in the latest versions of each study protocol are shown in the table below.

Table 8 – Inclusion Criteria for the Phase III 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 Authorisation 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		
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	

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 (±25% of current dose) for at least 2 weeks			X
Have an **Hgb ≤ 11.5 g/dl** at Day -10 (±4 days) and Day -5 (±3 days)		X	
Have an **Hgb ≤ 11.0 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 Rienso 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	

The final exclusion criteria of studies 62,745-6, 62,745-7 and 62,745-5 (post amendment part) were adequate.

Treatments

In the three pivotal studies, patients in the IV-Rienso groups received a 1.02 g course of elemental iron administered as two separate IV-doses of 510 mg Rienso from a 17 ml single use vial on Day 0 and Day 5 (± 3 days). The oral iron control group received Ferro-Sequels (containing 50 mg of ferrous fumarate per tablet combined with a stool softener sodium docusate), administered orally as two tablets twice daily starting at Day 0 through Day 21 (3 weeks). The daily dose was 200 mg of elemental iron resulting in a cumulative dose of 4.2 g.

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

Objectives

The objective of the main trials was to evaluate the safety and efficacy of 2 x 510 mg Rienso (to be administered within 5 ± 3 days; cumulative dose: 1020 mg) in patients with CKD related anaemia and to confirm superiority of this IV treatment over oral iron treatment (2 x 2 tablets of Ferro-Sequels containing 50 mg of ferrous fumarate per tablet combined with a stool softener sodium docusate 50 mg/tablet, for 21 days; cumulative dose: 4.2 g of iron).

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 / -7 and of the post amendment part of study 62,745-5.

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

Secondary efficacy endpoints were:

- Hgb Responders (increase ≥ 1.0 g/dl in Hgb at five weeks),
- Hgb and Ferritin Responder (increase ≥ 1.0 g/dl in Hgb at Day 21 or Day 35 plus increase ≥ 160 ng/ml in ferritin at Day 21 or Day 35).
- Mean change from Baseline in Ferritin at three weeks (Day 21).
- Additional Efficacy Measures included: Mean change from Baseline in Hgb at Day 21, - mean change from Baseline in Ferritin at Day 35,- Serum Iron, - % of Hypochromic RBCs, - Total Iron Binding Capacity (TIBC), - Reticulocyte count, - Transferrin Saturation (TSAT), - Reticulocyte Haemoglobin Content (CHr) at Day 21 and Day 35.

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. With the second amendment a sample size calculation was presented assuming a 0.6 g/dl difference between the two treatment groups in Hgb mean change from baseline and a common standard deviation of 1.2 g/dl. With 57 patients in the oral iron group and 171 patients in the Rienso group - according to the applicant - there should be 90% power to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (76 patients) drop out rate due to potential exclusions from the intent-to-treat population, 304 patients were assumed necessary for recruitement.

Study 62,745-5: Initially no formal sample size calculation was performed: at least 50 evaluable patients should receive oral iron (Group 1), 150 patients should receive 2 x 510 mg Rienso (Group 2) and 150 patients 4 x 255 mg Rienso (Group 3). The sample size was changed twice during the study and finally a formal sample size calculation using the same assumptions as in the other two studies was introduced, resulting in 86 patients for the oral iron group and 86 patients for the Rienso group, to providing 90% power to detect a difference using a two sample t-test with 5% Type I error. Assuming a 25% (58 patients) drop out rate due to potential exclusions from the intent-to-treat population, 230 patients were to be recruited in the post amendment part of study 62,745-5.

Randomisation

Studies 62,745-6 and 62,745-7: Simple blocked randomisation was used with a unique randomisation number assigned for each patient in a 1:3 ratio.

Study 62,745-5: Simple block randomisation was used as in the other two studies. Under the original protocol, each patient was assigned to one of the three treatment groups; oral iron, 2 doses of 510 mg Rienso or 4 doses of 255 mg Rienso with a 1:3:3 ratio. Under the final protocol, patients were assigned 1:1 to oral iron or 2 doses of 510 mg Rienso.

Blinding (masking)

The pivotal studies were all open label studies.

Statistical methods

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 pre-amendment data of study 62,745-5 were used for safety analysis and the efficacy data were analysed descriptively only.

The Intent-to-Treat (ITT) Population was defined as all subjects who were randomised. The ITT Population was used for the efficacy analyses. The Safety Population was defined as all subjects who were randomised and had at least one dose of study medication. The Safety Population was used for the safety analyses. Additional analyses were to be performed on the Efficacy Evaluable Population (EEP), which was pre-defined as all subjects who were randomised, did not violate any inclusion or exclusion criteria, were compliant with the study medication and did not violate against further pre-specified criteria (non-missing Baseline and Day 35 Hgb values, both Baseline Hgb blood draws within 15 days prior to dosing , Day 35 Hgb blood draw taken within 45 days post-dosing, no other iron products after the Day -10 lab draw, no start an ESA after the Day -10 lab draw, no ESA dose change greater than 25% of Baseline ESA and no transfusion of packed RBCs after the Day -10 lab draw).

As primary endpoint in the final protocols of the three studies the mean of patient-specific Day 35 visit haemoglobin change from baseline was compared across treatment groups, using a two-sided, two-sample t-test with a 5% Type I error. For baseline values the average of the two central lab tests performed at the Day -10 visit and Day -5 visit prior to initial dosing (Day 0) were used. No interim efficacy analyses was planned. However, an independent Data Monitoring Committee periodically reviewed safety analyses to ensure continued safety of the study participants. An analysis of covariance (ANCOVA) model was planned to assess the impact of site on the Day 35 visit haemoglobin change from baseline. A model included effects for treatment (categorical), baseline haemoglobin (continuous), site (categorical) and treatment by-site interaction. A global F-test was to be used to evaluate the effect of site and treatment by-site interaction separately with a 5% type I error.

The difference in the proportion of Hgb- and Hgb / Ferritin responders between the two treatment groups were analyzed using a two-sided chi-square test. Comparisons across treatment groups for Mean change from Baseline in Ferritin were made using a two-sided, two sample t-test.

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 had to assume no change from Baseline for that efficacy parameter and a value of zero was to be imputed for change from Baseline at that time point. In cases where laboratory panels were redrawn at either post-dose visit, the first non-missing lab value for each lab parameter was to be used for both safety and efficacy analyses.

Only in the studies 62,745-6 and 62,745-7 a confirmatory subgroup analysis was planned for subjects who were on ESA and who were not on ESA using the ITT Population to evaluate the primary efficacy endpoint. No subgroup analysis was planned in study 62,745-5.

Results

Participant flow

Proportion of completers in general was higher in the IV- treatment groups compared to the oral groups. In *Study 62,745-6* a total of 304 subjects was randomised (228 IV vs. 76 oral). The majority of subjects completed the study (91.2% IV vs. 82.9% oral). Twelve patients withdrew from the study prior to administration of study medication (11 IV vs. 1 oral). During the treatment more oral patients withdrew due to AE compared to IV (4 IV vs. 9 oral).

A total of 304 subjects were randomised in the Randomised Phase of *Study 62,745-7* (227 IV vs. 77 oral). One patient was erroneously randomised twice in the IV-group. Therefore the number of patients in the ITT Population is 226 instead of 227. The majority of subjects completed the study (94.7% IV vs. 87% oral). Ten subjects withdrew from the study prior to administration of study medication (7 IV vs. 3 oral). One IV-patient withdrew from the study due to AE compared to 7 oral patients.

In total 230 patients were randomised for the pivotal study 62,*745-5 post-amendment-part*. The majority of subjects completed the study-part (89.5% IV vs. 85.3% oral). Six subjects withdrew from the study prior to administration of the study drug (4 IV vs. 2 oral). Fewer IV patients withdrew due to an AE compared to oral (4 vs. 9).

The *pre amendment part of study 67,745-5* was terminated after 148 subjects had been enrolled and randomised (64 for 2 x 510 mg, 62 for 4 x 255 mg, 22 for oral). 84.4% of the patients in the 2 x 510 mg IV-group completed the treatment compared to 88.7% in the 4 x 255 mg IV-group and 72.7% in the oral group. Withdrawal due to AE occurred in 3 patients from the 4 x 255 mg group and 1 patient from the oral group.

Recruitment

Study 62,745-6: The first subject was randomised 10 May 2004, last subject completed 26 September 2006.

Study 62,745-7: The first subject was randomised 02 June 2004, the last subject completed 20 December 2006.

Study 62,745-5 (post amendment part): The first subject was randomised 09 August 2004, the last subject completed 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. The final SAPs described the principal features of the primary confirmatory analysis of the primary endpoint. Each SAP was finalized and signed off in advance of database lock for the relevant study.

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 in response to emerging data in the literature suggesting that targeting normal haemoglobin levels (> 13 g/dL) may potentially be detrimental, 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.

The 'post-amendment part' was presented in the application as the pivotal study to confirm efficacy in HD patients and the 'pre-amendment part' as supportive data only.

Baseline data

A summary of the demographic characteristics, including age, gender, and race of all randomised subjects across the pivotal studies is presented in the table below.

Table 9 – Demographics, Randomised Subjects (Modified ITT Population)

	N	Age (Years) Mean±SD	Gender (%) Male/Female	Race (%) C/B/O
Protocol 62,745-6				
Rienso 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				
Rienso 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				
Rienso 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				
Rienso 2 x 510 mg	58	57.10±14.15	41.4/58.6	39.7/51.7/8.6
Rienso 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				
Rienso 2 x 510 mg	605	63.39±14.55	42.6/57.4	54.9/39.3/5.8
Rienso 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

C=Caucasian; B=Black or African-American; O=Other (Asian, Pacific Islander, Native Hawaiian, American Indian, and Alaska Native)
SD=Standard deviation

Numbers analysed

Study 62,745-6: A total of 304 subjects were randomised, 228 patients to IV ferumoxytol and 76 patients to oral iron. The majority of subjects completed the study. Twelve patients withdrew from the study prior to administration of study medication. During the treatment phase 4 patients from the Rienso-group withdrew from the study due to AE compared to 9 oral iron-treated patients. The Efficacy Evaluable Population (EEP) consisted of 236 patients.

Study 62,745-7: A total of 304 subjects were randomised in the Randomised Phase of the study (Rienso 227 vs. oral-iron 77). One patient was erroneously randomised twice. Therefore the number of patients in the ITT Population is 226 instead of 227. The majority of subjects completed the study. Ten subjects withdrew from the study prior to administration of study medication. One patient on ferumoxytol withdrew from the study due to AE compared to seven oral iron-treated patients. The EEP consisted of 237 patients.

Study 62,745-5 post amendment: A total of 230 patients were randomised in a 1:1 ratio at 44 sites in the US in the Randomised Phase of the study (Post-amendment-part). The majority of subjects completed the study. Six subjects withdrew from the study prior to administration of study drug. Fewer

Rienso-treated subjects withdrew due to an AE relative to oral iron-treated subjects. The EEP consisted of 129 patients.

Outcomes and estimation

Outcomes of the primary and secondary endpoints of the main studies as specified in the final versions of the protocols are displayed in the following tables. Baseline Hgb values were comparable between treatment arms (with higher values in study 62,745-5 especially in the pre-amendment part, as expected). IV-treatment showed superior results for the primary and secondary endpoints in all pivotal studies.

Table 10 – Study 62,745 6 Summary of Primary and Secondary Efficacy (ITT Population)

Efficacy Endpoint (ITT Population)	**Rienso N=228**	**Oral Iron N=76**	**p-value [a]**
Primary:			
Hgb Baseline value	*9.96±0.69*	*9.95±0.78*	
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

Two sample t-test for evaluating a treatment difference. Statistically significant at a p value <0.05.

Table 11 – Study 62,745 7 Summary of Primary and Secondary Efficacy (ITT Population)

Efficacy Endpoint (ITT Population)	**Rienso N=226**	**Oral Iron N=77**	**p-value [a]**
Primary:			
Hgb Baseline value	*9.85±0.77*	*9.94±0.73*	
Change from Baseline in Hgb at Day 35, mean±SD g/dl	1.22±1.26	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

Table 12 – Study 62,745 5 Summary of Primary and Secondary Efficacy (Post-amendment ITT Population)

Efficacy Endpoint (ITT Population)	Rienso N=114	Oral Iron N=116	p-value [a]
Primary:			
Hgb Baseline value	*10.59±0.67*	*10.69±0.57*	
Change from Baseline in Hgb at Day 35, mean ± SD g/dl	1.02±1.13	0.46±1.06	0.0002
Secondary:			
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

Results in the EE Population (consisting of all completers without protocol violations) were similar to those in the primary ITT analysis (mean Hgb changes at Day 35 in study 62,745-6: 0.86 g/dl IV vs. 0.06 g/dl oral; study 62,745-7: 1.35 g/dl IV vs. 0.71 g/dl oral; study 62,745-5 post amendment: 1.13 g/dl IV vs. 0.46 g/dl oral).

In study 62,745-6 and study 62,745-5 (pre-amendment part) proportion of combined Hgb and ferritin responders after IV-treatment were higher than the proportion of Hgb responders which can be attributed to different time points of measurement.

Regarding dose response, the results for responder rates the pre-amendment part of study 62,745-5 suggest that the 4 x 255 mg dosing scheme was slightly more effective in HD patients compared to the 2 x 510 mg scheme (51.6% 4 x 255 mg vs. 35.9% 2 x 510 mg), but the number of patients treated with 4 x 255 mg was small limiting the relevance of this finding.

Subgroup analysis: ESA-therapy

In Study 62,745-6 mean change in Hgb was greater in the IV group compared to oral in both the ESA(+) and the ESA(-) subgroups (ESA(+): 1.16 vs. 0.19 g/dl; ESA(-): 0.62 vs. 0.13 g/dl). The IV treatment effect in the ESA(-) subgroup (0.62 g/dl) was larger than in the oral ESA+ subgroup (0.19 g/dl). Proportion of Hgb Responders, proportion of Hgb and Ferritin Responders, and mean change in ferritin at Day 21 (secondary efficacy endpoints) were all greater in the IV-subgroups compared to the oral subgroups whether or not taking ESA during the study (see 'Analysis performed across trials' below for distribution and impact of key potential confounders).

In Study 62,745-7 the mean change from Baseline in Hgb in the IV- ESA(-) subgroup was 0.91 g/dl compared to 0.86 g/dl in the oral iron ESA+ subgroup. Proportions of Hgb Responders, combined Responders, and the mean change in ferritin at Day 21 were all greater in the IV-group compared to oral whether or not taking an ESA during the study. No subgroup analyses were performed in study 62,745-5.

Change in Hgb from baseline(R) to day 35(R) - Readmission phase

In study 62,745-6 of the initially randomised IV patients 9.6% (22/228) entered the Readmission Phase for a second course of Rienso-treatment (vs. 52.6% [40/76] oral to receive Rienso first time). The second course of Rienso treatment resulted in an Hgb rise of 0.55 g/dl after 5 weeks (vs. +0.73 g/dl previous oral).

In study 62,745-7 of the randomised Rienso patients 9.3% (21/226) entered the Readmission Phase (39.0% [30/77] oral). Results in Hgb change after 5 weeks were +0.31 g/dl vs. +1.01 g/dl from previous oral.

In Study 62,745-5 of the randomised Rienso patients 10.8% (26/240) (2 x 510 mg or 4 x 255 mg) entered the Readmission Phase (35.5% [49/138] oral, pre- and post-amendment parts combined). Results in mean change in Hgb after 5 weeks were 0.56 g/dl (previous 2 x 510 mg [N=14]) versus 0.68 g/dl (previous 4 x 255 mg [N=12]) and 0.80 g/dl (previous oral) respectively. Response in the readmission patients who received Rienso for the first time was comparable to the results of the IV-treatment in the randomised phase of the trials. The effect of a second course of IV-iron was considerably lower than the effect of IV-treatment in the randomised phase.

Ancillary analyses

The other ancillary analyses (mean change from Baseline in Hgb at Day 21, mean change from Baseline in Ferritin at Day 35, Serum Iron, % of Hypochromic RBCs, Total Iron Binding Capacity (TIBC), Reticulocyte count, Transferrin Saturation (TSAT), Reticulocyte Haemoglobin Content (CHr) at Day 21 and Day 35) yielded results which paralleled the results of the primary and secondary endpoints. Only the change in percentage of hypochromic red cells showed no clear difference between IV and oral treatment, especially in study 62,745-5. Concomitant ESA therapy enhanced the effect of iron in all treatment groups as expected. No treatment by site interaction has been found in the main studies.

Summary of main studies

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).

Table 13 – Summary of Efficacy for Trial 62,745-7

Title: 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 identifier	62,745-7	
Design	Randomized, multicenter, open label; Active control, subjects with CKD Stages 1-5	
	Duration of main phase:	5 Weeks
	Duration of Run-in phase:	<not applicable>
	Duration of Extension phase:	Optional non-randomized readmission of 5 Weeks
Hypothesis	Superiority	

Treatment groups	Ferumoxytol- 2 dose regimen		2 x 510 mg IV doses of ferumoxytol within 5±3 days 227 randomized
	Oral Iron		21 consecutive days of 200 mg/day oral iron 77 randomized
	Ferumoxytol Readmission (not part of randomized population efficacy analysis)		2 x 510 mg IV doses of ferumoxytol within 5±3 days 51 non-randomized
Endpoints and definitions	**Primary:** Hemoglobin Response	Mean Hgb Change from Baseline at Week 5	The primary efficacy endpoint, Hemoglobin Response, was the mean change from Baseline in hemoglobin at five weeks (Day 35 visit) post initial dose of study medication.
	Secondary: Proportion of Hemoglobin Responders	>=1 Hgb increase at Week 5 Responders	Hemoglobin Responders: A secondary endpoint was the proportion of patients who had a rise of at least 1.0 g/dl in hemoglobin from Baseline at five weeks (Day 35 visit) post initial dose of study medication.
	Additional: Ferritin Response	Mean Ferritin Change at Week 5	Ferritin Response: mean change from Baseline in ferritin at five weeks (Day 35 visit) post initial dose of study medication.
Database lock	03 May 2007		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT (Randomized subjects)		
Descriptive statistics and estimate variability	**Treatment group**	Ferumoxytol 2 x 510 mg	Oral Iron 200 mg/day
	Number of subjects	226	77
	Primary Efficacy Endpoint- Mean Change from Baseline in Hgb at Week 5, Mean (g/dL)	1.2	0.5
	Std	1.3	1.00
	Method	Two sample t-test, p-value<0.0001	
	Secondary Efficacy Endpoint- Hgb Responders at Week 5, N (%)	117 (51.8)	15 (19.5)
	Std	NA	NA
	Method	Chi-square test, p-value<0.0001	
	Additional Efficacy Endpoint- Mean Change from Baseline in Ferritin at Week 5 Mean (ng/mL)	300.7	0.3
	Std	214.9	82.0
	Method	Two sample t-test, p-value<0.0001	

Table 14 –Summary of Efficacy for Trial 62,745-6

Title: 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 identifier	62,745-6		
Design	Randomized, multicenter, open label; Active control, subjects with CKD Stages 1-5		
	Duration of main phase: **Duration of Run-in phase:** **Duration of Extension phase:**		5 Weeks <not applicable> Optional non-randomized readmission of 5 Weeks
Hypothesis	Superiority		
Treatment groups	Ferumoxytol- 2 dose regimen		2 x 510 mg IV doses of ferumoxytol within 5±3 days 228 randomized
	Oral Iron		21 consecutive days of 200 mg/day oral iron 76 randomized
	Ferumoxytol Readmission (not part of randomized population efficacy analysis)		2 x 510 mg IV doses of ferumoxytol within 5±3 days 62 non-randomized
Endpoints and definitions	**Primary:** Hemoglobin Response	Mean Hgb Change from Baseline at Week 5	The primary efficacy endpoint, Hemoglobin Response, was the mean change from Baseline in hemoglobin at five weeks (Day 35 visit) post initial dose of study medication.
	Secondary: Proportion of Hemoglobin Responders	>=1 Hgb increase at Week 5 Responders	Hemoglobin Responders: A secondary endpoint was the proportion of patients who had a rise of at least 1.0 g/dl in hemoglobin from Baseline at five weeks (Day 35 visit) post initial dose of study medication.
	Additional: Ferritin Response	Mean Ferritin Change at Week 5	Ferritin Response: A secondary endpoint was the mean change from Baseline in ferritin at five weeks (Day 35 visit) post initial dose of study medication.
Database lock	03 May 2007		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT (Randomized subjects)		
Descriptive statistics and estimate variability	**Treatment group**	Ferumoxytol 2 x 510 mg	Oral Iron 200 mg/day
	Number of subjects	228	76
	Primary Efficacy Endpoint- Mean Change from Baseline in Hgb at Week 5 Mean (g/dL)	0.8	0.2
	Std	1.2	1.0
	Method	Two sample t-test, p-value <0.0001	
	Secondary Efficacy Endpoint- Hgb Responders at Week 5 N (%)	89 (39.0)	14 (18.4)
	Std	NA	NA
	Method	Chi-square test, p-value=0.001	
	Additional Efficacy Endpoint- Mean Change from Baseline in Ferritin at Week 5 Mean (ng/mL)	381.7	6.9
	Std	278.6	60.1
	Method	Two sample t-test p-value<0.0001	

Table 15 –Summary of Efficacy for Trial 62,745-5

Title: 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			
Study identifier	62,745-5		
Design	Randomized, multicenter, open label; Active control, subjects with CKD stage 5D on Hemodialysis who were receiving supplemental ESA therapy		
	Duration of main phase: **Duration of Run-in phase:** **Duration of Extension phase:**		5 Weeks <not applicable> Optional non-randomized readmission of 5 Weeks
Hypothesis	Superiority		
Treatment groups (Post Amendment)	Ferumoxytol -2 dose regimen		2 x 510 mg IV doses of ferumoxytol within 5±3 days 114 randomized:
	Oral Iron		21 consecutive days of 200 mg/day oral iron 116 randomized
	Ferumoxytol Readmission (not part of randomized population efficacy analysis)		2 x 510 mg IV doses of ferumoxytol within 5±3 days 75 non-randomized readmission total
Endpoints and definitions	**Primary:** Hemoglobin Response	Mean Hgb Change from Baseline at Week 5	The primary efficacy endpoint, Hemoglobin Response, was the mean change from Baseline in hemoglobin at five weeks (Day 35 visit) post initial dose of study medication.
	Secondary: Proportion of Hemoglobin Responders	>=1 Hgb increase at Week 5 Responders	Hemoglobin Responders: A secondary endpoint was the proportion of patients who have a rise of at least 1.0 g/dl in hemoglobin from Baseline at five weeks (Day 35 visit) post initial dose of study medication.
	Additional: Ferritin Response	Ferritin Mean Change at Week 5	Ferritin Response: A secondary endpoint was the mean change from Baseline in ferritin at five weeks (Day 35 visit) post initial dose of study medication.
Database lock	01 June 2007		

Results and Analysis			
Analysis description	**Primary Analysis Results from Post amendment**		
Analysis population and time point description	ITT (Randomized subjects)		
Descriptive statistics and estimate variability **POST-AMENDMENT**	**Treatment group**	Ferumoxytol 2 x 510 mg	Oral Iron 200 mg/day
	Number of subjects	114	116
	Primary Efficacy Endpoint- Mean Change from Baseline in Hgb at Week 5 Mean (g/dL)	1.0	0.5
	Std	1.1	1.1
	Method	Two sample t-test, p-value=0.0002	
	Secondary Efficacy Endpoint- Hgb Responders at Week 5 N (%)	56 (49.1)	29 (25.0)
	Std	NA	NA
	Method	Chi-square test p-value=0.0002	
	Additional Efficacy Endpoint-- Mean Change from Baseline in Ferritin at Week 5 Mean (ng/mL)	233.9	-59.2
	Std	207.0	106.2
	Method	Two sample t-test p-value<0.0001	

Analysis performed across trials (pooled analyses and meta-analysis)

A meta-analysis was performed on the modified ITT-population. This population included 605 (95.6%) patients in the 2 x 510 mg group, 60 (96.8%) for 4 x 255 mg and 279 (95.9%) oral patients. Overall, 879 (89.1%) randomised patients completed study treatment (579/605 [91.5%] 2 x 510 mg, 55/60 [88.7%] 4 x 255 mg, and 245/279 [84.2%] oral). Across all patients, the most common reason for withdrawal across all treatment groups was AE, which led to the withdrawal of 9/633 (1.4%) patients in the 2 x 510 mg group, 3/62 (4.8%) patients in the 4 x 255 mg group, and 25/291 (8.6%) oral

patients. The withdrawal rate due to AEs in the oral iron group was higher relative to the 2 x 510 mg group.

Demographics

The mean age for randomised patients (n = 944) was 63.04 years and was similar across individual treatment groups (2 x 510 mg: 63.39 years; 4 x 255 mg: 58.55 years and oral: 63.24 years). Overall, 56.1% of the patients were female, with similar distribution across individual treatment groups (2 x 510 mg: 57.4%; 4 x 255 mg: 56.7% and oral: 53.4%). Caucasian subjects comprised 52.0% of the patients enrolled across the studies with a similar trend in the 2 x 510 mg (54.9%) and oral groups (49.5%); Caucasians represented 35.0% of the 4 x 255 mg group. Black or African-American subjects comprised 42.2% of patients enrolled across the studies with a similar trend across treatment groups (39.5% 2 x 510 mg, 53.3% 4 x 255 mg and 45.9% oral).

Stage of kidney disease

Of the 944 randomised patients, the largest proportion at baseline had CKD stage 5D on HD (37.9%), followed by stage 4 (29.6%), stage 3 (23.3%), and stage 1 or 2 (1.1%). No randomised patient had CKD stage 5D on peritoneal dialysis. The distribution of CKD stages between the 2 x 510 mg and oral groups, respectively, was 33.7% and 26.9% for stage 4, 27.8% and 46.6% for stage 5D, and 26.8% and 20.8% for stage 3. All patients in the 4 x 255 mg IV group had CKD stage 5D on HD.

ESA Co-therapy

The largest percentage of patients (48.5%) at Baseline were receiving stable ESA therapy (458/944), followed by 37.2% who were not receiving ESA therapy and 14.3% who were started on ESA therapy or changed the ESA-dose by > 25%. The distribution of patients who did not receive ESA therapy and those who received stable ESA therapy, was equal in the 2 x 510 mg IV groups (44.1% each; n = 605). In the oral iron treatment groups (n = 279), the majority received stable ESA therapy (56.3%). Fewer patients in the oral groups did not receive ESA therapy (30.1%) compared to IV (44.1%).

The percentage of patients who were started on ESA or changed by > 25% was comparable between oral and 2 x 510 mg IV-groups (13.6% oral vs. 11.7% 2 x 510 mg). All patients in the 4 x 255 mg treatment group received ESA therapy with a high percentage of patients who were started on ESA or changed dose by > 25% (43.4% [26/60]). See below for a specific analysis of ESA as potential confounder.

Primary endpoint analysis (modified ITT Population)

A summary of the results is shown in the table below. Baseline values for Hgb across the three main studies were: 10.15 g/dl (2 x 510 mg group), 11.11 (4 x 255 mg-group) and 10.33 g/dl (oral group) respectively. Baseline values for ferritin were: 185 ng/ml (2 x 510 mg group), 312 ng/ml (4 x 255 mg-group) and 242 ng/ml (oral group) respectively. Overall the efficacy of IV-Rienso treatment was superior to 3 weeks of oral iron treatment.

Table 16 – Primary and Selected Secondary Efficacy Endpoints following Therapy with Ferumoxytol (2x510 mg) and Oral Iron in the Phase III Program by Study and Overall

	62745-5 pre		62745-5 post		62745-6		62745-7		All	
	Mean (95% CI)	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**	**Mean (95% CI)**	**P**
Haemoglobin (g/dL) mean change from Baseline to Week 5										
Ferumoxytol	0.78 (0.51, 1.04)		1.06 (0.84, 1.28)		0.86 (0.69, 1.03)		1.26 (1.09, 1.42)		1.03 (0.94, 1.13)	
Oral Iron	0.40 (-0.07, 0.87)		0.49 (0.29, 0.70)		0.21 (-0.03, 0.45)		0.54 (0.31, 0.77)		0.42 (0.30, 0.55)	
Diff	0.40 (-0.18, 0.92)	0.1814	0.57 (0.28,0.86)	0.0002	0.65 (0.33, 0.96)	<0.0001	0.72 (0.40, 1.04)	<0.0001	0.61 (0.44,0 .78)	<0.0001
Ferritin (ng/mL) mean change from Baseline to Week 3										
Ferumoxytol	457.4 (384.5,530.5)		369.6 (323.9,415.3)		544.3 (510.7,586.9)		428.0 (395.8,460.2)		461.9 (439.4, 484.5)	
Oral Iron	-27.2 (-52.1, -2.2)		-38.2 (-58.2, -18.2)		6.6 (-4.4, 17.5)		4.4 (-7.0, 15.8)		-14.3 (-23.9, -4.8)	
Diff	484.6 (349.1,620.1)	<0.0001	407.9 (358.8,456.9)	<0.0001	537.8 (465.1,610.5)	<0.0001	423.6 (367.7,479.49)	<0.0001	476.3 (442.5, 510.1)	<0.0001
Ferritin (ng/mL) mean change from Baseline to Week 5										
Ferumoxytol	318.3 (249.2,387.3)		256.2 (218.5,293.9)		404.3 (368.0,440.5)		308.8 (280.62,336.90)		334.4 (314.9, 353.8)	
Oral Iron	-51.3 (-75.8,-26.8)		-62.4 (-82.8, -42.0)		9.6 (-4.5, 23.7)		3.1 (-16.8, 23.0)		-25.2 (-36.5, -14.0)	
Diff	369.5 (241.5,497.6)	<0.0001	318.5 (276.3,360.8)	<0.0001	394.7 (332.5,456.9)	<0.0001	305.7 (255.8,355.5)	<0.0001	359.6 (329.9, 389.2)	<0.0001
TSAT (%) mean change from Baseline to Week 5										
Ferumoxytol	5.9 (3.1, 8.8)		6.4 (4.0, 8.7)		9.4 (8.2,10.6)		8.8 (7.6,10.0)		8.3 (7.5, 9.1)	
Oral Iron	0.2 (-4.5, 4.9)		0.5 (-1.0, 2.0)		1.2 (-0.2, 2.6)		0.2 (-0.9, 1.2)		0.6 (-0.2, 1.4)	
Diff	5.7 (0.0,11.5)	0.0499	5.8 (3.1, 8.6)	<0.0001	8.2 (6.0,10.5)	<0.0001	8.6 (6.4,10.8)	<0.0001	7.7 (6.4,9. 0)	<0.0001
Haemoglobin Responders – n (%) with ≥1 g/dL increase at week 5										
Ferumoxytol	19 (32.8)		57 (51.8)		89 (41.0)		118 (53.6)		283 (46.8)	
Oral Iron	5 (29.4)		30 (26.5)		15 (20.0)		14 (18.9)		64 (22.9)	
Diff (95%CI)	3.3 (-23.7, 31.8)	0.8338	25.3 (12.1, 38.3)	0.0002	21.0 (7.9, 34.1)	0.0016	34.7 (21.8, 47.4)	<0.0001	23.8 (17.0, 30.8)	0.0001
Hgb and Ferritin Responders – n (%) with Hgb ≥1 g/dL increase at week 3 or week 5 AND ferritin ≥160 at week 3 or week 5										
Ferumoxytol	25 (43.1)		61 (55.5)		101 (46.5)		121 (55.0)		308 (50.9)	
Oral Iron	5 (29.4)		27 (23.9)		4 (5.3)		5 (6.8)		41 (14.7)	
Diff (95%CI)	13.7 (-13.6,41.6)	0.3316	31.6 (18.5, 44.3)	<0.0001	41.2 (29.2, 53.4)	<0.0001	48.2 (36.1, 60.2)	<0.0001	36.2 (29.7, 42.8)	<0.0001

Dose regimens

A comparison of 2 x 510 mg Rienso versus 4 x 255 mg (versus 8 x 128 mg) in randomised and nonrandomised patients across trials (in the modified ITT-population) showed comparable results in the efficacy endpoints (Hgb change, Hgb responder-rate and Ferritin change). Efficacy values were lower in patients treated with 8 x 128 mg, but due to the small number no valid conclusions can be drawn.

Change in Ferritin and TSAT after 3 weeks

Results of the mean change from Baseline in ferritin and TSAT at week 3 paralleled those of the primary endpoint (TSAT-change at week 3: +9.5% IV-group vs. +1.83% oral group).

Subgroup analysis

Subgroup analyses were conducted in relevant demographic subgroups (age subgroups, gender subgroups and race subgroups). The greatest treatment difference between Rienso and oral iron regarding age groups was observed for patients in the ≥ 75 years subgroup; oral iron was the least effective (Hgb responder rate 10.2%) in this age group, where IV treatment was most effective.

The treatment effect was slightly larger in males compared to females in the IV-treatment group as well as in the oral treatment groups (the same difference was found in Hgb responder rates). The effect of Rienso was similar across all racial subgroups whereas oral iron was found to be more effective in Black or African-American patients compared to Caucasians and other race subgroups. Whether differences in compliance contributed to this finding has not been assessed.

Analysis of mean change of Hgb at Week 5 by treatment group and baseline clinical characteristics (i.e. CKD stages, kidney transplant status, Baseline Hgb, Baseline ferritin, ESA therapy status, other concomitant medications) suggests that with worsening of the kidney function the response to iron replacement therapy is decreasing in the IV-treatment groups. Patients with a functioning kidney transplant had a better response to IV-iron compared to those with native kidney, the number of patients with a transplant was very small though which precludes a definite conclusion, especially in the oral group. Regarding baseline Hgb values, larger mean increases in Hgb were observed in the IV-treatment subgroups with lower Baseline Hgb, which was true as well for the oral treatment subgroup at a lower level. Hgb responder rates in the subgroup of patients with baseline Hgb between 11 to 12 g/dl were similar in the IV-group and oral group (29.4% vs. 21.4%, respectively). Larger mean increases in Hgb were observed in subgroups with lower Baseline ferritin values after IV-treatment.

The presence or absence of ACE inhibitors / ARB or anticoagulants did not influence the primary efficacy endpoint substantially in the IV-treatment group. The use of calcium containing compounds as well did not alter the mean change in Hgb at Week 5. A positive effect on the mean change from Baseline in Hgb was consistently observed in the presence of ESA therapy in both treatment groups (IV vs. oral treatment), with baseline Hgb values being higher in patients on ESA-treatment.

Effect of Potential Confounders on Primary Endpoint – Adjusted Analyses

Additional analyses were done to determine whether there was any potential imbalance in ESA dosing characteristics between the two treatment groups, and to further assess ESA as a potential confounder of the primary efficacy result (change from Baseline in haemoglobin at Week 5). Overall, there were some differences between treatment groups in ESA dose characteristics. In studies 62745-6 and 62745-7, a slightly higher proportion of subjects in the oral iron treatment group were on ESA at Baseline, and only 9 subjects overall (6 ferumoxytol and 3 oral iron) initiated ESA after the first dose of study drug. Oral iron-treated subjects had a slightly higher mean weekly ESA dose at Baseline and mean cumulative ESA dose. The proportion of subjects in the 62,745-5 study on ESA was the same between treatment groups (100%) with a slightly lower mean weekly ESA dose at Baseline in ferumoxytol-treated subjects and lower cumulative ESA dose in the oral iron-treated group.

Across the three studies, there was no substantive difference between the two treatment groups (ferumoxytol 2 x 510 mg and oral iron) by study or overall in the proportion of subjects with low ferritin levels, suggesting no recent IV iron use.

As surrogates for inflammation/infection, a medical history of infection or inflammatory condition at Baseline or adverse event of infection during the study, white blood cell count (WBC) > 12,000 or platelet > 500,000 at Baseline or at any time during study or the use of systemic antibiotics or anti-inflammatory medications were examined, including an aggregate of any one of these terms, labelled infection / inflammation. Across the three studies, there was no substantive difference between the two treatment groups by study or overall in the proportion of subjects with clinical history or other parameters suggesting infection / inflammation).

Overall, there were no clinically meaningful or consistent differences between the two treatment groups in the proportion of subjects with any of these characteristics by study or in the consolidated analysis.

To assess the impact of these potential confounders (ESA dose characteristics, ferritin < 200 / < 100 ng/mL at Baseline, and infection/inflammation) on the primary endpoint analysis of the difference between treatment groups in the change in haemoglobin from Baseline to Day 35, a series of ANCOVA analyses were conducted utilizing the above ESA dose parameters, low ferritin < 200 / < 100 ng/mL, and the aggregate variable infection/inflammation.

Following adjustment for ESA dose parameters, there was negligible change in the estimate of the mean difference between treatment groups in haemoglobin change from Baseline, in analyses of the individual studies or in the integrated analysis of all Phase III studies. The estimates are not meaningfully different (≤ 10 % difference in the integrated analysis) from the unadjusted analyses, and all were highly statistically significant in each study and in the integrated analysis (p values 0.0006 to ≤ 0.0001).

Following adjustment for low ferritin < 100 / < 200 ng/mL alone or in combination with Baseline ESA dose and Baseline haemoglobin, the estimates are not meaningfully different (≤ 5% difference in the integrated (All) analysis from the unadjusted analyses, and all were highly statistically significant in each study and in the integrated (All) analysis (p values 0.0002 to ≤ 0.0001).

Adjustment for infection/inflammation similarly did not substantially change the estimate for the mean difference between treatment groups in haemoglobin change from Baseline, either in analyses of the individual studies or in the integrated analysis of all Phase III studies. Following adjustment for infection/inflammation alone or in combination with Baseline ESA dose and Baseline haemoglobin, the estimates were not meaningfully different (≤ 10% difference in the integrated (All analysis) from the unadjusted analyses), and all were highly statistically significant in each study and in the integrated (All) analysis (p values ≤ 0.0001).

Clinical studies in special populations

According to the claimed indication all efficacy trials were conducted in patients with CKD. No clinical studies were conducted in patients with hepatic impairment, however. A subpopulation analysis identified a total of 8 patients exposed to Rienso (2 x 510 mg) in the main studies who had a history of liver cirrhosis. This data base is too small for any conclusion of efficacy and safety in this subpopulation. Therefore, no specific dosing recommendations can be given until further data occurs. An appropriate warning has been implemented in the SmPC. The lack of a study in this special population is acceptable.

Supportive studies

Study 62,745-3 was a randomised open-label study to evaluate the safety and efficacy of two Rienso dose regimens (8 x 128 mg and 2 x 510 mg) controlled by oral iron in HD patients receiving supplemental EPO therapy. The primary objective was to assess the effect on Hgb and iron saturation levels. The secondary objective was to assess the impact of Rienso dosing on the time to achievement of the maximum iron saturation and Hgb levels. Participants were required to be ≥ 18 years, have Hgb ≤ 12 g/dl and TSAT ≤ 30% and be receiving stable EPO doses. A total of 36 patients were enrolled: 15 patients for 8 x 128 mg, 11 patients for 2 x 510 mg and 10 patients for 325 mg daily for oral iron. Efficacy assessments included the change from Baseline in Hgb, TSAT, haematocrit, serum iron, ferritin, and reticulocyte count. The primary endpoint was the mean changes in Hgb and TSAT for 8 weeks post initial dose.

Baseline Hgb was lower in the 8 x 128 mg group (10.89 mg/dl vs. 11.81 mg/dl 5 x 210 mg and 11.16 mg/dl oral). At Week 5 (Day 35), the mean change from Baseline in Hgb was 0.8 g/dl in the 2 x 510 mg group, 0.55 g/dl in the 8 x 128 mg group, and 0.29 g/dl oral group. The smaller improvement in the 8 x 128 mg group could be due to a lower mean cumulative dose of (2 x 510 mg, mean = 1020.00 mg vs. 8 x 128 mg, mean = 816.00 mg). Diverging results in mean change from Baseline in Hgb were presented for this study. The maximum effect in Hgb change was reached after 35 days in the 2 x 510mg group (and after 4 weeks in the 8 x 128 mg group).

Study 62,745-4 was an uncontrolled open-label study to evaluate the safety and efficacy of two dose regimens (4 x 255 mg, 2 x 510 mg) in patients with CKD stages 1 to 5 or CKD stage 5D receiving peritoneal dialysis. The primary objective was to assess the effect of Rienso dosing on Hgb and TSAT levels. A total of 21 patients were enrolled in the study: 10 patients to 4 x 255 mg and 11 patients for 2 x 510 mg. Participants were required to be ≥ 18 years and have Hgb ≤ 12 g/dl and TSAT ≤ 30%. Patients in the 2 x 510 mg group had a maximum absolute increase in mean Hgb of 1.00 g/dl vs. 0.88 g/dl in the 4 x 255 mg group. Mean times to maximum level were 35 days and 41 days, respectively. Mean TSAT values increased in both groups (12.4% 2 x 510 mg vs. 19.7% 4 x 255 mg). In general, maximum TSAT and serum ferritin values were reached in 16 to 19 days.

These two supportive studies consistently showed day 35 to be the time point with maximum effect of a 2 x 510 mg Rienso treatment course on Hgb change.

In *Study 62,745-5 (pre amendment)* efficacy parameters in the pre-amendment phase showed some comparative differences between two dosages favouring the 4 x 255 mg scheme considering the two endpoints Hgb responders and Hgb and ferritin responders. Although the Applicant concludes that these data show comparable efficacy, considering responders rates, it seems from this study that the 4 x 255 mg dosage could be more efficient then the 2 x 510 mg dosage scheme. An analysis across trials with different dosing schemes (8 x 128 mg, 4 x 255 mg and 2 x 510 mg) showed comparable efficacy of the different dosage schemes.

In the safety *study 62,745-8* efficacy parameters have been generated. These data following only one dose of 510 mg showed only a small increase in haemoglobin from Baseline to Day 14 (0.25 g/dL), which was not clinically meaningful. Small changes were also measured for ferritin and TSAT values. These results do not contradict the overall efficacy assessment.

2.5.3. Discussion on clinical efficacy

The Applicant submitted three pivotal clinical studies comparing a 2 x 510 mg Rienso 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. Analysis of the mean change in Hgb at Day 35 for each study as well as for the pooled data

showed that the IV-treatment was effective and that this treatment effect was superior to oral iron treatment with an overall increase of Hgb of 1.03 g/dl in the combined IV group versus 0.42 g/dl in the oral group.

The analysis of the ESA(-) cohort (non-dialysis patients) represents the original effect of the iron therapy alone (mITT-Hgb change IV vs. oral after 5 weeks); the mean changes in Hgb were 0.79 g/dl and 0.2 g/dl, respectively.

The 21 day period of oral iron treatment which was chosen as active comparator is considered too short to establish the maximum effect of oral iron therapy, but mean change in Hgb observed with oral iron in the Rienso studies falls within the broad range reported in published studies.

No formal dose-finding studies were preformed for this application. The 2 x 510 mg scheme (used in the pivotal studies) has been compared descriptively with 4 x 255 mg and 8 x 128 mg in supportive clinical studies with small patient numbers. The analysis across trials showed comparable efficacy of the different dosage schemes.

Based on Hgb, serum ferritin, and TSAT responses, the efficacy of one treatment course of Rienso in iron deficiency anaemia is comparable to that of other EU-approved IV iron therapies as published in the literature.

In addition, the applicant presented post-marketing observational data obtained from three separate haemodialysis clinics in the USA. 8666 patients were treated with a total of 33,358 doses of ferumoxytol, more than 50% of whom had received more than one course of treatment. On average patients were followed-up for ~ 5 months (max. 12 months). All patients were on ESA and ESA doses were adjusted at the discretion of the physician. In all clinics, haemoglobin values rose after the first course and then stabilised. The mean Hgb across the two clinics ranged from 11.0 to 11.7 g/dL over months 2 through 12; mean TSAT ranged from 25 to 40%; ferritin values ranged from 400 to 850 ng/mL. The proportion of all treated patients within the haemoglobin target range (between 10 and12 g/dL) was ~ 50 to 80% during the assessment period and remained relatively stable; patients received additional courses or doses of Rienso at the discretion of the treating physician. About 30% of patients received an uneven number of doses and ~ 12% received only 1 dose. Some patients in one clinic received a test dose.

The Rienso studies were not designed for the assessment of long term efficacy and safety and the data base of 69 patients who received two courses of Rienso treatment in the extension phase is too small to conclude on an acceptable level of efficacy and safety. This is appropriately labelled in the SPC. The additional supportive post marketing data, however suggest that Rienso treatment is effective to maintain the target Hgb in CKD patients over ½ to 1 year without relevant changes in the safety profile. Therefore the re-treatment of iron deficiency states in CKD patients is supported by the data provided.

2.5.4. Conclusions on the clinical efficacy

The clinical study data demonstrate efficacy of a 2 x 510 mg Rienso treatment course as well as superiority over oral iron treatment regarding the surrogate parameter raise in Hgb (after 5 weeks) in IDA patients with CKD. The cumulative dose of ~ 1 g of iron complies with the recommendations for IV iron replacement therapy in anaemic CKD patients in relevant clinical treatment guidelines. For CKD-patients not on HD, a gain in convenience and compliance can be assumed due to a reduction in the number of injections and a reduction in treatment duration. For patients on HD with regular dialysis treatment an advantage of the 2 x 510 mg scheme could only be attested if the safety profile of the Rienso treatment is superior to that of standard IV-iron preparations.

In summary, the submitted clinical data demonstrated short term clinical efficacy of the 2 x 510 mg ferumoxytol treatment scheme in IDA patients with CKD. Re-treatment of iron deficiency states in CKD patients is supported by the post marketing data submitted.

2.6. Clinical safety

Patient exposure

Data from 7 studies in CKD patients and 4 studies in "non-CKD" patients (healthy volunteers or imaging studies) have been provided. 1726 subjects have been exposed and more than 2,800 exposures to Rienso contributed to the safety evaluation.

Table 17 – Exposure to Study Medication by Cumulative Dose of Iron (mg) – CKD Subjects (Safety Population)

	N	Mean±SD (mg iron)	Median (range) (mg iron)
Randomised, Open-label, Controlled Studies [a]			
2 x 510 mg Rienso	605	1002±94	1020 (210-1050)
4 x 255 mg Rienso	60	981±147	1020 (255-1026)
Oral Iron	280	3782±964	4100 (0-5000)
Treatment Exposure [b]			
Rienso First Course	1562	766±264	1020 (60-1050)
Rienso Second Course	69	2019±103	2040 (1380-2046)
Oral Iron	290	3981±1700	4100 (0 -19500)
Rienso Dosing Regimen [b]			
1 x 125 mg	10	126±0	126 (126-126)
1 x 250 mg	10	252±0	252 (252-252)
1 x 510 mg	708	507±32	510 (60 -570)
8 x 128 mg	15	816±284	1020 (383-1020)
4 x 255 mg	58	980±150	1020 (255-1026)
2 x 510 mg	692	1004±89	1020 (210 -1050)
4 x 255 mg -> 2 x 510 mg	12	2041±2	2040 (2040-2046)
2 x 510 mg -> 2 x 510 mg	57	2014±113	2040 (1380-2040)

a. Safety data in the analysis by randomised, open-label, controlled studies were derived from the following protocols: 62,745-5, 62,745-6, and 62,745-7.
b. Safety data included in the analyses by treatment exposure and Rienso 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.
Note: Cumulative iron exposure was calculated for Rienso subjects using the volume of Rienso 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.

Adverse events

AEs and SAEs were collected from Day 0 through completion at Day 35, which is for 98% of the subjects about 27 - 32 days after the last injection, and only SAEs were reported through 30 days post the last study visit. Overall, less AEs were reported for CKD patients treated with Rienso compared to oral iron. Compared to placebo there was a higher rate of hospitalizations (3.7 vs. 2.0%) and a higher rate of SAEs (3.8 vs. 2.4%).

Table 18 – Adverse events in three pivotal studies (Safety Populations)

Study 62, 745-5 Post- Amendment

AE Category [a]	Ferumoxytol 2 x 510 mg N= 110		Oral Iron 200 mg/day N= 114	
	Events n	Subjects n (%)	Events N	Subjects n (%)
AEs [b]	121	54 (49.1)	157	65 (57.0)
Related AEs [c]	17	9 (8.2)	34	18 (15.18)
SAEs	19	14 (12.7)	22	14 (12.3)
Related SAEs [c]	1	1 (0.9)	0	0
AEs Resulting in Temporary Discontinuation of Study Medication	1	1 (0.9)	8	5 (4.4)
AEs Resulting in Permanent Discontinuation of Study Medication	8	4 (3.6)	21	9 (8.8)

Study 62, 745-6

AE Category [a,b]	Ferumoxytol 2 x 510 mg N= 217		Oral Iron 200 mg/day N= 75	
	Events n	Subjects n (%)	Events N	Subjects n (%)
AEs	158	77 (35.5)	102	39 (52.0)
Related AEs [c]	41	23 (10.6)	25	18 (24.0)
SAEs	15	10 (4.6)	11	7 (9.3)
Related SAEs [c]	0	0	0	0
AEs Resulting in Temporary Discontinuation of Study Medication	3	2 (0.9)	1	1 (1.3)
AEs Resulting in Permanent Discontinuation of Study Medication	3	3 (1.4)	25	9 (12.0)

Study 62, 745-7

AE Category [a,b]	Ferumoxytol 2 x 510 mg N= 220		Oral Iron 200 mg/day N= 74	
	Events n	Subjects n (%)	Events N	Subjects n (%)
AEs	298	123 (55.9)	101	43 (58.1)
Related AEs [c]	89	47 (21.4)	15	12 (16.2)
SAEs	29	17 (7.7)	18	10 (13.5)
Related SAEs [c]	0	0	1	1 (1.4)
AEs Resulting in Temporary Discontinuation of Study Medication	4	4 (1.8)	3	3 (4.1)
AEs Resulting in Permanent Discontinuation of Study Medication	11	4 (1.8)	15	6 (8.1)

a. Subjects may be counted in more than one AE category.
b. All AEs (occurring prior to or following dosing) for subjects who were randomised and received at least one dose of study medication in the Randomised Phase of the study.
c. Relationship classified by Investigator as related to study medication.

The most common AEs were reported in the gastrointestinal system (e.g. diarrhoea, nausea and constipation), the nervous system (dizziness and headache), and the vascular system (hypotension). GI disorders were higher in the oral iron subjects, hypotension was more common in Rienso (2.5 vs. 0.4 %,). GI disorders are known AEs for oral iron therapy and directly related to treatment compliance and efficacy.

Table 19 – Most Common TEAEs (≥ 1.0%) in the Rienso 2 x 510 mg Treatment Group in Randomised, Open label, Controlled Studies - CKD Subjects (Safety Population)

TEAE [a] System organ Class Preferred Term	Rienso 2 x 510 mg N = 605 n (%)	Oral Iron N = 280 n (%)	p-value [b]
Gastrointestinal disorders			
Diarrhoea	24 (4.0)	23 (8.2)	0.013*
Nausea	19 (3.1)	21 (7.5)	0.006*
Constipation	13 (2.1)	16 (5.7)	0.008*
Vomiting	9 (1.5)	14 (5.0)	0.003*
Abdominal Pain	8 (1.3)	4 (1.4)	0.949
General disorders & administration site conditions			
Oedema Peripheral	12 (2.0)	9 (3.2)	0.304
Oedema	9 (1.5)	4 (1.4)	0.895
Chest Pain	8 (1.3)	2 (0.7)	0.397
Pyrexia	6 (1.0)	2 (0.7)	0.650
Musculoskeletal & connective tissue disorders			
Back pain	6 (1.0)	0	0.024*
Muscle spasms	6 (1.0)	4 (1.4)	0.650
Nervous system disorders			
Dizziness	16 (2.6)	5 (1.8)	0.391
Headache	11 (1.8)	6 (2.1)	0.802
Respiratory, thoracic & mediastinal disorders			
Cough	8 (1.3)	4 (1.4)	0.949
Dyspnoea	6 (1.0)	3 (1.1)	0.956
Skin & subcutaneous tissue disorders			
Pruritus	7 (1.2)	1 (0.4)	0.225
Rash	6 (1.0)	1 (0.4)	0.302
Vascular disorders			
Hypotension	15 (2.5)	1 (0.4)	0.024*
Hypertension	6 (1.0)	2 (0.7)	0.650

a. Subjects may be counted under more than one preferred term. Within each preferred term, a subject was only counted once
b Post-hoc comparison of the 2 x 510 mg Rienso group and oral iron group using z test for proportions with two independent samples.
*Statistically significant at a p value < 0.05.
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.

The table below presents all adverse experiences observed during the clinical studies in which 1562 subjects with CKD received two injections of 510 mg of Rienso separated by an interval of 2 to 8 days and post-marketing experience.

Table 20 – Adverse reactions observed during clinical studies and post-marketing

SYSTEM ORGAN CLASS	COMMON (≥1/100 TO <1/10)	UNCOMMON (≥1/1,000 TO <1/100)	RARE (≥1/10,000 TO <1/1,000)	FREQUENCY NOT KNOWN (CANNOT BE ESTIMATED FROM AVAILABLE DATA)
Blood and lymphatic system disorders			Eosinophilia	
Immune system disorders		Hypersensitivity including anaphylaxis		Life-threatening Anaphylactic/Anaphylactoid

SYSTEM ORGAN CLASS	COMMON (≥1/100 TO <1/10)	UNCOMMON (≥1/1,000 TO <1/100)	RARE (≥1/10,000 TO <1/1,000)	FREQUENCY NOT KNOWN (CANNOT BE ESTIMATED FROM AVAILABLE DATA)
				reactions
Metabolism and nutrition disorders		Decreased appetite Increased appetite	Dehydration Gout Hyperkalaemia	
Nervous system disorders		Dizziness Dysgeusia Headache Somnolence Burning sensation	Paraesthesia	Syncope Unresponsiveness Loss of consciousness
Eye disorders			Lacrimation increased Vision blurred	
Cardiac disorders				Tachycardia/Arrhythmia, Cardiac arrest Cardio- respiratory arrest Myocardial infarction Cyanosis Congestive heart failure
Vascular disorders		Hypotension (hypotension, blood pressure decreased) Flushing (flushing, hot flush) Hypertension (hypertension, accelerated hypertension)		Vasodilation
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Epistaxis	Bronchospasm Cough Hyperventilation Hypoxia Laryngeal oedema Pharyngeal oedema Respiratory arrest Respiratory failure Throat irritation Throat tightness Wheezing
Gastrointestinal disorders		Diarrhoea Constipation Nausea Abdominal pain	Dry mouth Dyspepsia Glossodynia	Lip swelling Swollen tongue

SYSTEM ORGAN CLASS	COMMON (≥1/100 TO <1/10)	UNCOMMON (≥1/1,000 TO <1/100)	RARE (≥1/10,000 TO <1/1,000)	FREQUENCY NOT KNOWN (CANNOT BE ESTIMATED FROM AVAILABLE DATA)
		(Abdominal distension, abdominal pain upper, abdominal discomfort) Vomiting Faeces discoloured		
Hepatobiliary disorders			Hepatic function abnormal	
Skin & subcutaneous tissue disorders		Rash (rash, rash generalised, rash pruritic, urticaria) Pruritus (pruritus generalised) Ecchymosis Sweating (hyperhidrosis, night sweats) Skin hyperpigmentation Skin reaction		Angioedema
Musculoskeletal and connective tissue disorders		Muscle/joint pain or stiffness (arthralgia, myalgia, muscular weakness, musculoskeletal stiffness) Back pain Muscle spasms		
General disorders and administration site conditions	Injection site reactions (infusion/injection site bruising, pain, reaction, swelling, warmth, haemorrhage, irritation, rash)	Fatigue (asthenia, fatigue) Chest pain (chest discomfort, chest pain) Chills Fever (feeling hot, pyrexia)		Injection site discolouration Injection site pruritus
Investigations		Serum ferritin increased	Blood glucose decreased	Pulse absent Oxygen saturation decreased
Injury, poisoning and procedural complications		Contusion		

Serious adverse event/deaths/other significant events

The 31 reported deaths that occurred during clinical trials were not considered related to treatment with Rienso or oral iron, respectively. There are more deaths (2.8%) in the oral iron compared to the Rienso group (1.1%). This observation is consistent at all time points pre-dose, during the treatment phase and even more than 60 days after the last dose of the study treatment.

Table 21 – All Deaths in the Clinical Development Programme

Time relative to final dose of study drug	Rienso (N = 1726)	Oral Iron (N = 290)	Pre-dose	p-value[a]
Pre-dose	-	-	4	
Within 30 days post final dose	12 (0.7%)	4 (1.4%)	-	0.224
30-60 days post final dose	4 (0.2%)	3 (1.0%)	-	0.032*
More than 60 days post final dose	3 (0.2%)	1 (0.3%)	-	0.545
TOTAL	**19 (1.1%)**	**8 (2.8%)**	**4**	**0.023***

a Post-hoc comparison using z test for proportions with two independent samples.
*Statistically significant at a p value < 0.05.

As far as serious TEAEs are concerned there is no statistical significant difference between Rienso and oral iron. Also there were no imbalances unfavourable to the Rienso treatment. There were three cases of serious hypotension (0.2%) one of which was described as anaphylaxis. However, IV administration always carries a higher risk of vaso-vagal reactions than oral administration. Hypotension could also be observed in the placebo group (0.1%). Overall the SAE-rate is around 9.8 - 13.3% which can be considered relatively low taking into account the underlying medical condition in CKD patients.

Laboratory findings

Based on data provided, Rienso was not associated with clinically significant AE on haematology and chemistry laboratory parameters. The panel of tested measurements consisted of the usual set of panels in this type of population (WBC, platelets, bilirubin, ALT, AST GGT, ALP, LDH, K, Na, Ca, P, urea, creatinine, total proteins, ECG, vital signs, etc). The population analysed consisted of populations form two sets – pivotal CKD studies and all seven CKD studies in total.

Observed increases in Hgb and haematocrit levels from Baseline in Rienso and oral iron groups were considered as being consistent with the therapeutic effect of iron repletion therapy. No safety concerns related to haematology were identified. For iron panel values, expected increases in serum ferritin, serum iron, and TSAT and decreases in TIBC were observed. In all treatment groups, the most commonly observed serum chemistry abnormalities were elevations of GGT; a total of 8 patients exposed to Rienso 2 x 510 mg in the pivotal studies had a history of liver cirrhosis and in these subjects, the incidence of abnormal liver function serology was higher compared to those without a history of cirrhosis.

No clinically meaningful changes in blood pressure or heart rate were observed. However, T-wave changes in ECG were identified in 3/57 subjects (5.3%) receiving Rienso opposed to none in the control groups; these changes were transient and judged as being of no clinical significance.

Safety in special populations

Additional analyses of intrinsic factors on safety were performed including analyses based on age, gender, race, body weight, baseline Hgb, maximum Hgb, rate of Hgb increase, stage of CKD, and

hepatic function. Additional analyses of extrinsic factors on safety included kidney transplantation status and ESA dosage.

Overall, there was no safety concern regarding special populations. It seemed that healthy volunteers had significantly less adverse effects than the CKD patients. There are no data regarding patients with hepatic impairment which will be reflected in the SPC.

Safety related to drug-drug interactions and other interactions

No formal studies to evaluate the interaction of Rienso with other medications were performed which is considered acceptable.

Discontinuation due to adverse events

Fewer patients discontinued their treatment with Rienso compared to oral iron. The rates comparing Rienso to placebo are equally low. However, no valid data on compliance with re-treatment is available which will be addressed in ongoing studies.

Post marketing experience

The USA post marketing data gathered over 9 months seem to confirm the findings of the safety studies. No new information was obtained. However, the occurrence of hypersensitivity related reactions with Rienso appears to be confirmed by these data. AEs related to hypersensitivity are adequately reflected in SPC und PIL.

2.6.1. Discussion on clinical safety

The safety database consists of a total of 1,726 subjects who were enrolled into 11 completed AMAG studies of Rienso. Of those, 1562 subjects received Rienso in case of CKD. The primary safety information in support of Rienso in CKD population comes from 3 similarly designed pivotal studies (Study 62, 745-5 Pre-/Post-amendment, 62, 745-6 and 62, 745-7), which include 665 subjects who have received Rienso. Within this cohort, 605 subjects received the dosage applied for authorisation, and 69 subjects have received Rienso for repeat dosing. The development was focused on episodic short term use of single dosage (2 x 510 mg, 2 to 5 days apart) in CKD subjects. Although the main safety database consists of a rather big population (1,500 CKD subjects) the main issue is that they were followed mainly for short term (35 days). Long term use and repeated dosing will be addressed post-authorisation as reflected in the additional pharmacovigilance activities to be performed in accordance with the Risk Management Plan.

The safety population was defined as all patients who were randomised and had at least one dose of study medication and was used for the safety analyses. For both the Randomised Phases and Readmission Phases of the studies, safety assessments included AE monitoring, clinical laboratory evaluations, vital sign assessments, and physical examinations. Standard terminology (MedDRA v8.0) was applied.

There were 1,562 subjects in the combined studies who were exposed to one course of Rienso at a mean cumulative iron dose of 765.60 mg and a median exposure of 1020 mg, the full proposed therapeutic course of Rienso. A total of 69 subjects who participated in the three pivotal studies were exposed to a second course of Rienso (2 x 510 mg) during the Readmission Phases of the studies. The mean cumulative Fe dose for this Rienso second course treatment group was 2018.78 mg.

Finally, the number of applied dosage (2 x 510 mg) that was tested in safety population was accomplished in 97.5% (675/695) of patients. Maximal number of injections was 8 injections (tested for 125 mg Rienso dosage). In the 57 subjects receiving two courses of 2 x 510 mg, the number of days between the last injection of the first course and the first injection of the second course ranged from 30 to 356 days.

In pooled analysis of three pivotal studies, CKD patients were similar between the two treatment groups in all main demographic (age, gender and race) and the majority of clinical aspects. But the main CKD safety demographic and clinical characteristics of CKD population has some limitations as regards early CKD stages (CKD Stage 1 and 2), exposure period too short to have an understanding about the medium and long term AE profile, and that patients with any degree of liver failure have not been assessed.

The Applicant reported that ~35 to 55% of subjects in the core comparative studies experienced one or more AEs in Rienso group that was numerically comparable (in Study 62, 745-5 Post amendment and Study 62, 745-7) or lower (in Study 62, 745-6) than in oral Fe groups. None of these AE was exceeding 10% in either pivotal study.

AE and the proportions of subjects in HD population (Study 62,745-5 Post-Amendment) who experienced most common AE are diarrhoea (9%, 10/110 Rienso; 7.9%, 9/114 oral Fe), hypotension (4.5%, 5/110 Rienso; 0%, 0/114 oral Fe), cough (4.5%, 5/110 Rienso; 0.9%, 1/114 oral Fe), and pyrexia (3.6%, 4/110 Rienso; 0.9%, 1/114 oral Fe), nausea (~ 3%, 3/110 Rienso; ~ 8%, 9/114 oral Fe), constipation (1.8%, 2/110 Rienso; 4.4%, 5/114 oral Fe). Hypertension was comparable between Rienso and oral Fe groups (~ 2%, 2/110 Rienso; ~ 1%, 1/114 oral Fe). Thus, in HD population hypotension, cough and pyrexia seem numerically more pronounced in Rienso treated group, while dyspepsia symptoms seems numerically more often in oral Fe group.

AE and the proportions of subjects in non-HD population (Studies 62, 745-6 and 62, 745-7) who experienced most common AE in any of the study groups show similar trends in lower dyspepsia symptoms in Rienso group as compared to oral Fe, in particular, nausea (~ 3%, 7/217 Rienso; 8%, 6/75 oral Fe in Study 62, 745-6), diarrhoea (~ 3%, 7/217 Rienso; ~ 7%, 5/75 oral Fe in Study 62,745-6), constipation (~ 1%, 3/217 Rienso; ~ 9%, 7/75 oral Fe in Study 62,745-6). Similar findings were also noted to higher numerical incidence hypotension (5%, 11/220 Rienso; ~ 1%, 1/74 oral Fe in Study 62,745-7); relevant data are presented as syncopes, that are reported also numerically higher in the Rienso group (1.4%, 3/217 Rienso; 0% oral Fe in Study 62,745-6). Also slightly higher numerical incidences were noted also for pyrexia (~1.4%, 3/217 Rienso; 0% oral Fe in Study 62, 745-7). Thus, although low in incidence numbers, Rienso impact on hypotension and infection incidences can not be excluded.

In the pooled analysis of TEAEs from the 3 pivotal studies (for dose 2 x 510 mg), the frequency of AEs considered by the investigator as treatment-related at W5 was found statistically significant lower in the Rienso group (44%) than in the oral Fe group (~ 54%) with same tendency observed in related TEAEs (13.6% Rienso vs. 18.6% oral Fe, p = 0.053).

The Applicant reported incidences of deaths in 1.1%, 19/1726 of subjects in the Rienso group as compared to 2.8%, 8/290 in the oral Fe group. The overall incidence of SAEs was similar in HD population (in Study 62, 745-5): 12.7% in Rienso and 12.3% in oral Fe groups, and none of the individual SAE rates reported were markedly different between treatment groups. Incidences in SAE in non haemodialysis population were lower in Rienso group (4.6% and 1.8%, in Studies 62,745-6 and 62,745-7, respectively) and close to HD population in Study 62,745-6 (9.3%) while much lower in Study 62,745-7 (1.8%).

Several AEs of special interest for additional thorough analysis were selected based on the known pharmacological action as class effect. The Applicant claims that there were no signals observed from these analyses in comparison to oral Fe except for better safety profile for gastrointestinal symptoms (6 to 9% in Rienso group vs. 19% in oral Fe group and 4% in placebo groups). This comparative profile is relevant to oral Fe formulations only. The direct comparison with IV Fe formulations remains to be investigated post-marketing

Rienso was not associated with clinically significant AE on haematology and chemistry laboratory parameters. The panel of tested measurements consisted of usual set of panels that is usual in this type of population (WBC, platelets, bilirubin, ALT, AST GGT, ALP, LDH, K, Na, Ca, P, urea, creatinine, total proteins, ECG, vital signs etc). The population analysed consisted of populations form two sets – both pivotal CKD studies (605 subjects in Rienso 2 x 510 mg group, 60 subjects in Rienso 4 x 255 mg group and 280 subjects in oral Fe group) and all seven CKD studies in total (1,562 subjects in first Rienso course group, 69 in second Rienso course group and 290 subjects in oral Fe group).

The Applicant performed analysis of discontinuation due to AEs of randomised, controlled studies. Analysing permanent and temporary discontinuations in pivotal studies, lower incidences of TEAEs leading to discontinuation were noted in both groups with Rienso (~1 to 2%) vs. oral Fe (~4 to 9%). These rates should be seen as benefit for Rienso therapy as compared to alternative oral Fe therapy.

Some AEs were also reported during the postmarketing phase. During this period, a total of 267 spontaneous adverse drug experiences (ADEs) were received by the applicant, representing a reporting rate of 0.43% (267/62535); approximately 70% of these reports were confirmed to be in CKD patients. Among the 267 reports, 81 reports were considered to be SAEs, representing a reporting rate of 0.13%, which is lower than that observed for all SAEs reported in all Rienso clinical trials (7.1%) and those SAEs considered related (0.2%).

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

The use of Rienso is contraindicated in cases of:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Hypersensitivity to other iron preparations
- Evidence of iron overload
- Anaemia not caused by iron deficiency

Rienso can cause hypersensitivity reactions including serious and life-threatening anaphylactic/anaphylactoid reactions. Anaphylactic type reactions presenting with cardiac arrest/ cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in the post-marketing experience (see section 4.8). Patients should be observed for signs and symptoms of hypersensitivity for at least 30 minutes following each Rienso injection and the medicinal product should only be administered when staff trained to evaluate and manage anaphylactic reactions are immediately available. If at any time during the intravenous administration any signs of hypersensitivity reaction or intolerance are detected, administration must be stopped immediately. In patients with multiple substance allergies, the need for Rienso or alternative treatment options should be carefully considered.

Severe adverse reactions of clinically significant hypotension have been reported. Hypotension may follow Rienso administration with or without accompanying signs of hypersensitivity (see section 4.8). Patients should be monitored for signs and symptoms of hypotension following each Rienso administration.

2.6.2. Conclusions on the clinical safety

A sufficient number of patients have been exposed to the drug in clinical studies, Adequate safety regarding short term and episodic treatment have been provided and long term safety is supported by available US post marketing data. However data from long time exposure are limited. This deficiency will be addressed post-authorisation in comparison with licensed IV iron products.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Pharmacovigilance system is submitted:

- Timelines for the major ICSR processing steps should be included either in a table or in the flow chart.

Risk Management Plan

The applicant submitted a risk management plan.

Table 22 –Summary of the risk management plan

Safety issue	Agreed pharmacovigilance activities	Agreed risk minimisation activities
Hypotension	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** - The potential risk of hypotension will be further examined in five clinical studies in adults: ▪ *Study FER-CKD-201* Randomised, open-label, controlled study vs. iron sucrose in approximately 150 CKD subjects with IDA. ▪ *Study AMAG-FER-CKD-401* A Phase IV, Open- Label, Multicenter Trial of Repeated Doses of Ferumoxytol compared with Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Chronic Kidney Disease (CKD) Patients on haemodialysis over a One Year Period. ▪ *Study AMAG-FER-IDA-301* Double-blind, placebo-controlled trial in 800 subjects with IDA in whom oral iron cannot be used. ▪ *Study AMAG-FER-IDA-302* Randomised, open-label,	**Routine risk minimisation:** **Statements in Section 4.4 of the SmPC**: ▪ providing instructions for IV administration of ferumoxytol, especially in haemodialysis patients, ▪ for monitoring of patients for signs and symptoms of hypotension for 30 minutes post-administration. **Precaution for use in Section 4.4 of the SmPC:** ▪ that hypotension may follow Ferumoxytol administration, with or without accompanying signs of hypersensitivity (see section 4.8) and in some cases may lead to severe or serious outcomes. ▪ that patients should be monitored for signs and symptoms of hypotension for 30 minutes following ferumoxytol administration. **Additional risk minimisation:** None .

	controlled study vs. iron sucrose in 600 subjects with IDA in whom oral iron cannot be used. This study will include a subgroup analysis of AEs in IV iron-naïve patients (including patients who may be intolerant to IV iron). ▪ *Study AMAG-FER-IDA-303* Open-label extension study in up to 800 IDA subjects completing Study AMAG-FER-IDA-301 to investigate long-term/repeat dosing safety and efficacy of ferumoxytol over 6 months. ▪ *Medicare Claims Investigation of Hypersensitivity and Hypotension Occurring Subsequent to IV Iron Administration in Haemodialysis and CKD Non-dialysis Patients* Using the USRDS database and Medicare claims investigation, occurrence of hypersensitivity and hypotension reactions will be compared in patients using ferumoxytol, iron sucrose, iron dextran and ferric gluconate.	
Hypersensitivity reactions	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** The potential risk of hypersensitivity (including anaphylaxis and anaphylactoid reactions) will be further examined in three clinical studies in adults: ▪ *Study FER-CKD-201* Randomised, open-label, controlled study vs. iron sucrose in approximately 150 CKD subjects with IDA. ▪ *Study AMAG-FER-CKD-401* A Phase IV, Open- Label, Multicenter Trial of Repeated Doses of Ferumoxytol compared with Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Chronic Kidney Disease (CKD) Patients on haemodialysis over a One Year Period. ▪ *Study AMAG-FER-IDA-301* Double-blind, placebo-controlled trial in 800 subjects with IDA in whom oral iron cannot be used. ▪ *Study AMAG-FER-IDA-302* Randomised, open-label, controlled study vs. iron sucrose in 600 subjects with IDA in whom oral iron cannot be used. This study will include a subgroup analysis of AEs in IV iron-naïve patients (including patients who may be intolerant to IV iron). ▪ *Study AMAG-FER-IDA-303*	**Routine risk minimisation:** **Statement in section 4.2**: Rienso should only be administered by suitably trained staff in an environment where resources for managing hypersensitivity reactions are immediately available **Contraindication in Section 4.3 of the SmPC**: In patients with known hypersensitivity to ferumoxytol or any of its excipients. **Warning in Section 4.4 of the SmPC, and in PL**, that Ferumoxytol may cause serious hypersensitivity reactions (including anaphylaxis/anaphylactoid reactions). **Precaution for use in Section 4.4** that patients must be observed for signs and symptoms of hypersensitivity for at least 30 minutes following Ferumoxytol injection and that the drug should only be administered when appropriate medical support measures, including personnel and cardiopulmonary resuscitation equipment are readily available. **Additional risk minimisation:** None

	Open-label extension study in up to 800 IDA subjects completing Study AMAG-FER-IDA-301 to investigate long-term/repeat dosing safety and efficacy of ferumoxytol over 6 months. ▪ *Medicare Claims Investigation of Hypersensitivity and Hypotension Occurring Subsequent to IV Iron Administration in Haemodialysis and CKD Non-dialysis Patients* Using the USRDS database and Medicare claims investigation, occurrence of hypersensitivity and hypotension reactions will be compared in patients using ferumoxytol, iron sucrose, iron dextran and ferric gluconate.	
Long term organ deposition	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** A MRI study to evaluate evidence for organ deposition following treatment with IV iron	**Routine risk minimisation:** Contraindications in Section 4.3 of the SmPC: ▪ Evidence of iron overload ▪ Anaemia not caused by iron deficiency Warning in PL that Ferumoxytol should not be given if the patient has iron overload, or if their anaemia is not caused by iron deficiency. **Additional risk minimisation:** None
Cardiac Disorders	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** None.	Routine risk minimisation: Statement in Section 4.8 of the SmPC, and in the PL, that the following events occur with unknown frequency: cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, unresponsiveness, loss of consciousness, tachycardia/ rhythm abnormalities; angioedema; ischemic myocardial events, congestive heart failure, pulse absent; cyanosis
Safety in Pregnant Women	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** None.	**Routine risk minimisation:** Statement in Section 4.6 of the SmPC, and in the PL, that: There are no studies on the use of Rienso in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Rienso is not recommended during pregnancy and in women of childbearing potential not using adequate contraception. **PIL section 2** Rienso has not been tested in pregnant women. Studies in animals have shown reproductive toxicity. If you are pregnant, you should not receive Rienso. It is important to tell your doctor if you are pregnant, think you may be pregnant, or are planning to have a baby. If you are able to become pregnant, you must use birth control during treatment. If you become pregnant during treatment, you must ask your doctor for advice. **Additional risk minimisation:** None

Safety in Lactating Women	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** None.	**Routine risk minimisation:** SmPC section 4.6, It is unknown whether Rienso is excreted in human milk. Available pharmacokinetic data in animals have shown excretion of Rienso in milk (see section 5.3). A risk to breastfeeding newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Rienso therapy, taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the mother. **PIL section 2** It is not known whether the active substance in this medicine pass over to the breast milk. Available pharmacokinetic data in animals have shown excretion of Rienso in milk. If you are breast-feeding, ask your doctor for advice before you are given Rienso. **Additional risk minimisation:** None
Safety in Children	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** The safety of ferumoxytol in children will be evaluated in four clinical studies (including 3 studies in subjects with CKD) designed in accordance with an agreed PIP: ▪ *Study AMAG-FER-CKD-251* Randomised, open-label, controlled study vs. oral iron in 144 paediatric subjects (aged 6 months to < 18 years) with IDA and CKD Stage 5D (haemodialysis and peritoneal dialysis). ▪ *Study AMAG-FER-CKD-252* Randomised, open-label, controlled study vs. oral iron in 144 paediatric subjects (aged 6 months to <18 years) with IDA and non-dialysis dependent CKD. ▪ *Study AMAG-FER-CKD-253* Open-label extension study in paediatric CKD subjects (aged 6 months to <18 years) with IDA to investigate long-term/repeat dosing safety and efficacy of ferumoxytol over 2 years. *Study AMAG-FER-IDA-251* Randomised, open-label, controlled study vs. oral iron in 204 paediatric subjects (aged 6 months to <18 years) with IDA of various aetiologies.	**Routine risk minimisation:** Statement in Section 4.2 of the SmPC that the safety and efficacy of Ferumoxytol in children have not yet been established. The safety and efficacy of Rienso in children and adolescents below the age of 18 years has not been established. No data are available. Warning in PL that children under 18 years of age should not receive Ferumoxytol. **Additional risk minimisation:** None
Long-Term/Repeat Dosing Safety	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** The long-term/repeat dosing safety	**Routine risk minimisation:** None **Additional risk minimisation:** None

	of ferumoxytol was investigated in 69 CKD patients and will be examined in three additional studies: ▪ A Phase IV, Open- Label, Multicenter Trial of Repeated Doses of Ferumoxytol compared with Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Chronic Kidney Disease (CKD) Patients on haemodialysis over a One Year Period. ▪ Study AMAG-FER-IDA-303 in up to 800 IDA subjects completing Study AMAG-FER-IDA-301 (in whom oral iron cannot be used) over a period of 6 months. ▪ Study AMAG-FER-CKD-253 in up to 288 children with CKD and IDA over a period of 2 years. ▪ Study AMAG-FER-CKD-403, a 2 year MRI study to evaluate the potential for organ deposition following treatment with IV Ferumoxytol and Iron Sucrose	
Head-to-Head Comparison with IV Iron	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection **Additional pharmacovigilance:** ▪ *Study AMAG-FER-IDA-302* Randomised, open-label, controlled study vs. iron sucrose in 600 subjects with IDA in whom oral iron cannot be used. This study will include a subgroup analysis of AEs in IV iron-naïve patients (including patients who may be intolerant to IV iron). ▪ *Study AMAG-FER-IDA-401* A Phase IV, Open- Label, Multicenter Trial of Repeated Doses of Ferumoxytol compared with Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Chronic Kidney Disease (CKD) Patients on haemodialysis over a One Year Period	**Routine risk minimisation:** None **Additional risk minimisation:** None
Safety in patients with liver disorders.	**Routine pharmacovigilance:** - Analysis of reported adverse reactions - Follow-up of reports and signal detection	**Routine risk minimisation:** Statement in Section 4.2 of the SmPC, and in the PIL, that Rienso has not been specifically studied in patients with hepatic impairment; clinical experience is limited to 8 patients. In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. No change in dosage is recommended from section 4.2. PIL section 2, Take special care with Rienso, tell your doctor If you have a problem with your liver
Safety in patients on concomitant anticoagulants	**Routine Pharmacovigilance** The concomitant use of anticoagulants among patients with	

	history of thrombotic events in ongoing and any future studies will be evaluated. In addition, post-marketing safety surveillance will also continue to monitor for any emerging trends in the incidence of thrombotic events in relation to the use of anticoagulants to permit the rapid detection of any safety signal	
Safety in patients with immunologic disease, multiple drug allergies or in patients with active infection	**Routine Pharmacovigilance** - Analysis of reported adverse reactions - Follow-up of reports and signal detection	**Routine risk minimisation:** Statement in Section 4.4 of the SmPC, and in the PIL, that parenteral iron should be used with caution in cases of immunologic disease or acute or chronic infection. It is not recommended to administer Rienso to patients with ongoing bacteraemia. PIL section 2, Take special care with Rienso and tell your doctor If you have a history of drug allergy if you have problems with your immune system or any infections including infections which have spread to your blood stream

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Study FER-CKD-201 A Randomised, Multicenter, Trial of Ferumoxytol Compared to Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Adult Subjects with Chronic Kidney Disease	2Q 2012
Study AMAG-FER-CKD-401 Open- Label, Multicenter Trial of Repeated Doses of Ferumoxytol compared with Iron Sucrose for the Treatment of Iron Deficiency Anaemia in Chronic Kidney Disease Patients on haemodialysis over a One Year Period	4Q 2015
Study AMAG-FER-IDA-301 Randomised, Double-Blind, Placebo-Controlled Trial of Ferumoxytol for the Treatment of Iron Deficiency Anaemia	4Q 2012
Study AMAG-FER-IDA-302 Randomised, Open-label, Active-Controlled, Trial Comparing Ferumoxytol with Iron Sucrose for the Treatment of Iron Deficiency Anaemia	2Q 2012
Study AMAG-FER-IDA-303 Open-Label, i=single-arm, multicenter Extension study of the Safety and Efficacy of Ferumoxytol for the Episodic Treatment of Iron Deficiency Anaemia over a 6-month period	2Q 2013
Study AMAG-FER-CKD-403 MRI study to the potential for iron deposition in the heart, liver, pancreas and where possible other major organs following repeated IV iron administration for the treatment of iron deficiency anaemia in patients with chronic kidney disease over a two year period	3Q 2016
Epidemiologic study using USRDS data Evaluation of hypotension and hypersensitivity reactions in comparison of other parenteral iron formulations.	2Q 2012

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The Applicant submitted three pivotal clinical studies comparing a 2 x 510 mg Rienso 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. Analysis of the mean change in Hgb at Day 35 for each study as well as for the pooled data showed that the IV-treatment was effective and that this treatment effect was superior to oral iron treatment with an overall increase of Hgb of 1.03 g/dl in the combined IV group versus 0.42 g/dl in the oral group.

ESA co-treatment enhanced the effect of iron, IV treatment being superior to oral in ESA+ and ESA- subgroups. 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).

Post-marketing observational data from three separate haemodialysis clinics in 8,666 patients treated with a total of 33,358 doses, suggest that Rienso re-treatment is effective to maintain the target Hgb in CKD patients over ½ to 1 year without an increase in the rate of ADRs.

Rienso had a better non-compliance profile (3 to 4%) compared to oral iron (6 to 8%) for non-dialysis patients who are often treated with oral iron preparations.

Uncertainty in the knowledge about the beneficial effects.

The pivotal studies cover only a short period of time (in a chronic condition). There are insufficient clinical study data on the repeated use and no clinical study data on the long-term use of the product in patients. The submitted observational post marketing data have to be evaluated with caution due to potential bias. Further data are expected from the post-marketing studies to be conducted as part of the pharmacovigilance plan.

Risks

Unfavourable effects

AE are experienced in ~35 to 55% of subjects and are not higher (i.e. comparable or somewhat lower) to oral iron therapy. None of the AE was exceeding 10% in any pivotal study.

There were signals of possible hepatotoxicity; the incidence of abnormal liver function serology (GGT) was higher for subjects with a history of liver cirrhosis compared to those with no history of cirrhosis.

The T-wave changes in the ECGs that occurred in 5.3% of Rienso subjects compared to none in the control groups are not regarded as clinically relevant.

The safety profile appears similar to other EU-authorised IV iron therapies. The most common AEs were reported in the gastrointestinal system (e.g. diarrhoea and constipation), the nervous system (dizziness) and the vascular system (hypotension) as well as flushing, headache and rash. The GI disorders were higher in the oral iron subjects, whereas hypotension and hypertension was more common in the Rienso group (hypotension 2.5 vs. 0.4 %, hypertension 1.0 vs. 0.7).

There were three cases of serious hypotension and hypersensitivity (0.2 %) one of which was described as anaphylaxis. Hypotension could also be observed in the placebo group (0.1%).

Overall the SAE-rate is around 12.1-13.3% which can be considered relatively low considering the underlying medical condition in CKD patients.

Uncertainty in the knowledge about the unfavourable effects

Adverse drug reactions reported from the limited post-marketing experience, including these related to serious adverse reactions and hypersensitivity seem to be essentially consistent with that observed in clinical trials. However, this needs to be further monitored in the post-marketing studies to be conducted as part of the pharmacovigilance plan. In particular, the direct comparison with IV iron preparation and repeat dose use is agreed to be thoroughly investigated during the immediate post-marketing period.

Benefit-risk balance

Importance of favourable and unfavourable effects

Change in Hgb, proportion of Hgb responders and change in ferritin clearly indicate clinical efficacy of the acute treatment of iron deficiency states superior to oral iron treatment and comparable to the standard IV iron preparations on the market. The effect and its size observed in the Rienso group (Hgb increase of ~1 g/dl in ~50% of subjects) is a valuable clinical effect for the CKD population especially for Non HD-patients, making Rienso one of the IV iron treatment options.

The safety analysis of the Rienso treatment as compared to oral treatment is considered relevant for the indication applied for. Rienso has shown a superior safety profile versus oral iron treatment.

Benefit-risk balance

Superior efficacy in comparison to oral iron treatment has been demonstrated in CKD patients pre-dialysis and on haemodialysis with and without concomitant ESA-treatment; the safety profile in comparison to oral iron is considered to favour ferumoxytol.

Discussion on the benefit-risk balance

Clinical efficacy of Rienso for acute iron replacement therapy in CKD patients with IDA has been demonstrated since a clinically meaningful change in Hgb of ~1 g/dl (following a cumulative IV dose of ~ 1 g of iron) corresponds to the clinical response of other standard IV preparations as published in the literature. Efficacy is superior to oral iron treatment.

Post marketing data suggests that ferumoxytol re-treatment is effective to maintain the target Hgb over ½ to 1 year. However, the evaluation showed that ~30% of patients received an uneven number of doses, indicating that the proposed fixed dosing scheme does not fit all patients. Therefore, a

flexible patient adapted dosing recommendation for re-treatment is given in SmPC section 4.2. Further Rienso treatments may be given only after the patient has been re-assessed and the anaemic state is re-confirmed. For dosage and monitoring, a reference to the European Best Practice Guideline recommendations has been included in the SmPC. Rienso has shown an acceptable safety profile, superior to that observed with oral iron treatment.

A sufficient number of patients have been exposed to the drug in clinical studies, Adequate safety regarding short term and episodic treatment have been provided and long term safety is supported by available US post marketing data. However data from long time exposure are limited. This will be addressed post-authorisation in comparison with licensed IV iron products.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Rienso in the *intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). The diagnosis of iron deficiency must be based on appropriate laboratory tests (see section 4.2*), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent position to the majority recommendation is appended to this report.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that ferumoxytol is to be qualified as a new active substance.

Appendix 1

Divergent Position

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The safety database submitted in the marketing authorization application for Rienso (ferumoxytol) consists of a total of 1,726 subjects enrolled into 11 completed studies. Of those, 1,562 subjects received Rienso in case of chronic kidney disease (CKD). The primary safety information in support of ferumoxytol in CKD population comes from 3 pivotal studies with similar study design, which included 665 subjects treated with ferumoxytol.

Post marketing data derived from a survey on 3 US studies including > 8,500 patients with > 33,000 exposures to ferumoxytol has been submitted to further support the safety data. These data showed the overall rate of serious adverse events (SAEs) to be 0.2% in the post marketing survey compared with an overall rate of SAEs of 7.1% and related SAE rate of 0.2% in the pivotal studies.

Moreover, a recently published analysis reported AEs with different i.v. iron products in the US (Bailie GR. *American Journal of Health-System Pharmacy*; 2012 69(4):310-320). Iron sucrose and sodium ferric gluconate were associated with much lower rates of AEs per million units sold than iron dextran or ferumoxytol, for all reported AE classifications (ie, deaths, serious AEs, other major AEs, and other AEs). The huge difference (by roughly factors 10-100) in risk for hypersensitivity may be at least in part explained by a reporting period close to first availability of ferumoxytol on the US market. Nevertheless, this adds uncertainty to any conclusion from the limited available safety database.

There is no unmet medical need that would justify making ferumoxytol available to patients in the claimed indication despite this uncertainty around its risks. The benefit:risk ratio is thus considered negative for the time being.

Pierre Demolis	Andrea Laslop	Daniela Melchiorri
Sol Ruiz	Aranxta Sancho-Lopez	