Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

Ferinject 50mg iron/ml solution for injection/infusion

(Ferric carboxymaltose)

Procedure No: UK/H/0894/001/E/001

UK Licence No: PL 15240/0002

Vifor France

LAY SUMMARY

Ferinject 50 mg iron/mL solution for injection/infusion (Ferric carboxymaltose)

This is a summary of the Public Assessment Report (PAR) for Ferinject 50 mg iron/mL solution for injection/infusion (PL 15240/0002; UK/H/0894/001/E/001). It explains how the application for Ferinject 50 mg iron/ml solution for injection/infusion was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ferinject 50 mg iron/ml solution for injection/infusion.

The product may be referred to as 'Ferinject' in this Lay Summary.

For practical information about using Ferinject, patients should read the package leaflet or contact their doctor or pharmacist.

What is Ferinject and what is it used for?

Ferinject is a medicine with 'well-established use'. This means that the medicinal use of the active substance, (iron as ferric carboxymaltose, FCM) of Ferinject is well established in the European Union for at least ten years, with recognised efficacy and an acceptable level of safety.

Ferinject is an antianaemic preparation, a medicine that is used to treat anaemia.

Ferinject is used for the treatment of patients with iron deficiency, when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a lack of red blood cells due to iron deficiency.

How does Ferinject work?

Ferinject contains iron in the form of an iron carbohydrate (ferric carboxymaltose), as the active substance. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron is involved in many other functions necessary for maintenance of life in the human body.

How is Ferinject used?

Ferinject is a Prescription Only Medicine.

Ferinject is available as a solution for injection or infusion. It is administered by a health professional (doctor or nurse), undiluted by injection, during dialysis or diluted by infusion.

Ferinject will be administered in a facility where any immunoallergic events can receive appropriate and prompt treatment.

The patient will be observed for at least 30 minutes by the doctor or nurse after each administration.

Before administration, the patient's doctor will perform a blood test to determine the dose of Ferinject that the patient requires.

Please read the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

What benefits of Ferinject have been shown in studies?

The Marketing Authorisation Holder (MAH) has performed an extensive clinical programme with ferric carboxymaltose confirming the efficacy and safety of the product in the proposed indication.

What are the possible side effects of Ferinject?

Like all medicines Ferinject can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Ferinject, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Ferinject.

Why is Ferinject approved?

The MHRA concluded that, in accordance with EU requirements, the benefits of Ferinject outweigh the identified risks and recommended that the product be approved.

What measures are being taken to ensure the safe and effective use of Ferinject?

A Risk Management Plan has been developed to ensure that Ferinject is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Ferinject, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Ferinject

Initially, Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden and the UK agreed to grant a Marketing Authorisation for Ferinject 50mg iron/ml solution for injection/infusion (PL 15240/0002; UK/H/0894/001/DC) on 19 June 2007. A Marketing Authorisation was granted in the UK to Vifor France SA on 19 July 2007.

Subsequently, following this product going through a repeat-use Mutual Recognition Procedure (MRP; UK/H/0894/001/E/001) Belgium, Bulgaria, Cyprus, France, Hungary, Iceland, Italy, Malta, Norway, Romania and Slovenia agreed to grant a Marketing Authorisation for Ferinject (PL 15240/0002; UK/H/0894/001/E/001 on 09 March 2010 (Day 90).

Through a further repeat use MRP (UK/H/0894/001/E/002), Croatia agreed to grant a Marketing Authorisation for Ferinject (PL 15240/0002; UK/H/0894/001/E/002) on 18 July 2014.

The full PAR for Ferinject follows this summary.

For more information about treatment with Ferinject, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2017.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Background

This application was submitted by Vifor France SA for a generic version of Ferinject 50mg iron/ml Solution for Injection/Infusion, via the Decentralised (Mutual Recognition) Procedure.

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Ferinject 50mg Iron/ml Solution for Injection/Infusion could be approved in the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

The diagnosis of iron deficiency must be based on laboratory tests.

Marketing Authorisations for this product were initially approved in Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden and the United Kingdom via the Decentralised Procedure (UK/H/0894/01/DC), which ended successfully on 19th June 2007. There was a subsequent national phase and the licence was granted in the UK on 19th July 2007.

This product then went through a repeat-use Mutual Recognition Procedure (UK/H/0894/001/E/001/MR) involving Belgium, Bulgaria, Cyprus, France, Hungary, Iceland, Italy, Malta, Norway, Romania and Slovenia. This procedure was completed on 9th March 2010 (Day 90) and the MRP was finalised in the UK on 18th February 2011.

The product went through a further repeat use MRP (UK/H/0894/001/E/002) to include Croatia. This procedure was completed on 18 July 2014.

Overall Benefit/Risk Assessment

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found.

Clinical studies on Ferinject 50mg iron/ml solution for injection/infusion were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Ferinject 50mg iron/ml solution for injection/infusion provides satisfactory clinical benefits.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II QUALITY ASPECTS

3.2.S DRUG SUBSTANCE

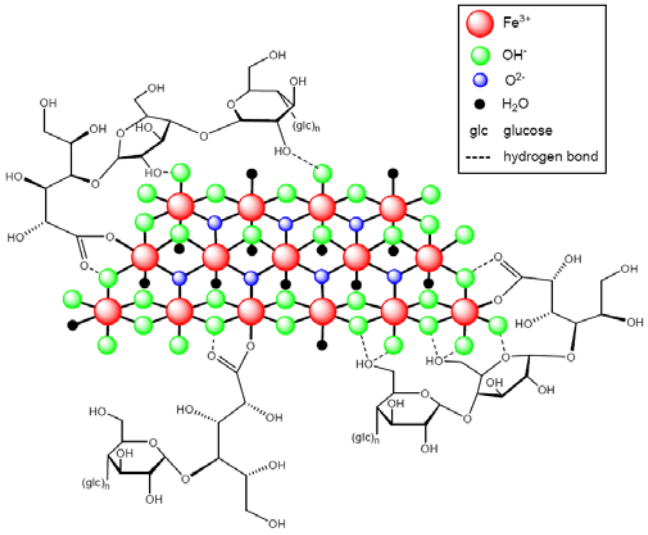
3.2.S.1 General Information

INN: Ferric carboxymaltose

Other names: Iron carboxymaltose, Eisencarboxymaltose, Iron polymaltose, VIT-45

Chemical Name: Polynuclear iron(III)-hydroxide 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate

Molecular Formula: $[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m$ $(C_6H_{12}O_7)\}_l]_k$, where l is the branching degree of the ligand



Appearance: Brown amorphous powder

Solubility: Readily soluble in water and insoluble in most organic solvents (including ethanol, acetone and ether).

3.2.S.2 Manufacture

A detailed description of the manufacture of the active substance ferric carboxymaltose from its starting materials has been provided. Satisfactory certificates of analysis have been provided for all starting materials. Suitable in-process controls are present and a satisfactory process validation data have been provided from production-scale batches.

3.2.S.3 Characterisation

Suitable data concerning the elucidation of structure and other characteristics have been provided. A review of the potential impurities present in the active substance has been provided.

3.2.S.4 Control of Drug Substance

A suitable drug substance specification has been provided. Details of all analytical methods used have been provided and these have been appropriately validated. Batch analysis data have been provided showing compliance with the active substance specification.

3.2.S.5 Reference Standards or Materials
Suitable certificates of analysis are provided for all reference standards used.

3.2.S.6 Container Closure System
The active substance is stored in polyethylene bags, which are sealed in drums to ensure that it is protected from light and moisture. Specifications have been provided for all packaging used. The primary packaging has been shown to comply with Directive 2002/72/EC and amendments, concerning the contact of materials with food.

3.2.S.7 Stability
Suitable stability data have been provided to support a retest period of 5 years when stored in the original container at or below 25^{o}C.

Suitable post approval stability commitments have been provided to follow up the current stability batches.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product
The drug product is a 5% m/V iron solution of ferric carboxymaltose in water for injections. Other ingredients consist of the pharmaceutical excipients sodium hydroxide, hydrochloric acid. The drug product has a physiological pH and its osmolarity is comparable to that of blood. It is available in terminally sterilised 2 ml (100 mg iron) and 10 ml (500 mg iron) vials.

3.2.P.2 Pharmaceutical Development
Suitable pharmaceutical development data have been provided.

3.2.P.3 Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the finished product. The results appear satisfactory.

3.2.P.4 Control of Excipients
All excipients comply with their European Pharmacopoeia monograph. None of the excipients contain materials of animal or human origin. Satisfactory certificates of analysis have been provided for all excipients.

3.2.P.5 Control of Drug Product
The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification.

3.2.P.6 Reference Standards or Materials
Certificate of analysis have been provided for all working standards used.

3.2.P.7 Container Closure System
The product is packed in clear Type 1 glass vials with a bromobutyl rubber stopper and an aluminium cap. Pack sizes are 5 x 2ml and 5 x 10ml.

Specifications are provided for all packaging. All primary packaging complies with current regulations concerning contact with products for parenteral use.

3.2.P.8 Stability

Stability data have been provided for batches of finished product, in accordance with ICH guidelines. The data support a shelf-life of 3 years, with storage conditions of "Store in original package", "Do not store above 30 degrees" and "Do not refrigerate or freeze".

SmPC, LABELS AND PACKAGE LEAFLET

The SmPC, labels and leaflet are supplied and are pharmaceutically satisfactory.

PHARMACEUTICAL CONCLUSIONS

The grant of a product licence is recommended.

III NON-CLINICAL ASPECTS

PHARMACOLOGY

Primary pharmacodynamics

The desired pharmacodynamic effect of proposed product is delivery of utilisable iron to the iron storage and transport proteins in the body (ferritin and transferrin). The applicant's primary pharmacodynamic studies have focussed on demonstrating that intravenous VIT-45 allows iron to be efficiently incorporated into red blood cells.

The applicant has provided two primary pharmacodynamic studies (Study A and Study B) in which ^{59}Fe labelled VIT-45 was administered intravenously to rats maintained on iron deficient diets. Some of the results are summarised in the tables below.

Table 1. Retrieved ^{59}Fe 14 days and 28 days after a single iv administration of ^{59}Fe-VIT-45 into the tail vein of iron deficient rats at a dose corresponding to 10mg Fe (Study A).

Organ	Mean activity relative to dose (%)	
	Day 14	Day 28
Liver	5.4	3.5
Spleen	0.9	0.7
Kidneys	0.5	0.6
Tail	38.7	40.9
Faeces	1.2	0.7
Urine	0.4	0.1
RBC	41.1	42.7
Serum	0.3	0.2
Total	88.4	89.3

Table 2. Retrieved ^{59}Fe after a single iv administration of ^{59}VIT-45 into the tail vein of anaemic rats at a dose corresponding to 5mg Fe (Study B). Results expressed as total % dose per organ.

Organ	168 h post dose		336 h post dose		504 h post dose		672 h post dose	
	Males	Females	Males	Females	Males	Females	Males	Females
Plasma*	0.2176	0.4084	0.1962	0.2919	0.1715	0.2824	-	0.2908
Whole blood*	58.69	34.42	79.18	55.37	89.41	64.93	90.87	66.95
Liver	27.52	42.37	16.84	32.61	10.91	21.96	9.518	19.21
Spleen	3.327	4.074	2.011	2.326	1.424	2.328	0.993	1.557
Kidney	0.8479	0.6601	1.027	0.7479	1.143	1.126	1.105	0.7910
Total	90.60	81.93	99.25	91.35	103.05	90.63	102.48	88.80

*calculated from estimated tissue weights

Table 3. Blood radioactivity concentrations over time in male and female rats following a single iv administration of ^{59}Fe-VIT-45 into the tail vein of anaemic rats at a dose corresponding to 5mg Fe (Study B). Concentrations are expressed as µg equivalents iron/g tissue.

Time after dosing	Mean radioactivity in whole blood		Mean radioactivity in plasma		Mean calculated radioactivity in blood cells	
	Males	Females	Males	Females	Males	Females

5 mins	174.3	226.6	262.5	373.2	NA	NA
10 mins	176.0	238.8	265.4	401.0	NA	NA
30mins	184.1	220.1	282.2	378.8	NA	NA
1 hr	158.6	185.9	239.7	321.2	NA	NA
2 hrs	123.9	153.5	194.7	262.9	NA	NA
3 hrs	97.43	105.7	149.0	171.2	NA	NA
4 hrs	69.98	65.70	105.1	104.2	NA	NA
6 hrs	38.25	36.48	56.46	57.24	NA	NA
8 hrs	24.26	16.22	32.94	25.87	NA	NA
16 hrs	12.92	8.473	5.308	7.168	NA	NA
24 hrs	17.20	12.69	1.956	4.496	NA	NA
48 hrs	42.96	22.68	0.927	-	NA	NA
72 hrs	62.27	39.05	-	1.601	194.0	118.8
120 hrs	86.17	57.46	-	1.406	260.2	170.5
168 hrs	109.1	79.72	0.712	1.663	321.6	203.9
336 hrs	129.8	121.1	0.567	1.120	381.5	334.9
504 hrs	140.8	157.2	0.472	1.201	366.7	424.4
672 hrs	125.0	144.9	-	1.114	372.1	398.5

NA = not available

Tables 1 and 2 show that high levels of radioactivity were seen in blood, liver and spleen. Data from Study B show that tissue radioactivity concentrations in liver, spleen and lymph nodes greatly exceeded those of plasma samples at corresponding time points (radioactivity levels were between 48 and 357 times greater in these tissues than in corresponding plasma samples).

Table 2 shows that as the proportion of radioactivity in liver and spleen declined, the amount of radioactivity in blood cells increased, and by 672 hours (28 days) after dosing 91 and 67% of radioactivity was found in whole blood in male and female rats, respectively. In Study A, a very substantial proportion of radioactivity was retained in the tail. The applicant has suggested that this may have arisen as a result of a proportion of the dose being injected outside the tail vein.

Table 3 shows that the greatest whole blood levels occurred within the first hour after dosing and that levels then decreased over the following 23 hours before increasing again over the next 3 weeks. Plasma levels declined in parallel with whole blood levels, but did not subsequently recover. Blood cell radioactivity was seen to peak at 336 hours post dose in males and 504 hours post dose in females. The applicant argues that as blood cell radioactivity was relatively similar at subsequent time points it can be concluded that uptake of administered ^{59}Fe was complete by 336 hours in males and 504 hours in females.

Examination of total iron concentrations in liver and spleen (Study B) demonstrated that, compared to iron concentrations in liver and spleen of non-anaemic controls, single iv administration of VIT-45 resulted in a correction of the dietary induced iron depletion in liver and spleen of both males and females. Corrected iron levels were still apparent in the spleen in males and females at 672 hours post-dose. Iron concentrations in liver were also corrected at all time points in females, while in males iron concentrations in liver fell below those of non-anaemic controls at 336 hours post-dose, perhaps indicating that further iron administration may be necessary in male animals to fully correct the iron depletion in the long-term.

The intravenous dosing data from Study B suggest a possible sex difference in the use of iron with 91% (males) and 67% (females) of administered iron reaching the blood cells, with the balance being in the liver and spleen in both sexes. The applicant suggests that female rats may have a higher storage capacity for iron, coupled with an increased retention period for iron stores in order to support the increased requirement of blood (and iron) during pregnancy. Of relevance to this is the finding that, prior to dosing, male rats reached the target haemoglobin concentration range for anaemic status (60-100g/l blood) after approximately 3 weeks on an iron deficient diet while haemoglobin concentrations declined more slowly in females and the target concentration range was eventually amended to <130g/l. It is

possible, therefore, that the less severe anaemic status of the females and/or their greater age (resulting from several additional weeks on an iron deficient diet prior to dosing in order to establish anaemic status) may be responsible for the sex differences noted in the use of iron following VIT-45 administration.

Secondary pharmacodynamics
No non-clinical studies have been performed. The applicant argues that no secondary pharmacodynamic effects of the complex or its breakdown product would be expected

Safety pharmacology
GLP compliant *in vivo* safety pharmacology studies have been performed to examine the potential for VIT-45 associated cardiovascular (in dogs), CNS, respiratory and renal (all in rats) effects. In all studies VIT-45 was administered as a single intravenous dose at 30 and 90mg Fe/kg. Control animals were dosed with 0.9% NaCl.

In the cardiovascular study, no effects on arterial blood pressure or heart rate were seen and there was no evidence of QT prolongation. Analysis of plasma iron indicated a dose related increase in group mean plasma iron content and TIBC.

In the CNS study, no effects were seen on behaviour, body temperature or spontaneous locomotor activity. VIT-45 at these doses produced no marked or statistically significant effects on plasma iron or total iron binding capacity.

In the respiratory study, VIT-45 produced no marked or statistically significant effects on respiration rate, tidal volume or minute volume. Dose dependent increases in plasma iron levels and TIBC were noted in both male and females.

Two renal function studies were performed. In both, animals received water at a dose of 20ml/kg by oral gavage immediately following drug administration. In the first study a transient decrease in urine output and electrolyte excretion with an increase in specific gravity was noted in females treated with 90mg Fe/kg. In the repeat study there was a significant reduction in urine output in both males and females up to 5 hours post dose. The effect was more pronounced in the males, where urine output was reduced by approximately 40% at all time points up to 5 hours. Total output at 24 hours was lower than controls but the difference was not statistically significant. Statistically significant decreases in Na^+ and Cl^- ion excretion were noted in males and females in the 90mg Fe/kg group, with levels reduced to approximately half those seen in the control group. Potassium ions were unaffected in males but reduced by approximately 40% in females. No marked effects were seen on urinary pH, specific gravity, protein excretion or urinary creatinine levels, and there were no changes in blood creatinine or blood urea levels. The lack of findings in the blood led the applicant to conclude that the effects seen were not indicative of renal insufficiency. At the 30mg Fe/kg dose there were no findings of note in either study. At both doses VIT-45 produced a statistically significant decrease in plasma iron after 24 hours in males and females. The effect was greater at the lower dose than at the higher dose. The applicant is unable to explain the reason for this inverse dose relationship. No effects on TIBC were noted.

Pharmacodynamic drug interactions
No non-clinical pharmacodynamic drug interaction studies have been performed. While VIT-45 may be administered with erythropoietin, the applicant argues that the potential for interactions should not be different to the potential for interactions between other parenteral iron preparations and erythropoietin.

Overall conclusions on pharmacology
The desired pharmacodynamic effect of proposed product is delivery of utilisable iron to the iron storage and transport proteins in the body (ferritin and transferrin) for the correction of iron deficiency (i.e.

incorporation into red blood cells and haemoglobin). Primary pharmacodynamic investigations in rats fed iron deficient diets have demonstrated that following intravenous administration of ^{59}Fe VIT-45, iron levels in serum decrease steadily with the bulk of the ^{59}Fe being distributed to red blood cells, liver and spleen. After an initial peak, radioactivity levels in liver and spleen decrease as levels in red blood cells steadily increase over a 4-week period. By 28 days after administration, approximately 91 and 67% of administered radioactivity was found in whole blood in male and female rats, respectively.

Examination of total iron concentrations in liver and spleen demonstrated that, compared to iron concentrations in non-anaemic controls, single iv administration of VIT-45 (5mg Fe) resulted in a correction of the dietary induced iron depletion in liver and spleen of both males and females.

Differences in the proportion of iron leaving the liver and spleen and reaching the blood cells in males and females were apparent and may represent a sex difference in the use of iron in this species.

GLP-compliant safety pharmacology studies examining cardiovascular, CNS and respiratory endpoints produced unremarkable findings. Safety pharmacology studies examining renal function revealed decreased urine output and electrolyte excretion following an intravenous administration of VIT-45 corresponding to 90mg Fe/kg. No changes in blood creatinine or urea levels were noted, leading to the conclusion that the changes seen did not represent renal failure. No effect on any parameter was seen in animals treated with 30mg Fe/kg.

Although identical doses of VIT-45 were used in all the safety pharmacology studies, the effect on plasma iron and total iron binding capacity appears to have been inconsistent. The applicant has argued that the differences in plasma iron levels were the result of differences in sampling times after VIT-45 administration and that the plasma iron data collected in the safety pharmacology studies are consistent with the kinetic data generated in the ADE studies. In addition, the applicant notes that the TIBC values are of limited value as VIT-45 has been shown to interfere with the analytical method for TIBC measurement.

No secondary pharmacodynamic or drug interaction studies have been performed. The applicant argues that due to the nature of the product, its breakdown products and its mode of action, no relevant effects are expected.

From a non-clinical point of view, SPC section 5.1 is acceptable.

PHARMACOKINETICS

Absorption

Whole blood, plasma and blood cell levels of ^{59}Fe have been recorded following administration of ^{59}Fe-VIT-45 to rats and dogs. Results are summarised in table 4.

Table 4. Summary of pharmacokinetic parameters following intravenous administration of ^{59}Fe-VIT-45

	Intravenous administration					
	Whole blood		Plasma		Blood cell	
	M	F	M	F	M	F
Single dose of ^{59}Fe-VIT-45 (5mg Fe) in healthy rats (3M & 3F per group) with bloods collected up to 672 hours post dose						
Tmax (hr)	0.083	0.083	0.083	0.083	672	672
Cmax (µg eq Fe/g)	242.9	269.9	417.3	481.4	342.3	316.2
AUC_{672} (µg eq Fe.h/g)	54839	50052	1560	1881	135840	127057
T1/2 (hr)	-	-	-	-	-	-
Single dose of ^{59}Fe-VIT-45 (5mg Fe) in anaemic rats (3M & 3F per group) with bloods collected up to 672 hours post dose						
Tmax (hr)	0.5	0.25	0.5	0.25	336	504
Cmax (µg eq Fe/g)	184.1	238.8	282.2	401.0	381.5	424.4
AUC_{672} (µg eq Fe.h/g)	76310	73340	1575	2354	215200	197600
T1/2 (hr)	-	-	2.7	2.8	-	-
Single dose of ^{59}Fe-VIT-45 (50mg Fe) in healthy dogs (4M in iv study) with bloods collected up to 672 hours post dose						
Tmax (hr)	0.00	-	0.00	-	-	-
Cmax (µg eq Fe/g)	44.41	-	76.92	-	-	-
AUC_{672} (µg eq Fe.h/g)	8981	-	72.89	-	-	-
T1/2 (hr)	3.2	-	3.1	-	-	-

In healthy and anaemic rats, following intravenous administration, whole blood radioactivity decreased to its lowest levels at 16 hours post dose and subsequently increased to 672 hours (healthy rats) and 504 hours (anaemic rats). In dogs, following intravenous administration, whole blood radioactivity decreased to its lowest level by 24 hours before increasing to a maximum at 504 hours post dose.

In healthy and anaemic rats, administration of VIT-45 led to ^{59}Fe blood cell levels of between 20 and 50% of those seen following intravenous administration.

Distribution

In normal and anaemic rats, ^{59}Fe-VIT-45 was steadily cleared from plasma with only trace amounts present at 16 hours post dose (see table 3 for data from anaemic rats).

In all studies, the organs exposed to substantial levels of ^{59}Fe following intravenous administration were the liver and the spleen, major iron storage sites. Radioactivity levels in these tissues gradually declined while blood cell levels steadily increased. High levels of radioactivity were also noted in lymph nodes.

Table 5. Distribution of ^{59}Fe following administration of ^{59}Fe-VIT-45 to rats and dogs.

Tissue/ Organ	Intravenous administration			
	168hrs		672hrs	
	M	F	M	F
Single dose of ^{59}Fe-VIT-45 (5mg Fe) in rats (3M & 3F per group) with bloods collected up to 672 hours post dose				
Blood cells	29.8	20.0	75.1	55.2
Liver	38.5	43.8	20.4	29.2
Spleen	4.1	4.1	1.6	3.5
Kidney	0.6	0.5	0.9	0.9
Muscle	-	-	-	-
(Dose site)				
Single dose of ^{59}Fe-VIT-45 (5mg Fe) in anaemic rats (3M & 3F per group) with bloods collected up to 672 hours post dose				
Blood cells	58.44	33.98	90.80	66.63
Liver	27.52	42.37	9.52	19.21
Spleen	3.33	4.07	1.00	1.56
Kidney	0.85	0.66	1.11	0.79
Muscle	-	-	-	-
(Dose site)				
Single dose of ^{59}Fe-VIT-45 (50mg Fe) in dogs (4M in iv study) with bloods collected up to 672 hours post dose				
Blood cells	-		43.87	
Liver	66.73		25.23	
Spleen	8.23		14.67	
Kidney	0.16		0.26	
Muscle	-		-	
(Dose site)				

In male anaemic rats, 91% of the injected ^{59}Fe was present in blood cells by 672 hours post dose, compared to 67% in females. For further detail of distribution between whole blood and plasma in the anaemic rat study see table 3. In healthy rats 75% of the injected ^{59}Fe was present in blood cells by 672 hours post dose, compared with 55% in females. In dogs 44% of injected ^{59}Fe was present in blood cells by 672 hours post dose.

Placental transfer of ^{59}Fe was assessed in rats following intravenous administration of ^{59}Fe-VIT-45 (at a dose equivalent to 5mg Fe/rat) on day 12 of gestation. Seven days after drug administration 3.1% of the dose was present in placenta and 9.2% in fetuses. Placental transfer was also assessed using an in vitro human placental perfusion model (Malek, 2005). In this study the concentration of ^{59}Fe-VIT-45 in the maternal circuit was seen to decrease by 10% but no transferred radioactivity was detected in the fetal circuit.

Distribution into maternal milk was assessed in 2 rat studies. In the first ^{59}Fe-VIT-45 was administered intravenously at a dose of approximately 5mg Fe/rat on day 7 post partum. Milk concentrations were 2% of plasma concentrations at 1 hour post dose and exceeded plasma concentrations at 24 hours post dose (milk:plasma ratio of 1.39). Thereafter milk concentrations declined more rapidly than plasma concentrations and ^{59}Fe was undetectable in milk at 240 hours post dose. In the second study 10mg Fe/rat ^{59}Fe-VIT-45 was administered intravenously immediately post-partum and radioactivity was monitored for 4 weeks. The amount of radioactivity found in milk was below 1% of the administered dose on all occasions. A total of 12.2% of the administered dose was recovered from the carcasses of the offspring at 28 days post-partum.

Metabolism

In vitro studies have been performed to examine the carbohydrate breakdown products of VIT-45. Incubation with α-amylase for 60 minutes led to approximately 70% degradation of VIT-45, with the production of maltotriose, maltose and glucose. Incubation with rat liver S9 fraction at 37ºC produced

maltotetraose as well as the products seen following incubation with amylase – VIT-45 was approximately 47% degraded after 15 hours incubation.

The studies suggest that the carbohydrate portion of VIT-45 is degraded into simple oligo-glucose units, such as maltotetraose, maltotriose, maltose and glucose.

Excretion
Urinary and faecal ^{59}Fe were assessed over 168 hours following dosing of ^{59}Fe-VIT-45 to healthy and anaemic rats. In both studies urinary ^{59}Fe was seen to account for less than 0.1% of the administered dose while faecal ^{59}Fe accounted for less than 1%. More than 94% of radioactivity was found to be retained in the carcasses in both studies.

In study, faecal and urinary ^{59}Fe was determined following administration of ^{59}Fe-VIT-45 to dogs. During the sampling period (672 hours following dosing), less than 0.2% of administered radioactivity was recovered in urine and no radioactivity was recovered in faeces.

Pharmacokinetic drug interactions
No pharmacokinetic drug interactions are expected.

Assessor's overall conclusions on pharmacokinetics
Following intravenous administration of ^{59}Fe-VIT-45, radioactivity was steadily cleared from plasma in rats and dogs. Whole blood radioactivity levels fell over the first 24 hours, but increased thereafter until peak levels were seen at 3 to 4 weeks after dosing. Organs exposed to substantial levels of ^{59}Fe-VIT-45 were the liver and spleen, major iron storage sites. After 7 days, levels in these organs were seen to gradually decline as radioactivity in blood cells steadily increased. High levels of radioactivity were also noted in lymph nodes. Following administration in rats, the tissue into which the dose was administered was seen to retain a substantial proportion of the administered radioactivity. This effect was less marked in dogs.

In vitro degradation studies suggest that the carbohydrate portion of VIT-45 is degraded into simple sugars, including glucose, maltose, maltotriose and maltotetraose.

Following intravenous administration of ^{59}Fe-VIT-45 to pregnant rats, radioactivity was detected in fetuses – 7 days after drug administration 9.2% and 3.1% of the administered dose was present in fetuses and placentas, respectively. Intravenous administration of ^{59}Fe-VIT-45 to lactating rats led to low levels of radioactivity (<1% of administered dose) in milk. However, by 28 days after drug administration to lactating animals the carcasses of their offspring retained as much as 12.2% of the maternally administered dose.

From a non-clinical point of view, SPC section 5.2 is acceptable.

TOXICOLOGY

Single-dose toxicity
GLP compliant acute toxicity studies have been performed in mice, rats and dogs. The results are summarised in table 6.

Table 6. Summary of acute toxicity studies

Study outline	Main findings
Intravenous bolus dose of 1000mg Fe/kg or 2000mg Fe/kg in mice	• 2000mg Fe/kg caused a number of deaths • 1000mg Fe/kg was considered a non-lethal dose • Both doses associated with enlarged spleens at necropsy
Intravenous bolus dose of 250mg Fe/kg in mice	• Iron deposits seen in a number of organs, particularly the liver and spleen • Some iron was detected in parenchymal cells (approximately 10-20% of iron in liver was present in parenchymal cells)
Intravenous bolus dose of 1000mg Fe/kg in rats	• Swollen and dark-discoloured limbs and extremities noted post dosing but regressed by day 3 • Enlarged spleens in 9/10 animals • 1000mg/kg considered a non-lethal dose
1 hour iv infusion at doses of 60, 120 and 240mg Fe/kg in rats	• Elevated plasma transaminase levels (particularly ALT) in all groups • Brown discolouration of pancreas in 240mg Fe/kg group
1 hour iv infusion at doses of 60, 120 and 240mg Fe/kg in dogs	• Slight increases in plasma transaminase and alkaline phophatase levels in all groups • Increased APTT in 240mg Fe/g group • Dark discolouration of lymph nodes in 120 and 240mg Fe/kg groups

All studies included control animals dosed with 0.9% NaCl
APTT: activated partial thromboplastin time, RES: reticuloendothelial system

Repeat-dose toxicity

The repeat dose studies performed are outlined in table 7 below.

Table 7. Outline of repeat dose studies

Study details	Reported NOAEL (mg Fe/kg/week)	Relative amount of iron in liver at NOAEL
13 week study in rats. Animals dosed once weekly with 1 hour iv infusions of 9, 30 or 90mg Fe/kg	9	-
13 week study in rats. Animals administered iv bolus doses of 1, 3, 10 or 30mg Fe/kg 3 times per week (ie weekly doses of 3, 9, 30 or 90mg Fe/kg)	9	4.5 times control value
26 week study in rats with 6 week recovery period Animals administered iv bolus doses of 1, 3 or 10mg Fe/kg 3 times per week (ie weekly doses of 3, 9 or 30mg Fe/kg)	3	≥ 2.2 times control value
13 week study in dogs Animals administered once weekly 1 hour iv infusions at doses of 9, 30 and 90mg/kg/week	9	-
26 week study in dogs with a 6 week recover period Animals administered iv bolus doses of 1, 3 or 10mg Fe/kg 3 times per week (ie 3, 9 or 30mg Fe/kg/week).	9	≥ 12.4 times control value

All studies included control animals dosed with 0.9% NaCl

Consistent signs of toxicity were seen across the repeat-dose studies and are considered to be representative of iron overload. Toxicity was most apparent in the 30 and 90mg Fe/kg/week groups. Findings reported include:

- Dose-related increases in serum iron and decreases in total iron binding capacity (TIBC)
- Reduced weight gain and food intake
- Elevated transaminase (ALT and AST) and alkaline phosphatase levels, particularly in the 90mg Fe/kg/week groups
- Elevated beta globulin levels and blood urea nitrogen at 90mg Fe/kg/week
- Increased liver and spleen weights across the groups, most pronounced at high doses
- Modest increases in kidney and lung weights, particularly at the highest doses

- Histology revealed widespread iron deposition in a number of tissues, particularly liver, spleen, kidneys and lymph nodes. In the majority of tissues the iron was present within macrophages and sometimes vascular endothelium with no histopathological changes in other cells. A dose relationship was seen in incidence and degree of these findings. In liver, kidneys, adrenals and spleen iron was also present in parenchymal cells (in a dose related manner)
- In dogs, toxic changes in the liver were seen (perivascular fibrosis and one animal with hepatocyte necrosis at 90mg Fe/kg/week) in the 13 week study
- At 90mg Fe/kg/week levels of iron in the liver were up to 60 times those seen in controls
- Dose-related reductions in red cell parameters
- Increased severity of extramedullary haemotopoiesis in liver in 30mg Fe/kg/week group (in dog studies). This was considered an adaptive response to reduced red blood cell parameters
- Increased plasma cholesterol in 90mg and sometimes 30mg Fe/kg group
- Increased urine volume and decreased specific gravity, particularly in 90mg Fe/kg group
- High platelet and white cell counts and reduced APTT
- Clinical signs of toxicity were rare although in the 13 week dog study yellow discolouration of eyes and gums was noted in the 90mg Fe/kg/week group, as well as dose related increase in incidence of liquid faeces

Two studies included 6-week recovery periods, but signs of recovery were not seen.

While the reduced red cell parameters in animals administered VIT-45 may seem a paradoxical finding for a treatment effect of a parenteral iron complex, the applicant reports that similar findings have been reported in toxicity studies with other parenteral iron complexes. Free iron, present as a result of iron overload, may have an adverse effect on reticulocyte populations and haem synthesis.

One study included additional groups of animals administered VIT-45 for 4 weeks for the purposes of an immunotoxicity study in which the response to a T-cell-dependent antigen (sheep red blood cells – SRBC) was examined. No evidence of immunotoxicity was seen.

Genotoxicity
The *in vitro* genotoxic effects of VIT-45 were examined in a bacterial reverse mutation assay, a mammalian chromosome aberration test using human lymphocytes, and a mammalian cell mutation assay using L5178Y cells, all with and without metabolic activation. No evidence of mutagenicity was seen in the bacterial mutation assay or in the chromosome aberration test. In the mammalian cell mutation assay statistically significant increases in mutant frequency were seen, but only at cytotoxic doses (>625μg/ml).

In an *in vivo* mouse micronucleus assay, intravenous VIT-45 at single doses of up to 500mg Fe/kg did not reveal any evidence of genotoxic potential.

Carcinogenicity
No carcinogenicity studies have been performed. The applicant argues that this is justified as the product is a replacement therapy and these may be exempt from the need for carcinogenicity data. Additionally, the breakdown products are simple glucose oligomers, the product did not show signs of genotoxic potential, and preneoplastic signs were not seen in the repeat dose studies.

Reproductive and developmental toxicity
Effects of VIT-45 on fertility and early embryonic development were assessed in a GLP compliant study in rats with male and female animals dosed with 3, 9 and 30mg Fe/kg three times per week by 1-hour intravenous infusions (i.e. 9, 27 and 90mg Fe/kg/week). Signs of toxicity due to iron overload were apparent in adults in the 27 and 90mg Fe/kg/week groups. Indices of fertility and early embryonic

development were unaffected. The NOAEL for fertility and early embryonic development was considered to be 90mg Fe/kg/week.

GLP compliant embryo-fetal toxicity studies were performed in the rat (doses of 3, 9 and 30mg Fe/kg/day) and rabbit (doses of 4.5, 9, 13.5 and 18mg Fe/kg/day). Clear signs of maternal toxicity were seen in the rats at 30mg and 9mg Fe/kg/day and in the rabbits at 18 and 13.5mg Fe/kg/day). In the rat study, there were no adverse effects on embryo-fetal survival or growth although a small number of fetuses were found to have thickened/kinked ribs in the 30mg Fe/kg/day group at the detailed skeletal examination, an effect that was considered treatment related. At a dose of 9mg Fe/kg/day, no effects on fetal rib morphology were seen and this was considered to be the NOAEL for embryo-fetal development. In the rabbit study, there was an increase in pre-implantation loss with a resultant reduction in the mean number of implantations and live young in the 18mg Fe/kg/day group. No effects on embryo-fetal survival were seen at the lower doses. Embryo-fetal abnormalities were noted in all treatment groups and consisted of domed cranium (18, 13.5 and 9mg Fe/kg/day) flexed bilateral forepaw/limb (18mg Fe/kg/day), hydrocephaly, incomplete ossification of cranial centres, enlarged fontanel, unossified phalanges and cervical ribs (13.5mg Fe/kg/day). The only effect noted in the 4.5mg Fe/kg/day group was an increased incidence of unossified phalanges.

In a GLP compliant pre- and post-natal development study, female rats were dosed with VIT-45 by 1-hour intravenous infusions from day 6 to 19 after mating, and then on days 1, 4, 7, 10 and 14 of lactation. The dose levels were 3, 9 and 18mg Fe/kg/day. In the F0 females, reduced food intake and weight gain was seen in the 9mg and 18mg Fe/kg/day groups, as well as a dose-related increase in incidence of orange discolouration of tissues noted at necropsy. Female F1 offspring in the 18mg Fe/kg/day group had statistically significant lower body weight gains (12% lower) than controls from days 1 to 10 of age. Subsequent weight gains were comparable with controls. F2 litter parameters and offspring necropsy findings were comparable in all groups. The applicant concludes that the NOAEL for maternal toxicity was 18mg Fe/kg/day and the NOAEL for toxicity to offspring was 9mg Fe/kg/day.

Local tolerance
Local tolerance was examined in rabbits following intravenous, intra-arterial and perivenous VIT-45 administration. In the intravenous and intra-arterial studies, rabbits were dosed with 0.5ml of 50mg Fe/ml VIT-45 (i.e. 25mg Fe), while in the perivenous study rabbits were dosed with 0.2ml of 50mg Fe/ml VIT-45 (i.e. 10mg Fe). In all studies the injection site was on the left ear with a saline injection administered to the contralateral ear as a control. All animals were killed and assessed on the 5th day after a single drug administration. There were no macroscopic or microscopic findings considered to be drug-related.

The haemocompatability of VIT-45 was investigated *in vitro* by incubation of VIT-45 with human blood. No haemolytic or other adverse reaction with plasma was noted.

Other toxicity studies
Antigenicity
An antigenicity study assessed the potential for VIT-45 to cross react with anti-dextran antibodies using passive cutaneous anaphylaxis (PCA) in guinea pigs as the end point. Rabbits were immunised with a dextran conjugate (molecular weight 10000) prepared with bovine serum albumin. Blood samples were collected and various dilutions of serum tested for a PCA response in guinea pigs. Rabbit serum was injected intradermally on the shaven backs of the guinea pigs and three hours later an intravenous injection of dextran in Evan's Blue was made. The sera of rabbits that showed good positive PCA responses were used to examine the response to VIT-45. Challenge with VIT-45 3 hours after injection of rabbit serum showed no PCA response. The applicant concludes that VIT-45 did not cross react with anti-dextran antibodies and that there should be minimal risk of an immunological reaction if VIT-45 were administered to a patient that had previously been sensitised to iron dextran.

Studies on impurities
The applicant has provided a list of the actual metal levels present in the drug product and drug substance. Data have also been provided to show that these metals are adequately controlled to suitable levels in the proposed product.

Ecotoxicity/environmental risk assessment
An environmental risk assessment has been provided and is considered satisfactory. VIT-45 is not considered to represent a risk to the environment.

Assessor's overall conclusions on toxicology
Toxicity seen in the single- and repeat-dose studies is considered to be reflective of iron overload. Iron is reported to be relatively non-toxic as long as it is maintained in storage forms, associated with iron binding proteins such as transferrin or ferritin, principally within the cells of the reticulo-endothelia system. It is only when these mechanisms are saturated and free iron accumulates in parenchymal tissues that tissue damage and toxicity occurs.

In single-dose i.v. infusion studies with 240mg Fe/kg in dogs, there were signs of disturbed liver function (elevated serum transaminases) suggesting that at this dose there was probably exposure of the liver parenchyma to excess iron, resulting in some toxicity.

Repeat-dose (13- and 26-week) toxicity studies in rats and dogs showed clear evidence of toxicity associated with iron overload at dosages of 30 and 90mg Fe/kg/week. In rats, weight gain and food intake was reduced while reductions in red cell parameters were observed in both species. The liver was a target in both species, with alterations being seen in serum enzyme activities. Histological examination revealed widespread iron deposition in a number of tissues and in dogs toxic changes in the liver (perivascular fibrosis and one animal with hepatocyte necrosis at 90mg Fe/kg/week) were noted in the 13-week study. Measurement of tissue iron levels at the end of these studies showed extensive iron accumulation, particularly in the liver, with levels up to 60 times that of control animals recorded at the higher dose level.

In all but one of the repeat intravenous dose studies, the NOAEL was considered to be 9mg Fe/kg/week, and in the remaining study (26-week rat study) the NOAEL was considered to be 3mg Fe/kg/week. These values are below the maximum recommended human dose of 15mg Fe/kg/week. However, the applicant points out that iron replete animals were used in the toxicity studies and these animals would be expected to readily show signs of iron overload. Consequently the toxicity studies do not provide a parallel to the clinical situation, in which patients will be iron deficient and the dose of VIT-45 will be calculated for each patient based on their haemoglobin and total body iron store deficit. This should minimise the risk of iron overload occurring. It may be concluded, therefore, that the safety margins derived from the animal toxicity studies are not relevant to the patient population.

The applicant further argues that as iron from VIT-45 is cleared from the body only very slowly, the toxicity seen in the repeat dose studies may be more closely related to the total dose of iron administered than to the weekly dose. The applicant argues that the maximum expected dose during a clinical course of treatment would be 30mg Fe/kg and that this is clearly substantially less that the total dose of 117mg Fe/kg administered at the NOAEL (9mg Fe/kg/week) in the 13-week studies.

While the non-clinical overview reports that the proposed product may be used chronically/intermittently (in combination with erythropoietin) in patients with chronic renal disease, the applicant has not performed a chronic non-rodent study or carcinogenicity studies. The applicant argues that this is justified as the product is a replacement therapy and these may be exempt from these requirements. Additionally, the breakdown products are simple glucose oligomers, the product did not

show signs of genotoxic potential, and preneoplastic signs were not seen in the repeat-dose studies. It is noteworthy that there have been a number of reports of animal studies in which iron dextran-induced sarcoma following repeat high intramuscular or subcutaneous doses, and two cases of sarcoma after intramuscular injection of iron dextran were reported in humans. The applicant argues that in the animal studies the large doses would have behaved as slowly dissociating depots of iron and this would have allowed considerable local tissue damage, leading to sarcoma formation.

In the rat embryo-fetal development study, the only fetal effect seen was a small number of fetuses with thickened/kinked ribs in the 30mg Fe/kg/day group. The NOAEL for embryo-fetal development was considered to be 9mg Fe/kg/day. In the rabbit embryo-fetal development study there was an increase in pre-implantation loss and a resultant reduction in the mean number of implantations and live young in the 18mg Fe/kg/day group. Additionally, embryo-fetal abnormalities were noted in all treatment groups (domed cranium, flexed bilateral forepaw/limb, hydrocephaly, incomplete ossification of cranial centres, enlarged fontanel, unossified phalanges and cervical ribs). The only effect noted in the low-dose group (4.5mg Fe/kg/day) was an increased incidence of unossified phalanges.

The authors of the embryo-fetal development study reports indicate that parenteral dosing of iron compounds have previously produced similar findings to those seen with VIT-45. The rabbit study author argues that treatment with VIT-45 was associated with an increased incidence of minor skeletal abnormalities, suggesting a slight delay in development of the fetal skeleton compared to controls. The study author concludes that the changes seen at the low-dose (unossified phalanges) are likely to be transitory in nature and should not be considered adverse effects. The applicant concludes that this dose represents the NOAEL for rabbit embryo-fetal toxicity.

Local tolerance studies using intravenous, intra-arterial and perivenous administration revealed no findings of note, and an *in vitro* haemocompatability study using human blood found no haemolytic or other adverse effect of VIT-45 on plasma.

An antigenicity study investigating the potential for VIT-45 to cross react with anti-dextran antibodies found no evidence of a cross reaction, leading the applicant to conclude that the use of VIT-45 in patients sensitised to iron dextran is unlikely to lead to serious immunological reactions.

The preclinical aspects of the SPC are satisfactory. The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacology study programme

Three clinical pharmacology studies were performed with VIT-45. The aim of these studies was to obtain data on:

- The ferrokinetics of VIT-45, iron utilisation and preliminary safety
- Pharmacokinetic and pharmacodynamic (efficacy) properties of VIT-45 after single dose administration in iron deficiency patients
- Pharmacokinetic and pharmacodynamic (efficacy) properties after multiple-dose administration in iron deficiency patients

Summary of clinical pharmacology studies

Phase	Type of Study	Objectives	Number of Patients	Study Number
I/II	PET study on ferrokinetics and RBC iron utilisation	To prove the safety and efficacy of iron (III)-hydroxide dextrin complex (iron dextrinate) by measuring the distribution of ^{52}Fe by PET technique and the incorporation of ^{59}Fe into the RBCs in patients with IDA or renal anaemia.	Total: 6 VIT-45: 6	VIT-IV-CL-001
I/II	Dose-finding, placebo-controlled, blinded	To obtain PD / PK (efficacy) and safety information on ascending single doses of VIT-45 in volunteers with mild IDA.	Total: 32 VIT-45: 24	VIT-IV-CL-02
I/II	Dose-finding, non-controlled	To obtain information on the PD/PK/(efficacy) and safety after multiple doses of VIT-45 in patients with moderate IDA.	Total: 46 VIT-45: 46	VIT-IV-CL-03

Physicochemical and pharmacodynamic properties of VIT-45

A 5% iron m/V solution of VIT-45 is a colloid with spheroidal iron-carbohydrate nanoparticles. Each particle consists of an iron-hydroxide core (iron[III]-hydroxide) and a carbohydrate shell that surrounds and stabilises the core. The chelation of iron(III)-hydroxide with a carbohydrate shell confers to the particles a structure resembling ferritin that is suggested to protect against the toxicity of unbound inorganic ferric iron (iron[III]).

Mechanism of action

VIT-45 is suggested to replenish body iron stores, to reverse iron depletion and iron-deficient erythropoiesis, and to correct iron deficiency.

After i.v. administration, VIT-45 is mainly found in the reticuloendothelial system (RES) of the liver, in the spleen and in the bone marrow. The iron is split off the complex and is efficiently used in the bone marrow for haemoglobin synthesis.

Since the iron is predominantly deposited in the RES, and not in the parenchyma, iron-induced radical-forming lipid peroxydation, which takes place in the parenchyma only, is not triggered by VIT-45. Liver injuries are not expected. The results from a single-dose non-clinical histotoxicological investigation confirms that VIT-45 does not cause any necroses in the liver, and no changes were detected in kidney, adrenal, lung and spleen tissue following VIT-45 administration. Except for the spleen, only a small amount of iron is found in these latter organs, which is due to high iron-complex stability.

Clinically, the main pharmacodynamic effects of VIT-45 will result in transient elevations of serum iron levels, transferring saturation (TfS) and serum ferritin. The increase in serum ferritin levels illustrates the replenishment of the depleted iron stores, which is a well-identified and desired effect of iron therapy. In addition, transiently elevated TfS indicate that iron-binding capacity is almost fully utilised following parenteral iron administration.

Pharmacokinetic properties of VIT-45

Ferrokinetics

Pharmacokinetic and red blood cell (RBC) measurements of $^{52}Fe/^{59}Fe$-labelled VIT-45 following i.v. administration using the PET technique in six patients showed a rapid distribution in the circulation. During the study period of 8 hours, the majority of the injected dose was cleared from the circulation and distributed in the liver, spleen, and bone marrow (study VIT-IV-CL-001). The relative distribution of iron as VIT-45 showed a much higher uptake by the bone marrow in relation to the spleen and liver uptake. Incorporation into RBC increased rapidly during the first 6 to 9 days and was greater in patients with iron deficiency anaemia (IDA: 91-99% after 24 days) than in renal anaemia patients (61-84% after 24 days). Comparing these results with an analogous study of iron sucrose shows that the utilisation in the same patients groups is similar.

Distribution

PK analyses in the two clinical Phase I/II studies using VIT-45 revealed increases in exposure roughly proportional with VIT-45 dose (C_{max} approximately 150µg/mL and 320µg/mL following 500mg and 1,000mg iron doses, respectively).

Metabolism

The carbohydrate part of VIT-45 is metabolised with help of the glycolytic pathway. Degradation products of VIT-45 are iron, glucose, the (α 1-4)-linked glucose dimer maltose, and as oligomers maltotriose and maltotetraose, respectively.

Elimination

In study VIT-IV-CL-001, the terminal $t_{1/2}$ for VIT-45 was calculated to be approximately 16 hours, compared to about 6 hours for iron sucrose.

In studies VIT-IV-CL-02 and VIT-IV-CL-03, VIT-45 demonstrated a mono-exponential elimination pattern with a $t_{1/2}$ in the range of approximately 7 to 18 hours. There was negligible renal elimination.

Drug interactions

No specific drug interactions for VIT-45 have been described.

Pharmacokinetics

Study VIT-IV-CL-001

To obtain data on the ferrokinetics of VIT-45 and incorporation of radio-labelled iron into RBCs (RBC utilisation; pharmacodynamics) in clinical use, a non-controlled, single-centre, open-label Phase I/II trial using the positron emission tomography (PET) technique was conducted in patients with IDA or stable iron-replete renal failure patients with anaemia (VIT-IV-CL-001).

All six patients fulfilled the inclusion criteria with a mean haemoglobin concentrations of 90 to 130 g/L and serum ferritin <30 µg/L (IDA patients) or <200 µg/L (patients with renal anaemia). The higher margin for serum ferritin in patients with renal anaemia is in line with the revised European Best Practice Guidelines for the management of anaemia in patients with chronic renal failure, 2004 (EBPG II Working Group 2004). Clinically these patients with functional iron deficiency show normal or even elevated serum ferritin values despite increased iron demands.

During the study, the patients received a single i.v. injection of 100 mg iron as $^{52}Fe/^{59}Fe$-labelled VIT-45 corresponding to a radiodose of 20MBq. For pharmacokinetic determination of isotope uptake and distribution characteristics, PET scans were performed from zero to 8 hours post-administration in liver, spleen, bone marrow and heart ventricle (for blood activity). For determination of pharmacodynamic properties, incorporation of radio- labelled iron into RBCs was determined in blood samples during a

follow-on period of 24 days. Together with the determination of further parameters on iron status such as Hb, serum iron, total iron-binding capacity (TIBC) and serum ferritin, the results of this study also provided first data for the efficacy of VIT-45 in humans. In addition, a preliminary safety evaluation was performed. Descriptive statistical analysis was performed, including median, mean, and standard deviation for pre- and post-treatment values as well as changes from pre- to post-treatment.

Evaluation of PET images for ferrokinetics of iron administered with VIT-45 showed a rapid distribution in the circulation. During the study period of 8 hours, the majority of the injected dose was cleared from the circulation and distributed in the liver, spleen and bone marrow. By using logarithmic interpolation of the terminal elimination $t_{1/2}$ and molecular weights of iron sucrose and iron dextrin, and from the molecular weight of VIT-45 (~150,000 Da), a terminal $t_{½}$ of about 16 hours for VIT-45 can be calculated. The profile of the relative distribution of VIT-45 indicated a higher uptake by the bone marrow than by the liver and spleen (standardised uptake values of about 60, 27 and 16, respectively). The plasma to bone marrow transfer rate constant was steady, irrespective of the plasma iron concentration, indicating that there was no saturation of the transport system to the bone marrow at this dose level. Slopes of the bone marrow lines were up to about 16 times the slopes of the liver lines. The shorter equilibration time for the liver (25 minutes) indicated a minimal role for the liver in direct distribution of the complex.

In all patients, the utilisation of radio-labelled iron increased rapidly up to Days 6 to 9. Thereafter, utilisation increased at a much slower rate. Patients with IDA showed a RBC incorporation of 91 to 99% after 24 days compared to 61 to 84% for patients with renal anaemia.

Mean (±standard deviation) haemoglobin levels increased from baseline (117.7±10.9 g/L) to Day 16 (126.0±3.6 g/L) and then stabilised for the remainder of the study. A noticeable increase in transferrin saturation (TfS) was measurable on Day 1 (74.18±22.62% versus 17.73±15.25% at baseline), decreasing again during the following days. Serum ferritin levels increased from baseline to Day 3, and then returned to baseline. The increase in serum ferritin levels illustrates the replenishment of the depleted iron stores, a desired effect of iron supplementation treatment.

The dose of 100 mg iron administered i.v. as VIT-45 was considered to be safe and well-tolerated.

Study VIT-IV-CL-02
Study objectives and design:
This Phase I/II study was a single-centre, randomised, double-blind, placebo-controlled, single-dose escalation study. The study objectives were to assess the pharmacology, safety, and tolerability following single i.v. doses of iron as ferric carboxymaltose (VIT-45) at iron doses ranging from 100 to 1,000mg in volunteers with mild IDA.

The pharmacokinetic endpoints were:

- Total serum iron
- Total iron in urine
- Model-independent parameters derived from total iron concentrations in serum and urine (with and without baseline adjustments), e.g. C_{max}, T_{max}, AUC_{0-t}, AUC_{0-24}, AUC_{0-72}, $t_{1/2}$, C_L, $V_{d,area}$, $V_{d,ss}$, MRT for total serum iron and A_e for total iron in urine
- Model-dependent half-lives derived from total serum iron concentrations: α-half-life

The pharmacodynamic endpoints were:
Serum ferritin and transferrin, latent iron binding capacity (LIBC), % TfS_{post}, haemoglobin, reticulocyte count and soluble transferring receptors (sTfR) concentration

In addition, safety parameters were assessed.

Study population and main criteria for inclusion:
The study was conducted in 32 subjects, selected from a pool of volunteers. Male and female Caucasians between 18 and 45 years with mild IDA (90 ≤Hb<120 g/L, women;
90 ≤Hb<130 g/L, men), serum ferritin<20 µg/L, and TfS<16% were eligible for enrolment.

The four dose groups were well-balanced with regards to demographic characteristics. The mean age was 31 years, mean height was 171.1 cm, mean weight was 64.44 kg, and mean body mass index (BMI) was 22 kg/m^2. Most of the included patients were female (N=30; 94%), while only two male patients (6%) participated in the study. Haemoglobin concentrations were between 92 and 119 g/L and serum ferritin was below 10 µg/L in most of the patients and did not exceed 18.3 µg/L. Except for two subjects with a TfS>16%, all patients complied with the inclusion criteria for this study.

Treatment:
Patients were randomised to four different dose groups. Six patients per dose group received VIT-45 and two patients each received placebo. Each patient received a single i.v. administration of VIT-45 or placebo in the fasted state each morning, starting on Day 1. The doses under investigation were 100, 500, 800 and 1,000 mg iron as VIT-45.

The eligibility of the patients for the different dose levels was evaluated according to the patients' potential iron requirement as calculated from haemoglobin levels and body weights using the formula of Ganzoni 1970. To ensure that patients were assigned to a VIT-45 dose level that would not exceed the individually required amount of iron to a relevant extent (<10%), patients were assigned as follows:

Patient assignment to dose levels according to their haemoglobin level at screening and their individual iron requirement°

Patients' Hb level	Potential iron requirement	Randomisation to i.v. dose level of iron as VIT-45
90-130 g/L (males) 90-120 g/L (females)	740-1,796 mg	100 to 800 mg iron or placebo
90-130 g/L (males) 90-120 g/L (females)	* 980-1,796 mg	1,000 mg iron or placebo

Source: Study Report VIT-IV-CL-02, Text Table 3
* Potential iron requirement had to be ≥980 mg for inclusion at the 1,000 mg dose level
° Calculation according to the formula of Ganzoni 1970 [5.4.15]

In the first dose group, patients received a dose of 100mg iron as VIT-45 undiluted within 1 minute as bolus injection. At the three higher dose levels, the injection bolus was diluted to achieve a volume of 250 mL infusion solution using physiological saline. The administered dose was infused at a variable i.v. dose rate, but at constant infusion time and infusion volume, in a superficial vein via an infusion pump. Infusion was stopped at 15 minutes post dose.

Pharmacokinetic and pharmacodynamic measurements:
Blood samples for determination of concentrations of serum iron (pre-dose) or total serum iron (post-dose), serum ferritin, transferrin and TfS (pre-dose) and unsaturated iron binding capacity (UIBC post-dose) were collected at 8:00, 12:00, 16:00, 20:00 and 24:00 hours in the morning prior to Day 1 (i.e. on Day –1), and within 10 minutes before and at several time points after the dose (28x). The last sample was taken at 168 hours after the dose (i.e. on Day 8). Urine samples for determination of total iron concentrations were obtained 24 hours prior to dosing and at the 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hour post-dose collection intervals.

Inductively coupled plasma (ICP) Optical Emission Spectrometry applying validated methods was used for the determination of total iron in serum and urine samples. Serum ferritin was assessed by a validated

enzyme-immunoassay on an Abbott Axsym instrument using Abbott assay kits. Transferrin was assayed by a validated immuno-turbimetric assay method on a Roche Hitachi Modular instrument using Roche Hitachi assay kits. UIBC in serum was determined according to a validated analytical method. TfS in serum was calculated from serum iron and transferrin concentrations before dose administration and from UIBC and transferrin concentrations after administration.

Pharmacokinetic variables:
Based on the serum and urine concentration data of total iron at post dose, model-independent pharmacokinetic parameters were determined for all patients from the different dose levels, but not for patients randomised to placebo. Parameters were derived from individual concentration profiles either with or without correction for different individual baseline levels.

Pharmacodynamic variables:
Serum ferritin and transferrin concentrations, TfS and UIBC in serum were assessed as pharmacodynamic variables. In addition, haemoglobin levels, reticulocyte count and sTfR concentrations were also to be considered as pharmacodynamic variables.

Pharmacodynamic Results:
Mean serum ferritin levels started to rise at about 6 to 12 hours after dosing in all actively treated patient groups, reaching highest serum concentrations between 48 hours (100 mg iron asVIT-45) and 120 hours (800 and 1,000 mg iron as VIT-45) after dosing. After peak concentrations were reached, serum levels decreased but were still elevated at the end of the observation period. This increase in serum ferritin concentrations was dose-dependent, but not strictly dose-linear. No changes were observed after placebo administration. Maximum serum ferritin concentrations after dosing and the respective pre-dose concentrations are summarised below.

Pre-dose and maximum serum ferritin concentrations after administration of VIT-45

		Treatment / Iron as VIT-45 (mg)				
Serum ferritin	**Statistics**	**Placebo**	**100**	**500**	**800**	**1,000**
Serum ferritin, pre-dose concentration (ng/mL)	Mean (SD)	5.8 (6.0)	2.1 (1.5)	5.2 (6.6)	4.0 (2.5)	3.1 (2.0)
Serum ferritin, max. concentration (ng/mL)	Mean (SD)	6.8 (4.4)	48.5 (20.0)	423 (400)	488 (165)	652 (218)
Time of peak (h)	-	24	48	96	120	120

Source: Study Report VIT-IV-CL-02, Text Table 10
max. = maximum; SD = standard deviation

Transferrin levels showed a trend towards lower concentrations after i.v. administration of different doses of VIT-45, compared to pre-dose levels. These changes were similarly seen in the placebo group. The overall decline in all treatment groups was small and changes were not clinically relevant and without clear relationship toward treatment.

TfR concentrations showed minor fluctuations after i.v. application of VIT-45 and no clear trend was observed.

Administration of VIT-45 led to a steep decline in UIBC, in particular after the 800 and 1,000 mg doses. Iron binding capacity was only about 14% after 24 hours in the 100 mg group and <5% at 36 hours after dosing in the 800 and 1,000 mg group. Percentage of UIBC reached pre-dose values in the 100 mg group only at the end of the observation period, but remained lower in the 800 and 1,000 mg groups.

The percentage of TfS was clearly increased following VIT-45 injection, while no changes were observed after placebo dosing. The maximum changes from baseline after 24 to 36 hours of treatment are summarised below.

Maximum mean changes in transferrin saturation from baseline at 24 to 36 hours after administration of VIT-45

TfS	Treatment / Iron as VIT-45 (mg)			
	100	**500**	**800**	**1,000**
TfS, max. mean changes (±SD) in %	+63 (±22)	+76 (±8)	+63 (±5)	+71 (±6)

Source: Study Report VIT-IV-CL-02
max. = maximum; SD = standard deviation

At these assessment points, TfS in the 100 mg dose group was about 86% and was essentially complete in the three higher dose groups (>95%). Approximately one-third (500 mg iron as VIT-45) to one-half (800 and 1,000 mg iron as VIT-45) of the protein was still utilised for iron binding at the end of the observation period.

Haemoglobin concentrations at screening were similar in the placebo group (94 to 125 g/L) compared to those in the pooled VIT-45 groups (90 to 125 g/L). Individual values after dosing were similar to pre-dose figures, tending to be somewhat lower than at pre-dose assessment. Haemoglobin levels after treatment ranged between 99 and 130 g/L (placebo) and 88 and 137 g/L for pooled VIT-45 groups.

Reticulocyte counts showed a clear treatment-related increase in VIT-45-treated patients 8 days after dosing (i.e. at the post-study visit), whereas no changes were seen after placebo administration. Highest individual values were obtained on Day 8, showing increases up to 54% in the 500 mg group. Mean reticulocyte counts in actively treated patient groups were between 24 and 35% at the post study visit compared to 12% in the placebo group.

Pharmacokinetic Results:
All 32 patients completed the study. In most patients, total serum iron concentrations were below the quantification limit at baseline assessment. Following VIT-45 dosing, a rapid, dose-dependent increase in (total) serum iron levels was seen. The highest mean serum concentrations were reached immediately after the bolus injection of 100 mg iron as VIT-45 or at 15 minutes (500 mg iron as VIT-45) and at 30 minutes (800 and 1,000 mg iron as VIT-45) after start of the infusion. As expected, no changes were observed in the placebo group. Mean maximum concentrations were between 36.9±4.4 µg/mL after 100 mg and 317.9±42.3 µg/mL after 1,000 mg VIT-45. After peak concentrations were reached, the mean concentration-time curves constantly declined.

Concentrations of total iron in urine were below detection levels for most of the patients after VIT-45 application, except for two patients in the 800 mg iron group and four patients in the 1,000 mg iron group showing measurable urine concentrations during the 0-4-hour sample interval, but not at later time intervals.

Pre-dose concentrations of serum iron were similar between all treatment groups. No major change was noted after placebo administration. Following administration of VIT-45 at doses of 100 to 1,000 mg iron, a rapid dose-dependent increase in total serum iron concentrations was observed. After this initial phase, the mean concentration-time profiles continuously declined until approximately 48 to 96 hours after dosing. The late phase (until 168 hours post dose) was characterised by a slow decrease with serum iron concentrations approaching baseline.

Maximal total serum iron concentrations increased with increasing doses. While maximum concentrations were approximately doubled in the 1,000 mg vs the 500 mg iron dose group, the 800 mg iron dose deviated from a dose-linear increase. Maximal concentrations were usually reached rapidly following injection or infusion of VIT-45. However, increasing VIT-45 doses led to a shift of T_{max} that was approximately 1 hour or longer at 800 to 1,000 mg.

Using non-compartmental analysis methods, the average serum exposure to iron, as expressed by C_{max} and AUC, increased with incremental doses, but did not occur in an exactly dose-proportional manner. In particular, AUC values were higher with increasing doses than expected from dose linearity. However, the deviation from dose linearity was mainly driven by a total of three patients in the 800 and 1,000 mg groups. MRT of iron complex particles was calculated to be less than 24 hours on average, and study drug was cleared from serum with a $t_{1/2}$ in the range from 10 to 18 hours. Total body clearance was between 2.6 and 3.4 mL/min and volumes of distribution at steady state and during elimination were similar, ranging from 2.6 to 4.7 L and 2.4 to 5.2 L, respectively.

Pharmacokinetic parameters of total serum iron are summarised below.

Pharmacokinetic parameters of total serum iron (168 h post-dose, non-compartmental analysis)

Parameter: serum iron	Statistics	Treatment / Iron as VIT-45 (mg)			
		100	500	800	1,000
C_{max} (µg/mL)	N	6	6	6	6
	Mean (±SD)	37 (3.6)	157 (19.4)	324 (63.8)	333 (42.1)
	G Mean (±GSD)	37 (1.10)	156 (1.12)	319 (1.23)	331 (1.13)
T_{max} (h)	N	6	6	6	6
	Mean (±SD)	0.26 (0.29)	0.34 (0.12)	0.99 (0.62)	1.21 (0.56)
	Median	0.08	0.27	0.88	1.26
AUC_{0-t} (µgxh/mL)	N	6	6	6	6
	Mean (±SD)	432 (75)	2,470 (407)	5,306 (1,098)	6,455 (1,558)
	G Mean (±GSD)	426 (1.20)	2,443 (1.18)	5,218 (1.22)	6,311 (1.26)
AUC_{0-24} (µgxh/mL)	N	6	6	6	6
	Mean (±SD)	338 (61)	1,851(245)	4,015 (752)	4,751 (793)
	G Mean (±GSD)	333 (1.21)	1,838 (1.14)	3,958 (1.20)	4,699 (1.18)
AUC_{0-72} (µgxh/mL)	N	6	6	6	6
	Mean (±SD)	432 (75)	2,365 (332)	5,252 (1,042)	6,415 (1,516)
	G Mean (±GSD)	426 (1.20)	2,345 (1.15)	5,171 (1.21)	6,277 (1.25)
$T_{1/2}$ (h)	N	6	6	6	6
	Mean (±SD)	19.0 (7.78)	16.4 (5.51)	12.3 (2.71)	10.5 (2.58)
	G Mean (±GSD)	17.7 (1.52)	15.5 (1.44)	12.1 (1.23)	10.3 (1.29)
CL (mL/min)	N	6	6	6	6
	Mean (±SD)	3.36 (0.79)	3.37 (0.53)	2.56 (0.48)	2.67 (0.55)
	G Mean (±GSD)	3.28 (1.26)	3.33 (1.18)	2.52 (1.21)	2.61 (1.25)
$V_{d,ss}$ (mL)	N	6	6	6	6
	Mean (±SD)	4,701 (845)	4,221 (1,151)	2,607 (425)	2,644 (366)
	G Mean (±GSD)	4,635 (1.20)	4,073 (1.35)	2,578 (1.18)	2,624 (1.15)
MRT (h)	N	6	6	6	6
	Mean (±SD)	24.2 (6.16)	21.5 (7.07)	17.2 (1.84)	17.0 (2.55)
	G Mean (±GSD)	23.6 (1.26)	20.5 (1.41)	17.1 (1.11)	16.9 (1.17)

Source: Study Report VIT-IV-CL-02, Text Table 7
N = Statistical number of observation; SD = Standard deviation; G Mean = Geometric Mean; GSD = Geometric SD

The pharmacokinetic profiles used for the optimal regression fit of the elimination phase were truncated at 24 hours in the 100 mg group and at 72 hours in the 500, 800 and 1,000 mg groups, as this served to better characterise the pharmacokinetic profile of total serum iron after i.v. injection/infusion, thereby excluding a “new” post treatment baseline after replenishment of the iron stores. This baseline is characterised by different kinetic processes between protein-bound iron (i.e. via transferrin) and tissues of utilisation such as the RES. With this approach, the average plasma exposure was similar across all treatments when compared to the values based on censored data (i.e. censoring occurred after the first value was below LOQ), and estimates of $t_{1/2}$, MRT, and volumes of distribution at equilibrium and during elimination ($V_{d,ss}$ and $V_{d,area}$) were slightly lower when compared to non-truncated data.

Practically, this approach shows that the majority of administered iron complex was utilised or excreted within 24 hours after a low dose of 100 mg iron as VIT-45 and within 72 hours after higher doses of 500-1,000 mg iron as VIT-45, respectively.

Pharmacokinetic parameters of total serum iron (72 hours post-dose, non-compartmental analysis)

Parameter: Serum iron	Statistics	Treatment / Iron as VIT-45 (mg)			
		100	500	800	1,000
C_{max} (µg/mL)	N	6	6	6	6
	Mean (±SD)	37 (3.6)	157 (19.4)	324 (63.8)	333 (42.1)
	G Mean (±GSD)	37 (1.10)	156 (1.12)	319 (1.23)	331 (1.13)
T_{max} (h)	N	6	6	6	6
	Mean (±SD)	0.26 (0.29)	0.34 (0.12)	0.99 (0.62)	1.21 (0.56)
	Median	0.08	0.27	0.88	1.26
AUC_{0-24} (µgxh/mL)	N	6	6	6	6
	Mean (±SD)	338 (61)	1,851 (245)	4,015 (752)	4,751 (793)
	G Mean (±GSD)	333 (1.21)	1,838 (1.14)	3,958 (1.20)	4,699 (1.18)
AUC_{0-72} (µgxh/mL)	N	-[a]	6	6	6
	Mean (±SD)	-	2,365 (332)	5,252 (1042)	6,415 (1516)
	G Mean (±GSD)	-	2,346 (1.15)	5,171 (1.21)	6,277 (1.25)
$T_{1/2}$ (h)	N	6	6	6	6
	Mean (±SD)	7.4 (0.61)	12.3 (2.14)	10.3 (1.20)	9.6 (1.65)
	G Mean (±GSD)	7.4 (1.09)	12.1 (1.20)	10.3 (1.13)	9.5 (1.20)
CL (mL/min)	N	6	6	6	6
	Mean (±SD)	4.41 (0.92)	3.50 (0.50)	2.59 (0.46)	2.68 (0.55)
	G Mean (±GSD)	4.33 (1.22)	3.47 (1.15)	2.55 (1.21)	2.63 (1.25)
$V_{d,ss}$ (mL)	N	6	6	6	6
	Mean (±SD)	2,912 (495)	3,472 (627)	2,476 (457)	2,596 (355)
	G Mean (±GSD)	2,879 (1.18)	3,421 (1.21)	2,442 (1.20)	2,576 (1.14)
MRT (h)	N	6	6	6	6
	Mean (±SD)	11.2 (1.15)	16.8 (2.66)	16.1 (1.05	16.6 (2.41)
	G Mean (±GSD)	11.2 (1.11)	16.6 (1.18)	16.1 (1.07)	16.5 (1.16)

Source: Study Report VIT-IV-CL-02, Text Table 8
N = Statistical number of observation; SD = Standard deviation; G Mean = Geometric Mean; GSD = Geometric SD; [a] PK profile was truncated at 24 hours post-dose

Assessment of dose linearity of VIT-45, dose- and b.w.-adjusted total iron pharmacokinetic parameters revealed a significant deviation for AUC_{0-t} ($p<0.001$) and a borderline significance for C_{max} ($p=0.077$). This deviation was mainly due to the results from the 800 mg group, as values were higher than expected from a dose-linear increase, while the increase in C_{max} for the 100-, 500-, and 1,000 mg groups was compatible with linearity. Regarding AUC, deviation from dose linearity was mainly due to three outlying patients in the higher dose groups.

Renal elimination of iron was negligibly small and did not contribute to the overall elimination of VIT-45. The percentage of A_e was about 0.0005% for the 800- and 1,000 mg groups.

ANOVA for the assessment of dose linearity of VIT-45

Serum iron (mg/kg)	Source	Estimate [90% CI]
C_{max} (µg/mL)*	LS means 100 mg	3.12 [3.03; 3.21]
	LS means 500 mg	3.05 [2.96; 3.14]
	LS means 800 mg	3.25 [3.15; 3.34]
	LS means 1,000 mg	3.07 [2.98; 3.17]
AUC_{0-t} (µgxh/mL)**	LS means 100 mg	5.55 [5.43; 5.68]
	LS means 500 mg	5.80 [5.68; 5.92]
	LS means 800 mg	6.04 [5.92; 6.17]
	LS means 1,000 mg	6.02 [5.90; 6.14]

Source: Study Report VIT-IV-CL-02, Text Table 9
* p=0.0768; ** p<0.001; LS= Least square; CI=Confidence Interval

Pharmacodynamic Conclusions:
A dose-dependent, but not dose-linear, increase in serum ferritin concentrations was observed in the actively treated patient groups compared to placebo with peak levels approximately 48 to 120 hours post dose. Treatment with different doses of VIT-45 generally did not have significant impact on serum transferrin levels or sTfR concentrations over the observation period. Changes were small and without clear relationship to treatment or dose level.

Iron binding capacity was almost fully utilised after doses of 500, 800 and 1,000 mg iron as VIT-45, as indicated by an unsaturated iron binding capacity (UIBC) <5% or a TfS>95%, respectively. The effect began shortly after infusion of VIT-45 and lasted for 2 to 3 days. Only at the dose level of 100 mg iron as VIT-45 the iron binding capacity of the serum was not fully saturated. At the end of the observation period (Day 8), approximately one-third (500 mg iron as VIT-45) to one-half (800 and 1,000 mg iron as VIT-45) of the protein was still utilised for iron binding, which can be considered a normal finding in a sufficiently treated anaemic patient.

Haemoglobin levels did not significantly change during the 8-day observation period, if the baseline values are compared to the outcome at the post-study visit. In contrast, the mean haemoglobin levels during the clinical part of the study rather tended to be slightly lower compared with the pre-dose assessment. However, any improvement in haemoglobin levels after such a short time was not to be expected in anaemic patients and would have required a longer follow-up. In addition, the amount of blood required for the investigations in this study could have led to a slight decrease in haemoglobin.

Reticulocyte counts clearly increased in actively treated patients 8 days after dosing with VIT-45. This pharmacodynamic effect indicates activation of the haematopoietic system in anaemic patients after the supplementation treatment with iron.

Pharmacokinetic Conclusions:
Infusion or injection of VIT-45 led to a rapid increase in (total) serum iron levels in 24 anaemic patients. However, increasing VIT-45 doses led to a shift of T_{max} that was approximately 1 hour or longer at doses of 800 to 1,000 mg iron as VIT-45. This considerably exceeded the end of the infusion and may be explained by differences of individual redistribution from initial sites of uptake, such as liver, spleen and bone marrow.

C_{max} and AUC of iron serum exposure increased with ascending doses in a non-proportional manner, in particular regarding AUC. Based on non-compartmental analysis, MRT was less than 24 hours on average and study drug was cleared from serum with a $t_{1/2}$ of 10-18 hours. Total body clearance was between 2.6 to 3.4 mL/min. The volumes of distribution at steady state and during elimination were similar (2.4-5.2 L).

Using truncated pharmacokinetic profiles for optimal regression fit, the overall plasma exposure the average plasma exposure was similar across all treatments when compared to the values based on censored data (i.e. censoring occurred after the first value was below LOQ), and estimates for $t_{1/2}$ (7.4-12.1 hours), MRT (11.2-16.6 hours), $V_{d,ss}$ and $V_{d,area}$ were slightly lower as compared to non-truncated data.

The elimination pattern for VIT-45 appeared to be mono-exponential. Two elimination phases, as required by the two-compartment model, could not be separated if the post treatment baseline was excluded from consideration. Therefore, a calculation by the two-compartment model was not deemed meaningful for the characterisation of the pharmacokinetic profile of VIT-45.

Renal elimination of iron was negligibly small and did not contribute to the overall elimination of VIT-45. However, the assay methodology did not permit exact quantification of low urine concentrations of total iron, thus the true amount and renal clearance of total iron could not be reliably evaluated.

Study VIT-IV-CL-03
Study Objectives and Design:
This Phase I/II study is a multi-centre, open-label, uncontrolled, multi-dose study. The study objectives were to evaluate safety and tolerability of VIT-45 following i.v. administration of 500 mg (Cohort 1) or 1,000 mg (Cohort 2) iron as VIT-45 given in multiple doses once weekly for up to 4 weeks (Cohort 1) or 2 weeks (Cohort 2) in patients with moderate stable iron deficiency anaemia secondary to gastrointestinal disorders.

The main endpoints of the study were:

- To evaluate safety and tolerability
- To provide preliminary information on the therapeutic benefit of VIT-45, based on the time-course and magnitude of changes in haemoglobin and iron storage parameters
- To provide pharmacokinetic data on iron levels
- To provide preliminary data on inter-patient variability with regards to the safety, iron status and pharmacokinetic parameters assessed

Study population and main criteria for inclusion:
Recruitment continued until approximately 18 patients started therapy in order to include 12 patients in each cohort. Male and female patients aged between 18 and 60 years with moderate IDA secondary to a gastrointestinal (GI) disorder and a calculated total iron requirement of at least 1,000 mg were eligible for enrolment. At least 50% of patients in each cohort should require ≥1,500 mg total iron. Patients could be out-patients or in-patients.

Patients were considered completers if they received all scheduled doses of VIT-45 (as calculated from total iron requirement), or if, as measured on Days 7, 14, or 21, their haemoglobin levels returned to normal range (NR). All enrolled patients to whom at least one dose of study medication was administered were considered for analysis (full-analysis set). The safety set included all enrolled patients.

A total of 73 patients were screened. Of these, 46 patients fulfilled the criteria for inclusion and were enrolled into the study. Twenty patients were enrolled into Cohort 1, 14 of them completed the study. In Cohort 2, a total of 26 patients were enrolled and 19 patients completed the study.

The two cohorts were very similar with regards to baseline characteristics. The mean age was 42.9 years, mean height was 168.4 cm, and mean weight was 71.6 kg. Thirty-six females were included, 15 in Cohort 1 and 21 in Cohort 2, while only 10 men in total were enrolled (five per cohort). All patients reported a medical history in the abdominal and GI system, as expected for this patient population. Serum iron, haemoglobin and serum ferritin levels were below NR in both cohorts. TfS levels were below NR and transferrin levels were generally within or above the limits of NR, as expected for patients with IDA.

Treatment:
Treatment began with the first dose of VIT-45 (Day 1). In Cohort 1, all patients received 500 mg iron as VIT-45 i.v. infusions, once weekly for up to 4 weeks. In Cohort 2, all patients received 1,000 mg iron as VIT-45, once weekly for up to 2 weeks. In both cohorts, the last dose could be lower than the preceding ones depending on the patients' total iron requirements, as calculated using the formula of Ganzoni 1970 [5.4.15]. VIT-45 was infused i.v. over 15 minutes into a peripheral vein at a total volume of 250 mL.

Pharmacodynamic and pharmacokinetic measurements:
A baseline assessment was performed up to 3 days prior to treatment. At 3 and 6 days after the last dose (Days 4 and 7), iron status, pharmacokinetic parameters and safety were evaluated. Blood for pharmacokinetic parameter analysis was additionally taken immediately pre-dose and at 15 minutes, 1, 2, 4, and 6 hours after each study medication administration. Post-treatment follow-up assessments of safety, pharmacokinetic and iron status were performed 2 weeks (±2 days) and 4 weeks (±2 days) after the last dose of VIT-45.

Parameters assessed were serum iron, serum ferritin, transferrin and TfS. UIBC, representing the amount of unsaturated transferrin in serum, was measured in order to determine TfS. Hb was measured as part of the haematology panel. Total serum iron was determined using a validated analytical method using ICP emission spectrometry. Serum ferritin was determined using a validated enzyme-immunoassay on an Abbott Axysm instrument using Abbott assay kits. Transferrin was assayed by a validated immuno-turbimetric assay method on a Roche Hitachi Modular instrument. UIBC was measured using a validated analytical method (Roche Diagnostics).

Pharmacodynamic Results:
At baseline, almost all patients had haemoglobin levels below the lower limit of the NR. At all timepoints from Day 7 onwards, mean haemoglobin levels were elevated compared to baseline in both cohorts. By Day 14, 27% and 44% of patients, respectively, in Cohorts 1 and 2 had achieved a ≥20 g/L increase in haemoglobin on at least one occasion. Mean haemoglobin levels showed a steady increase during the study and the follow-up phase, and were 32 g/L and 33 g/L above baseline in Cohorts 1 and 2, respectively, at the 4-week follow-up visit. At this timepoint, 37% and 48% of patients, respectively, had achieved normal haemoglobin levels, and 75% and 73%, respectively, in Cohorts 1 and 2 had achieved a ≥20 g/L increase in haemoglobin on at least one occasion. Over 97% of patients showed a medicinally meaningful response in terms of haemoglobin level increase.

Haemoglobin levels at baseline and over time

		Hb (g/L)	
		Cohort 1	**Cohort 2**
Baseline	N Mean [95% CI]	20 87.1 [82.5; 91.7]	26 87.0 [80.1; 94.0]
Day 4	N Mean [95% CI]	20 90.1 [84.3; 95.8]	26 88.5 [82.2; 94.8]
Day 7	N Mean [95% CI]	20 91.8 [87.8; 95.8]	26 93.8 [88.5; 99.2]
Day 14	N Mean [95% CI]	15 99.5 [94.7; 104.3]	18 101.8 [97.2; 106.3]
Day 21	N Mean [95% CI]	15 107.9 [104.8; 111.1]	-
Day 28	N Mean [95% CI]	6 118.3 [106.7; 129.9]	-
2-week follow-up	N Mean [95% CI]	11 116.9 [111.7; 122.1]	25 111.3 [108.6; 113.9]
4-week follow-up	N Mean [95% CI]	19 119.6 [114.4; 124.7]	25 121.2 [117.2; 125.2]

Source: Study Report VIT-IV-CL-03, Text Table 4
NR=140-180 g/L for males, 120-160 g/L for females

Except for one patient, serum ferritin levels were below the lower limit of NR at baseline. In both cohorts, serum ferritin increased rapidly from baseline and was significantly elevated at all time points from Day 4 onwards. Mean serum ferritin values were within the target range of 100-500 μg/L from Day 4 until Day 28 or the 2-week follow-up visit. All patients responded to treatment in terms of serum ferritin. At the 4-week follow-up visit, mean serum ferritin levels were within NR but below the target range. The patients in Cohort 2 showed higher values of serum ferritin during the first 2 weeks of treatment, and many patients in Cohort 2 had serum ferritin values above the upper limit of the normal range during this time.

Serum ferritin levels at baseline and over time

		Serum ferritin (µg/L)	
		Cohort 1	**Cohort 2**
Baseline	N Mean [95% CI]	20 4.9 [0.5; 9.4]	26 3.3 [2.2; 4.4]
Day 4	N Mean [95% CI]	20 238.2 [190.8; 285.5]	26 460.3 [413.0; 507.7]
Day 7	N Mean [95% CI]	20 167.5 [127.1; 207.8]	26 487.2 [412.5; 561.8]
Day 14	N Mean [95% CI]	14 183.2 [125.4; 240.9]	18 404.5 [330.9; 478.0]
Day 21	N Mean [95% CI]	15 224.7 [170.8; 278.6]	-
Day 28	N Mean [95% CI]	5 147.2 [61.5; 232.9]	-
2-week follow-up	N Mean [95% CI]	11 128.2 [81.3; 175.1]	25 209.9 [173.8; 246.1]
4-week follow-up	N Mean [95% CI]	19 61.7 [36.7; 86.7]	25 98.7 [80.4; 116.9]

Source: Study Report VIT-IV-CL-03, Text Table 5
NR=20-500 µg/L

At screening, all but one patient had TfS values below the lower limit of NR (i.e. <16%). In both cohorts, serum TfS increased after each VIT-45 infusion, before reducing again prior to the next infusion. This pattern was observed after each VIT-45 infusion, although the greatest increase occurred after the first infusion. At the 4-week follow-up visit, mean serum TfS values were 41% and 39.1% for Cohort 1 and 2, respectively (NR: 16-45%).

Pharmacokinetic Results:
At pre-dose on Day 1, mean serum iron levels were 1.03 µg/mL in Cohort 1 and 0.94 µg/mL in Cohort 2. Following i.v. infusion on Day 1, a rapid increase in serum iron levels was observed being at maximum 1 hour after the dose (Cohort 1: 154.1 µg/mL, Cohort 2: 306.4 µg/mL). Mean serum iron levels in Cohort 2 were almost double compared to those in Cohort 1, reflecting the larger doses given in this group (1,000 mg vs 500 mg iron as VIT-45 in Cohort 1). Levels slowly decreased and were back to baseline levels by Day 7 (0.94 µg/mL, both cohorts).

On Day 8, a similar pattern was seen for total serum iron, with a rapid increase in total serum iron that was highest at the first post-dose sampling point and slowly reduced up to the 6-hour time-point. In Cohort 2, the magnitude of the elevation of total serum iron following the second infusion was less than after the first infusion, reflecting the fact that many patients received less than 1000 mg doses at this time-point (most patients had iron deficit <2000 mg). By Day 11, mean total serum iron levels were 1.0 µg/mL and 1.1 µg/mL in Cohorts 1 and 2, respectively, and had returned to baseline levels by Day 4.

On Days 15 and 22, similar patterns and time-courses of serum iron levels increasing to maximum doses and returning to baseline levels were observed for Cohort 1. Increases in serum iron levels were less pronounced after the last dose, as lower doses were applied according to the patients' requirements.

At the 2- and 4-week follow-up visits, both cohorts showed serum iron levels similar to pre-dose values.

Pharmacokinetic conclusion:
Following VIT-45 infusion, total serum iron in blood was significantly above NR for the first 6 hours, as expected for i.v. iron supplementation. Following the first infusion on Day 1, the increase in Cohort 2 was almost twice that in Cohort 1, reflecting the larger (i.e. two-fold) dose applied in this group. Serum iron levels returned to baseline within 4 to 7 days after infusion. This pattern was similarly observed for the following doses given. At all times, serum iron levels immediately prior to the next dosing stayed within the NR and did not increase with repeated infusions. Thus, administration of VIT-45 did not result in accumulation of serum iron.

Pharmacodynamic Conclusion:
Most pharmacodynamic parameters were below NR at baseline, as expected for a patient population experiencing IDA. Analysed parameters showed a trend towards normalisation during the treatment period. Haemoglobin levels continued to improve during the follow-up period, indicating the long-term benefit of VIT-45 as iron supplementation. Over 97% of the patients showed a medicinally meaningful benefit from VIT-45 therapy with regards to haemoglobin levels. 36.8% of patients in Cohort 1, and 48% of patients in Cohort 2 achieved normal haemoglobin levels at the 4-week follow-up visit.

Serum ferritin and TfS values showed that iron stores were successfully filled up during study participation. Mean serum ferritin levels of the treated patients were above normal range during the study participation and in the target range (100-500 µg/L) at all time points, except the 4-week follow-up visit.

Conclusions:
Pharmacokinetic evaluation of VIT-45 using the PET technique showed a rapid distribution in the circulation. During the study period of 8 hours, the majority of the injected dose was cleared from the circulation and distributed in the liver, spleen, and bone marrow. The relative distribution of iron as VIT-45 showed a much higher uptake by the bone marrow in relation to the spleen and liver. Uptake of VIT-45 by the RES of spleen and liver (target tissue) reflects its safety. Incorporation of radio-iron into RBCs increased rapidly during the first 6 to 9 days, indicating the potential efficacy of VIT-45 as an iron replacement treatment. After 24 days, iron utilisation was greater in IDA (91 - 99%) than in patients with renal anaemia (61-84%). The transient increase in serum ferritin levels illustrated the replenishment of the depleted iron stores. Parenteral iron (100 mg) administered as VIT-45 was well-tolerated.

Pharmacokinetic evaluation has shown that VIT-45 was distributed in the liver, spleen, and bone marrow. RBC utilisation increased rapidly during the first 6 to 9 days. The distribution volume of iron polymaltose complexes almost corresponds to that of plasma.

The iron is rapidly cleared from the plasma, the terminal half-life ranged from 7 to 12 hours, the mean residence time from 11 to 18 hours. There was negligible renal elimination. No accumulation of iron with repeated study drug administration was observed. The carbohydrate part of VIT-45 is metabolised by means of the glycolytic pathway.

The clinical studies performed with VIT-45 have demonstrated that it is an effective and safe ferric carboxymaltose complex for delivery of iron to target tissues in the treatment of patients with iron deficiency. No significant new or unexpected safety concerns were found during the clinical development.

CLINICAL EFFICACY

Overview of Efficacy

Introduction
The overall objective of the clinical programme was to establish the efficacy and safety of VIT-45 for the intended labelling claim treatment of patients with iron deficiency.

Overview of clinical studies on safety and efficacy of VIT-45

	Diagnosis	Patients (N) analysed for efficacy (PP analysis set)[a]		Patients (N) analysed for safety (Safety set)	
	IDA associated with	Treatment	Comparator	Treatment	Comparator
Study 53214 [5.3.5.2.1]	Chronic renal failure	VIT-45: 147	-	VIT-45: 163	-
VIT-IV-CL-015 [5.3.5.1.1]	Chronic renal failure	VIT-45: 97	Venofer®: 86	VIT-45: 119	Venofer®: 118
VIT-IV-CL-008 [5.3.5.1.2]	IBD	VIT-45: 111	Ferrous sulphate: 49	VIT-45: 136	Ferrous sulphate: 60
VIT-IV-CL-009 [5.3.5.1.3]	Post-partum	VIT-45: 179	Ferrous sulphate: 89	VIT-45: 227	Ferrous sulphate: 117
1VIT03001 [5.3.5.1.4]	Post-partum	VIT-45: 162	Ferrous sulphate: 150	VIT-45: 174	Ferrous sulphate: 178

[a] 'Evaluable population' in study 1VIT03001

Study 53214 [5.3.5.2.1] was considered a pilot study and differed from the other studies as the primary objective of this study was to evaluate the safety of intravenous VIT-45 therapy. The secondary objective was to assess the clinical response to intravenous VIT-45 therapy in terms of the correction of iron deficiency and Hb concentration in patients on haemodialysis with IDA. In the other studies the primary objective was the evaluation of clinical response, whereas safety was defined as a secondary objective.

Relevant Features of the Patient Populations

Demographic features for studies conducted in patients on haemodialysis with IDA (Study 53214 [5.3.5.2.1] and Study VIT-IV-CL-015 [5.3.5.1.1]) and in patients with IDA secondary to IBD (VIT-IC-CL-008 [5.3.5.1.2]) were comparable. The mean age of the patients included in these clinical studies, in which efficacy parameters were evaluated, was between 40.7 and 52.6 years. The youngest patients included were between 18 and 22 years in the individual studies, whereas the oldest patients were between 65 and 80 years of age.

In Study 53214, patients between the age of 18 and 65 years were eligible, whereas in the controlled efficacy and safety studies VIT-IV-CL-015 and VIT-IV-CL-008 adult patients up to the age of 80 years were allowed for inclusion. The proportion of patients who were older than 65 years was 18.1% and 9.5%, respectively, in these studies. Thus elderly patients were included in these studies.

In the study conducted in women suffering from post-partum anaemia (VIT-IV-CL-009 [5.3.5.1.3] and 1VIT03001 [5.3.5.1.4]) demographic characteristics differed from those in the other studies. The mean age in these studies was 27.6 years (range 18 to 44 years) in study VIT-IV-CL-009 and 26.93 / 26.03 years (range 14.95 - 49.15 years) in study 1VIT3001 in the groups treated with VIT-45 / ferrous sulphate, respectively.

In general, for patients suffering from IDA it can be assumed that the patient population included in these clinical studies in support of the efficacy and safety of VIT-45 reflects the population that is proposed to be treated with VIT-45.

Study Design

Selection of patients:

Patients could be included for participation in the studies if the degree of iron deficiency required replacement treatment with parenteral iron.

A summary of the inclusion criteria with regard to haemoglobin, TfS, or serum ferritin and the range of the individual calculated iron deficit can be found below.

Inclusion criteria for haemoglobin, transferrin saturation and serum ferritin

	Hb, Tfs or serum ferritin inclusion criteria
53214 [5.3.5.2.1]	Hb ≤ 110 g/L and TfS <20% and/or serum ferritin ≤200 µg/L
VIT-IVCL-015 [5.3.5.1.1]	Hb ≤ 115 g/L and TfS <20% and/or serum ferritin<200 µg/L
VIT-IV-CL-008 [5.3.5.1.2]	Hb ≤ 110 g/L and TfS <20% and/or serum ferritin <100 µg/L
VIT-IV-CL-009 [5.3.5.1.3]	Hb ≤ 105 g/L
1VIT03001 [5.3.5.1.4]	Hb ≤ 100 g/L

Iron deficit at baseline

	Calculated iron deficit (range)
53214 [5.3.5.2.1]	933 - 2,169 mg
VIT-IV-CL-015 [5.3.5.1.1]	989 - 2,057 mg
VIT-IV-CL-008 [5.3.5.1.2]	937 - 2,102 mg
VIT-IV-CL-009 [5.3.5.1.3]	720 - 2,062 mg
1VIT03001 [5.3.5.1.4][a]	500 – 2500 mg

[a] For study 1VIT03001 the calculated iron deficit was not given. Therefore the calculated dose of VIT-45 was included in this table.

Thus only IDA patients with a considerable iron deficit were included in the clinical studies conducted in support of the efficacy and safety of VIT-45.

Duration of studies:
In Study 53214 and VIT-IV-CL-015, patients on haemodialysis had a treatment period with a maximum of up to 6 weeks and an observation period for one month after the last dose of study medication. They received 200 mg iron as VIT-45 i.v. at the applicable haemodialysis session. In Study VIT-IV-CL-015 the comparator group received 200 mg iron as Venofer® i.v. (iron-sucrose complex formulation for parenteral use). The dosing frequency was two or three times weekly (depending on the timing of dialysis sessions).

In study VIT-IV-CL-008, conducted in patients with IBD, and in studies VIT-IV-CL-009 and 1VIT03001, conducted in women with post-partum anaemia, VIT-45 was compared to an oral iron preparation (ferrous sulphate). VIT-45 was given once weekly for 1–3 weeks, depending on the individual iron deficit (patients with ≤66 kg b.w. received a minimum dose of 200 mg iron and a maximum dose of 15 mg iron/kg b.w. as VIT-45 on each dosing occasion. Patients with >66 kg b.w. received a dose of 1,000 mg iron as VIT-45 on the first dosing occasion, a minimum dose of 200 mg iron and a maximum dose of 1,000 mg iron as VIT-45 on each subsequent dosing occasion.). In Studies VIT-IV-CL-008 and -009, oral ferrous sulphate capsules 100 mg iron were given twice daily (BID) for 12 weeks. The last visit for all patients was on Week 12. In study 1VIT03001, patients received oral ferrous sulphate tablets 65 mg iron three times daily (TID) for a study period of 6 weeks.

Mean treatment period

	VIT-45	Comparator[a]
53214 [5.3.5.2.1]	15.9 days	-
VIT-IV-CL-015 [5.3.5.1.1]	15.8 days	16.2 days
VIT-IV-CL-008 [5.3.5.1.2]	11.1 days	12 weeks
VIT-IV-CL-009 [5.3.5.1.3]	8.2 days	12 weeks
1VIT03001 [5.3.5.1.4]	not given	6 weeks

[a] Venofer® in study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008, –009, and 1VIT03001

Choice of endpoints:
In all clinical studies the change of the haemoglobin level was evaluated as the primary efficacy endpoint. In Study 53214, treatment responders were defined by an increase of haemoglobin >10g/L from baseline at any point during the study. In Study VIT-IV-CL-015, the percentage of patients reaching an increase in haemoglobin of ≥10 g/L at 4 weeks was defined as the primary efficacy endpoint. In Study VIT-IV-CL-008 and Study VIT-IV-CL-009, the change from baseline levels of haemoglobin to Week 12 was defined as the primary efficacy endpoint, whereas in Study 1VIT03001 the primary endpoint was 'success' defined as number of subjects with an increase in haemoglobin levels of ≥20 g/L anytime between baseline and Week 6 (end of study).
Secondary efficacy endpoints were the serum values of the proteins of iron storage and transport. Levels of serum ferritin and TfS were determined at the scheduled study visits and change from baseline was calculated. Moreover, the haemoglobin values during the course of the study were defined as an additional secondary endpoint.

Additional secondary efficacy endpoints were defined individually for each study. In study 53214, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) were evaluated. In the other studies, the values for MCV, MCH and MCHC were evaluated as well, but were not defined as secondary endpoints.

In study VIT-IV-CL-015, AUC of change from baseline levels of haemoglobin, serum ferritin and TfS were determined, and in study VIT-IV-CL-008, disease-specific parameters (Crohn's Disease Activity Index or Colitis Activity Index) and quality of life (QoL) were analysed. Mean improvement in the QoL was likewise assessed in study 1VIT03001.

Endpoints in clinical studies

	Primary efficacy endpoint	Secondary efficacy endpoints	Secondary response rate (definition of treatment responders)	Additional efficacy criteria
53214 [5.3.5.2.1]	Treatment responders: increase of Hb >10 g/L from baseline at any point during the study	Hb, Tf, SF, TfS, serum iron		MCV, MCH, MCHC
VIT-IV-CL-015 [5.3.5.1.1]	Percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks after baseline	Hb, SF, TfS	Hb (≥110 g/L in patients with a baseline Hb ≤100 g/L or ≥120 g/L in patients with a baseline Hb >100 g/L to ≤115 g/L), serum ferritin (200 to 800 µg/L), TfS (20 - 50%)	AUC of change from baseline levels of Hb, serum ferritin and TfS
VIT-IV-CL-008 [5.3.5.1.2]	Change from baseline levels of Hb to Week 12	Hb, SF, TfS	Hb (135 to 180 g/L for males and 120 to 160 g/L for females), serum ferritin (100 to 800 µg/L), TfS (20 - 50%)	QoL (SF-36), Crohn's Disease Activity Index (CDAI)/Colitis Activity Index (CAI)
VIT-IV-CL-009 [5.3.5.1.3]	Change from baseline levels of Hb to Week 12	Change from baseline for Hb at Weeks 2 , 4, SF, TfS	Hb 120 to 160 g/L ferritin (50 to 800 µg/L) TfS (20 - 50%)	AUC of change from baseline levels of Hb, serum ferritin and TfS; number of patients who needed transfusions; iron in breastmilk (substudy)
1VIT03001 [5.3.5.1.4]	'Success' defined as number of subjects with an increase in Hb levels of ≥20 g/L anytime between baseline and Week 6 (end of study)	N and % of patients attaining a Hb level of ≥ 120 g/L at anytime during the study, SF, TfS	% of patients with an increase in Hb level of ≥30 g/L at anytime during the study, time to success, change from baseline to highest Hb during the study	Reticulocyte count and Hb content, QoL

Statistics:
For Studies VIT-IV-CL-008, -009, and 1VIT03001, in which the therapeutic response of VIT-45 was compared to oral iron therapy, a non-inferiority approach was chosen.

In Studies VIT-IV-CL-008 and -009, the non-inferiority margin for the primary efficacy endpoint (change from baseline levels of haemoglobin to Week 12) was set at 5 g/L. (A clinically relevant change in haemoglobin is estimated as 10 g/L. For the purposes of these studies, non-inferiority was defined as half of that estimate).

For patients who discontinued participation in the study before Week 12, their individual last haemoglobin level was taken to determine the increase from baseline (last value approach).

The null hypothesis and the alternative hypothesis assessed were:

$$H0: \mu v < \mu 0 - 5 \text{ versus } H1: \mu v \geq \mu 0 - 5$$

Where μv and μ0 denoting the mean change in haemoglobin from baseline after administration of VIT-45 and oral ferrous sulphate, respectively. The analysis was performed by calculating the two-sided 95% confidence interval (CI) for the difference "VIT-45 minus oral ferrous sulphate" in haemoglobin change, and non-inferiority of VIT-45 compared to oral ferrous sulphate was concluded if the lower limit of the CI was equal to or greater than -5 g/L.

The CI was derived from analysis of covariance (ANCOVA) with 'treatment', 'sex', and 'country' as fixed effects and with baseline haemoglobin as covariate. If non-inferiority was established according to the procedure specified above, superiority of VIT-45 compared to the control treatment was assessed and established if the lower limit of the 95% CI was equal to or greater than zero.

Terms for interactions between treatment and the other fixed effects were included for an additional exploratory analysis of potential interactions.

In Study 1VIT03001, the non-inferiority of the proportion of subjects who achieved success for VIT-45 relative to oral ferrous sulphate was based on a 1-sided 97.5% CI on the treatment difference with a non-inferiority margin of 15%. The CI was constructed from the unstratified comparison of success rate using the normal approximation to the binomial distribution. If non-inferiority was established as described above, superiority of VIT-45 compared to oral ferrous sulphate was assessed and was declared if the lower bound of the CI was greater than zero. Haemoglobin values obtained from Point of Care laboratories or obtained from subjects after intervention were excluded from analysis.

The primary endpoint was summarised for each treatment group within each of the following subgroups: Baseline haemoglobin 91-100 g/L; baseline haemoglobin 81-90 g/L; baseline haemoglobin ≤8.0 g/L; baseline TfS >20% and serum ferritin >50 mg/mL; baseline TfS ≤ 20% or serum ferritin ≤50 g/L; method of delivery (vaginal, C-section); age (<19, ≥19 years); and race (white, nonwhite). The proportion of subjects who achieved success was summarised for each treatment group and study site. Study sites with no subjects in a treatment group were combined for this summary.

According to the Note for Guidance on "The choice of control groups in clinical trials" (CPMP/ICH/364/96) in a trial that is intended to demonstrate efficacy by showing a test treatment to be non-inferior to an active control, an efficacy endpoint with evidence of sensitivity to drug effects should be chosen. An acceptable non-inferiority margin should be defined taking into account historical data and relevant clinical and statistical considerations. Furthermore, in a non-inferiority trial the active control treatment needs to be of established efficacy at the dose used under the conditions of the study. In general, this means it should be a drug acceptable in the region to which the studies will be submitted for the same indication at the dose being studied. All these criteria described in the guideline have been considered in the design of Studies VIT-IV-CL-008, -009, and 1VIT03001.

Results
A comparison of the response to treatment as documented in the clinical studies revealed that treatment with VIT-45 resulted in increased levels of haemoglobin, serum ferritin and TfS, which will be described in more detail below for the intent-to treat (ITT) population.

Primary efficacy endpoints:
As outlined previously, four different primary efficacy endpoints, all related to the change of the haemoglobin level, were chosen for the five studies in which data about the response to treatment with VIT-45 were obtained.

In Study 53214 treatment responders were to have an increase of haemoglobin >10 g/L from baseline at any point during the study. Two weeks and 1 month after the last study medication, this haemoglobin increase had been reached by 45.1% (73/162) and 61.7% (100/162) of the patients, respectively.

In study VIT-IV-CL-015, the percentage of patients with an increase in haemoglobin of ≥10 g/L at 4 weeks after baseline was defined as the primary efficacy endpoint. This was achieved by 44.1% (52/118) of patients in the ITT population treated with VIT-45 and by 35.3% (41/116) of the patients treated with the active comparator Venofer®.

In studies VIT-IV-CL-008 and VIT-IV-CL-009 the primary efficacy endpoint was change from baseline levels of haemoglobin to Week 12. In study VIT-IV-008 the mean increase in haemoglobin concentration from baseline to Week 12 was 38.5 g/L in the VIT-45 group and 37.5 g/L in the ferrous sulphate group, and the mean haemoglobin concentrations at Week 12 were 123.9 g/L and 125.1 g/L, respectively, in the Per-Protocol population.

In study VIT-IV-009 the mean increase in haemoglobin concentration from baseline to Week 12 was 33.7 g/L in the VIT-45 group and 32.9 g/L in the ferrous sulphate group, and the mean haemoglobin concentrations at Week 12 were 130.4 g/L and 128.9 g/L, respectively.

In study 1VIT03001 the primary efficacy endpoint was ‘success’ defined as number of subjects with an increase in haemoglobin levels of ≥20 g/L anytime between baseline and Week 6 (end of study). The proportions of patients who achieved success were similar between the VIT-45 (96.4%) and ferrous sulphate (94.1%) treatment groups, and non-inferiority of VIT-45 relative to oral iron was demonstrated. Greater proportions of patients treated with VIT-45 compared to patients on ferrous sulphate achieved success on or before each visit; differences between the treatment groups were statistically significant at Days 7, 14, and 28. Patients in the VIT-45 group achieved success earlier compared with patients in the ferrous sulphate group, with statistically significant differences observed as early as Day 7 (58.3% vs. 38.5%). Additionally, the median time to success was statistically significantly shorter for patients treated with VIT-45 (7.0 days) compared with patients receiving ferrous sulphate (14.0 days).

Secondary efficacy endpoints:
In studies VIT-IV-CL-015, -008, and -009, maximum increase and change from baseline were determined for haemoglobin, serum ferritin and TfS. In Study 53214, these parameters were also evaluated, but maximum increase was not evaluated. Moreover, in Studies VIT-IV-CL-015, -008, and -009, treatment responders with regard to the achievement of target values of haemoglobin, serum ferritin and TfS were defined.

In Study 1VIT03001, the definition of secondary endpoints was slightly different from the other studies. However, among several secondary endpoints the highest changes in haemoglobin, serum ferritin, and TfS over baseline were also determined. For reasons of comparison, only these results are summarised in the following section.

Haemoglobin:
For haemoglobin, the results obtained after 2, 4 and 12 weeks are summarised below. In study VIT-IV-CL-008 additional measurements were performed after 8 weeks. A different time schedule was used in study 1VIT03001: the change from baseline for haemoglobin values was determined on Days 14, 28 and 42, respectively.

Haemoglobin: Mean change from baseline (ITT set)

Study	Baseline [g/L] (SD)		Change from baseline [g/L] (SD) 95% CI					
			2 weeks (Day 14)[c]		4 weeks[a] (Day 28)[c]		12 weeks[b] (Day42)[c]	
	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[d]
53214 [5.3.5.2.1]	90.6 (13.0)	-	5.3 (7.5) 4.0, 6.7	-	10.1 (11.7) 8.2, 11.9	-	12.4 (14.4) 10.1, 14.7	-
VIT-IV-CL-015 [5.3.5.1.1]	94.8 (13.0)	95.4 (12.5)	3.4 (7.5) -	2.2 (8.7) -	9.0 (10.7) -	6.1 (10.5) -	11.9 (13.2) -	8.6 (13.6) -
VIT-IV-CL-008 [5.3.5.1.2]	85.4 (15.4)	78.7 (15.1)	20.6 (13.7) 18.3, 23.0	13.7 (14.7) 9.8, 17.7	31.7 (17.5) 28.6, 34.7	24.7 (17.6) 19.9, 29.4	36.0 (19.7) 32.7, 39.4	32.9 (20.9) 27.5, 38.2
VIT-IV-CL-009 [5.3.5.1.3]	96.7 (14.7)	96.0 (12.8)	22.9 (14.2) -26, 61	22.8 (11.1) -6, 53	29.6 (16.1) -16, 86	29.9 (13.2) -2, 59	33.4 (17.9) 31.0, 35.8	31.8 (17.6) 28.5, 35.2
1VIT03001 [5.3.5.1.4]	90 (9.1)	90 (9.3)	30 (8.0) 29.1, 31.5[e]	25 (8.5) 23.3, 25.e[c]	38 (10.6) 36.7, 40.0[e]	31 (10.6) 29.4, 32.7[e]	42 (12.4) 39.9, 43.8[e]	33 (11.9) 31.2, 35.0[e]

[a] In Study 53214: 2 weeks after last study medication administration
[b] 1 month/ 4 weeks after last study medication administration in Study 53214/ VIT-IV-CL-015
[c] In Study 1VIT03001, determination of secondary endpoints was performed on Days 7, 14, 28, and 42, respectively. For additional data on Day 7 please refer to Section 2.7.3.
[d] Venofer® in Study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008, -009, and 1VIT03001
[e] 95% CI of mean

Treatment with VIT-45 can thus be seen to result in an early increase of haemoglobin, which continued through Week 12.

With regard to the values for the change in haemoglobin levels it has to be taken into account that in the studies conducted in haemodialysis patients with IDA, the study drug was administered during the dialysis sessions (2 or 3 times weekly) at a dose of 200 mg iron/administration. This low dose of VIT-45 has the advantage that it can be injected directly into the haemodialysis venous line, whereas for higher doses a short-term infusion becomes necessary. Moreover, the parenteral iron preparation Venofer® (iron sucrose), which was used as comparator in Study VIT-IV-CL-015, can only be applied by i.v. injection into a haemodialysis venous line at doses up to 200 mg iron (slow injection over 10 minutes). Higher doses of Venofer® have to be administered as i.v. infusion.

This dosing regimen resulted in a weekly dose of 400-600 mg iron as VIT-45 (in Studies 53214 and VIT-IV-CL-015), whereas in studies VIT-IV-CL-008, VIT-IV-CL-009 and 1VIT03001 the first dose consisted in 1,000 mg iron as VIT-45 (or 15 mg/kg in patients with a body weight ≤66 kg) and was continued until the individual iron deficit had been replenished.

As can be seen in the table above, the mean change from baseline for haemoglobin in patients treated with VIT-45 was higher in Studies VIT-IV-CL-008, VIT-IV-CL-009 and 1VIT03001 at both 2 weeks and 4 weeks than in Study VIT-IV-CL-015. In all studies, patients received iron as VIT-45 in accordance with their individual iron deficit. Due to different dosing schedules the mean duration of treatment was longer in studies 53214 and VIT-IV-CL-015 (15.9 and 15.8 days, respectively) than in Studies VIT-IV-CL-008 and VIT-IV-CL-009 (11.1 and 8.2 days, respectively).

The efficacy of treatment with VIT-45 with regard to an increase in haemoglobin values is reflected by the secondary response rates. In study VIT-IV-CL-015 the proportion of patients who achieved

haemoglobin target levels (≥110 g/L in patients with a baseline haemoglobin ≤100 g/L or ≥120 g/L in patients with a baseline haemoglobin >100 g/L to ≤115 g/L) 4 weeks after the final dose of study medication was 30.9% in patients treated with VIT-45 and 23.3% in patients treated with Venofer®.

In studies VIT-IV-CL-008 and VIT-IV-CL-009, the proportion of patients reaching haemoglobin values in the normal range (135-180 g/L for males and 120-160 g/L for females) after 12 weeks was 47.1% and 76.7%, respectively, for patients treated with VIT-45 versus 40.0% and 76.1%, respectively, for patients treated with ferrous sulphate. In study VIT-IV-CL-008 the percentage of responders was significantly higher for VIT-45 than for ferrous sulphate at Week 4.

Secondary response rate for haemoglobin: treatment responders (ITT set)

	Treatment responders			
	VIT-IV-CL-008		**VIT-IV-CL-009**	
N (%) **95% CI**	**VIT-45** **(N = 136)**	**Ferrous sulphate** **(N = 60)**	**VIT-45** **(N = 227)**	**Ferrous sulphate** **(N = 117)**
Week 2	11 (8.1) 4.6 – 13.9	3 (5.0) 1.7 – 13.7	108 (47.6) 41.2 – 54.1	52 (44.4) 35.8 – 53.5
Week 4	43 (31.6) 24.4 – 39.8	11 (18.3) 10.6 – 29.9	157 (69.2) 62.9 – 74.8	74 (63.2) 54.2 – 71.4
Week 8	68 (50.0) 41.7 – 58.3	23 (38.3) 27.1 – 51.0	-	-
Week 12	64 (47.1) 38.9 – 55.4	24 (40.0) 28.6 – 52.6	174 (76.7) 70.7 – 81.7	89 (76.1) 67.6 – 82.9

Serum ferritin:
Mean changes from baseline for serum ferritin are summarised below.

Serum ferritin: Mean change from baseline (ITT set)

Study	Baseline [µg/L] (SD)		Change from baseline [g/L] (SD) 95% CI					
			2 weeks (Day 14)[c]		4 weeks[a] (Day 28)[c]		12 weeks[b] (Day42)[c]	
	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[d]
53214 [5.3.5.2.1]	67.3 (106.7)	-	447.26 (233.6) 405.03, 489.48	-	403.1 (294.4) 353.12, 452.95	-	239.88 (208.7) 204.87, 274.90	-
VIT-IV-CL-015 [5.3.5.1.1]	114.5 (207.6)	116.0 (178.2)	621.1 (287.2) -	474.3 (285.4) -	548.4 (334.9) -	402.3 (240.2) -	370.6 (225.3) -	302.2 (206.4) -
VIT-IV-CL-008 [5.3.5.1.2]	12.7 (36.4)	19.8 (54.8)	403.2 (337.0) 345.1, 461.2	12.7 (52.1) -1.3, 26.7	157.3 (150.2) 131.2, 183.5	21.1 (99.9) -5.7, 49.9	67.3 (104.2) 49.4, 85.3	18.3 (55.2) 3.8, 32.8
VIT-IV-CL-009 [5.3.5.1.3]	45.5 (110.9)	33.4 (27.7)	456.5 (313.1) 412.1, 500.8	1.9 (34.8) -4.9, 8.8	272.5 (208.8) 242.8, 302.3	2.8 (32.4) -3.5, 9.1	115.1 (163.7) 92.2, 138.1	8.1 (43.2) -.3, 16.5
1VIT03001 [5.3.5.1.4]	26.2 (36.7)	23.1 (23.4)	551 (223.3) 516.8, 585.2[c]	-1.3 (23.4) -4.97, 2.31[c]	302.7 (151.2) 279.3, 326.2[c]	-0.3 (24.8) -4.1, 3.6[c]	-	-

[a] In Study 53214: 2 weeks after last study medication administration
[b] 1 month/ 4 weeks after last study medication administration in Study 53214/ VIT-IV-CL-015
[c] In Study 1VIT03001, determination of secondary endpoints was performed on Days 7, 14, 28, and 42, respectively. For additional data on Day 7 please refer to Section 2.7.3.
[d] Venofer® in Study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008, -009, and 1VIT03001
[e] 95% CI of mean

Parenteral administration of iron, as VIT-45 or Venofer® (study VIT-IV-CL-015), resulted in a rapid and very pronounced increase of serum ferritin values at Week 2. This value declined somewhat during the period between 2 and 4 weeks, but remained high. This decrease may reflect the utilisation of stored iron during the weeks of increased haematopoiesis following VIT-45 administration. In the comparator group in Studies VIT-IV-CL-008 and –009, in which patients were treated with oral ferrous sulphate, serum ferritin increased only slowly from baseline to Week 2 and again to Week 4. Even at Week 12, the increase in serum ferritin was only 18.3 and 8.1 µg/L in studies VIT-IV-CL-008 and VIT-IV-CL-009, respectively. In Study 1VIT03001, treatment with oral ferrous sulphate did not result in an increase in serum ferritin. This may indicate that iron absorbed from the intestine does not lead to a fast build-up of iron stores due to continuous iron utilisation by the bone marrow. Despite the decrease relative to Week 2 values, serum ferritin levels remained considerably above the baseline values until the end of the study, even though the patients typically received their last infusion at Week 2 or 3.

In studies VIT-IV-CL-008, VIT-IV-CL-009, and 1VIT03001 the differences between treatment with VIT-45 and that with ferrous sulphate were significant for all visits.

The definition with regard to the response rate for serum ferritin was different in the individual studies. In Study VIT-IV-CL-015 in dialysis patients, target ranges (200-800 µg/L) higher than the normal range were defined in order to allow for optimal haematopoiesis with the given EPO levels. In Study VIT-IV-

CL-008 in IBD patients, the target ranges were set at 100-800 µg/L, whereas in study VIT-IV-CL-009 in patients with post-partum anaemia the target ranges were 50-800 µg/L. In Study 1VIT03001, no definition with regard to the response rate for serum ferritin was determined.

The percentages of patients reaching levels that qualified them as treatment responders are given below.

Serum ferritin treatment responders (ITT set)

Study	Treatment responders (N/N; %)95% CI						
		2 weeks		4 weeks		12 weeks[b]	
	Target range for treatment responders	VIT-45	Compa-rator[a]	VIT-45	Compa-rator[a]	VIT-45	Compa-rator[a]
VIT-IV-CL-015 [5.3.5.1.1]	200 - 800 µg/L	74/118 (62.7) 53.7, 70.9	83/116 (71.6) 62.8, 79.0	71/118 (60.2) 51.2, 68.5	84/116 (72.4) 63.7, 79.7	87/118 (73.7) 65.1, 80.9	79/116 (68.1) 59.2, 75.9
VIT-IV-CL-008 [5.3.5.1.2]	100 - 800 µg/L	121/136 (89.0) 82.6, 93.2	3/60 (5.0) 1.7, 13.7	85/136 (62.5) 54.1, 70.2	3/60 (5.0) 1.7, 13.7	36/136 (26.5) 19.8, 34,5	2/60 (3.3) 0.9, 11.4
VIT-IV-CL-009 [5.3.5.1.3]	50 - 800 µg/L	145/227 (63.9) 57.4, 69.8	17/117 (14.5) 9.3, 22.0	164/227 (72.2) 66.1, 77.7	20/117 (17.1) 11.3, 24.9	157/227 (69.2) 62.9, 74.8	32/117 (27.4) 20.1, 36.1

[a] Venofer® in Study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008 and –009
[b] 4 weeks after final dose of study medication in study VIT-IV-CL-015

As expected, after parenteral iron therapy with VIT-45 (or Venofer® used as active control in Study VIT-IV-CL-015) the majority of patients reached serum ferritin levels that qualified them to be treatment responders, whereas oral iron therapy resulted in serum ferritin levels above the threshold for responders in only a minority of patients.

At all visits in Studies VIT-IV-CL-008 and –009 the increase of serum ferritin in the ITT set was significantly higher after treatment with VIT-45 as compared to treatment with ferrous sulphate ($p<0.001$).

Transferrin saturation:
The other clinically relevant parameter in diagnosing iron deficiencies is TfS, which reflects iron available for erythropoiesis. Mean changes from baseline for TfS are summarised below:

Transferrin saturation: Mean change from baseline (ITT set)

Study	Baseline		Change from Baseline [%] (SD) 95% CI					
			2 weeks (Day 14)[c]		4 weeks[a] (Day 28)[c]		12 weeks[b] (Day42)[c]	
	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[d]	VIT-45	Comparator[b]
53214 [5.3.5.2.1]	17.4 (9.1)	-	21.7 (16.0) 18.81, 24.57	-	16.0 (15.16) 13.43, 18.57	-	12.74 (11.25) 10.86, 14.63	-
VIT-IV-CL-015 [5.3.5.1.1]	21.7 (14.5)	25.1 (25.9)	22.6 (25.7) -	12.6 (16.4)	17.8 (19.8)	13.9 (15.6)	13.5 (18.7) -	8.7 (22.2) -
VIT-IV-CL-008 [5.3.5.1.2]	6.2 (5.8)	10.5 (11.3)	20.8 (16.2) 17.9, 23.8	16.2 (30.2) 7.7, 24.7	22.2 (17.2) 19.0, 25.4	12.5 (22.9) 6.1, 19.0	17.2 (16.9) 14.1, 20.3	19.4 (24.3) 12.7, 26.1
VIT-IV-CL-009 [5.3.5.1.3]	12.1 (9.9)	12.8 (9.5)	22.8 (19.8) 20.0, 25.5	14.2 (23.3) 9.6, 18.8	26.7 (18.4) 24.1, 29.3	14.8 (17.1) 11.5, 18.1	22.2 (18.0) 19.7, 24.6	14.5 (14.3) 11.8, 17.3
1VIT03001 [5.3.5.1.4]	10.6 9.0)	9.8 (4.3)	24.6 (14.1) 22.4, 26.7[c]	16.2 (19.5) 13.1, 19.2[c]	26.8 (13.8) 24.7, 29.0[c]	15.9 (17.5) 13.1, 18.6[c]	-	-

[a] In Study 53214: 2 weeks after last study medication administration
[b] 1 month/ 4 weeks after last study medication administration in Study 53214/ VIT-IV-CL-015
[c] In Study 1VIT03001, determination of secondary endpoints was performed on Days 7, 14, 28, and 42, respectively. For additional data on Day 7 please refer to Section 2.7.3.
[d] Venofer® in Study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008, -009, and 1VIT03001
[e] 95% CI of mean

Mean TfS levels increased markedly in most studies from baseline to Week 2 and stayed similar until the end of the respective study. Mean values in the groups of patients treated with VIT-45 were constantly above 20%, which is the threshold for definition of IDA. Changes from baseline of mean TfS values were not significant between the treatment groups.

In Studies VIT-IV-CL-015, -008, and -009 the secondary response rate for TfS was defined as achieving levels of 20 - 50%. In Study 1VIT03001, no secondary response rate for TfS was defined.

Transferrin saturation treatment responders (ITT set)

Study	Treatment responders (N/N; %)95% CI					
	2 weeks		4 weeks		12 weeks[b]	
	VIT-45	Comparator[a]	VIT-45	Comparator[a]	VIT-45	Comparator[a]
VIT-IV-CL-015 [5.3.5.1.1]	70/118 (59.3) 50.3, 67.8	70/116 (60.3) 51.2, 68.8	75/118 (63.6) 54.6, 71.7	70/116 (60.3) 51.2, 68.8	80/118 (67.8) 58.9, 75.6	76/116 (65.5) 56.5, 73.5
VIT-IV-CL-008 [5.3.5.1.2]	76/136 (55.9) 47.5, 64.0	17/60 (28.3) 18.5, 40.8	74/136 (54.4) 46.0, 62.5	21/60 (35.0) 24.2, 47.6	55/136 (40.4) 32.6, 48.8	26/60 (43.3) 31.6, 55.9
VIT-IV-CL-009 [5.3.5.1.3]	143/227 (63.0) 56.5, 69.0	40/117 (34.2) 26.2, 43.2	145/227 (63.9) 57.4, 69.8	55/117 (47.0) 38.2, 56.0	157/227 (69.2) 62.9, 74.8	70/117 (59.8) 50.8, 68.3

[a] Venofer® in study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008 and -009
[b] 4 weeks after final dose of study medication in study VIT-IV-CL-015

In Study VIT-IV-CL-015, the response rate was similar for patients treated with VIT-45 or with Venofer®. In Studies VIT-IV-CL-008 and VIT-IV-CL-009, the percentage of responders was significantly higher in the VIT-45 group at Week 2 and Week 4 (approximately 60% versus approximately 30%), which corresponds with the more rapid increase in haemoglobin values observed in the VIT-45 group.

Summary and Conclusion:
All the parameters chosen to assess therapeutic response showed that administration of VIT-45 was effective in treating IDA due to various causes.

Haemoglobin levels increased significantly to expected and clinically acceptable levels.

In the non-controlled study 53214, the majority of haemodialysis patients (61.7%) could be classified as responders, as they achieved a clinically significant increase of haemoglobin of at least 10 g/L at any point during the study.

In Study VIT-IV-CL-015, the primary response rate for haemodialysis patients, defined as an increase in haemoglobin of at least 10 g/L 4 weeks after baseline, was 46.4% in the VIT-45 group and 37.2% in the Venofer® group.

In Studies VIT-IV-CL-008 and -009, based on the primary efficacy variable (increase in haemoglobin from baseline to Week 12), VIT-45 was non-inferior to ferrous sulphate in treating patients with IDA secondary to IBD and in patients with post-partum anaemia, respectively.

In Study 1VIT03001, the proportion of patients who achieved an increase in haemoglobin levels of ≥20 g/L anytime between baseline and Week 6 (end of study) was 96.4% in the VIT-45 group and 94.1% in the ferrous sulphate group, and non-inferiority of VIT-45 relative to oral iron was demonstrated.

The changes in serum ferritin and TfS confirmed successful repletion of deficient iron stores in patients treated with VIT-45.

Serum ferritin levels were raised rapidly by treatment with VIT-45, and the pre-defined target range for serum ferritin was reached by the majority of patients treated with VIT-45. In the studies in which VIT-45 was compared to oral ferrous sulphate treatment (VIT-IV-CL-008, VIT-IV-CL–009, and 1VIT03001), the increase of serum ferritin was significantly higher at all visits in patients treated with VIT-45 than in patients treated with ferrous sulphate.
TfS levels moved from suboptimal levels to the internationally accepted target range (20-50%) within 2 weeks after start of medication with VIT-45.

In conclusion, VIT-45 has been shown to be an effective treatment option for patients with IDA. Based on the data from studies VIT-IV-CL-008, VIT-IV-CL–009, and 1VIT03001, VIT-45 is non-inferior to ferrous sulphate for the increase in haemoglobin levels from baseline to Week 6 (1VIT03001) or Week 12 (VIT-IV-CL-008 and -009) for effectively treating patients with IDA secondary to IBD or patients with post-partum anaemia. VIT-45 is a convenient treatment as less doses of iron are necessary to achieve the same increase in haemoglobin from baseline to study end if compared to oral iron treatment. However VIT-45 was superior with respect to the replenishment of iron stores. The short treatment time (1-2 weeks versus 12 weeks) may be considered of significant clinical advantage in specific patients populations needing iron treatment.

CLINICAL SAFETY

Overview of Safety

VIT-45 is a type I iron complex that has been developed in order to deliver bioavailable iron to the iron-binding proteins in a controlled manner with little risk of release of free iron.

Key safety concerns regarding parenteral preparations include hypersensitivity reactions. There appear to be two types of reactions to i.v. iron. The first is a type I IgE-mediated anaphylactic reaction, which is seen exclusively to iron dextran and is due to anti-dextran antibodies. The second reaction is anaphylactoid. This may be due to transient overload of the transferrin molecule, resulting in small amounts of free iron in circulation.

A second safety concern is the potential for haemosiderosis. Thus, it is important to calculate the individual iron deficit of the patient and to supplement only the amount of iron needed.
Any event reflecting the intended effect of treatment on iron parameters are not considered as adverse events.

Relevant Animal Toxicology

Data from primary pharmacodynamic and pharmacokinetic, distribution and excretion studies show VIT-45 to be an efficient iron-carbohydrate complex for the delivery of iron to the target tissue (red blood cells) and iron storage tissues (principally the liver and spleen).

Data from the repeated-dose toxicity studies using high iron doses showed the expected pattern of changes associated with iron overload in experimental animals. There is uptake and retention of iron in the cells of the RES in the major storage organs, and toxicity only occurs when the RES storage capacity is exceeded and significant accumulation of iron occurs in the tissue parenchyma.

VIT-45 showed no activity in genetic toxicity tests. Thus the genetic toxicity data, together with knowledge of the nature of the VIT-45, the breakdown products of the complex and the lack of any findings indicative of pre-neoplastic lesions in the chronic toxicity studies, suggest a very low risk for carcinogenic potential of the product.

Data from the reproductive and developmental toxicity studies did not reveal any data other than that which might be expected from iron-overloaded animals. The reproductive safety profile of the product seems good based on the animal studies performed, such that administration of VIT-45 to pregnant or nursing female patients should not be associated with any undue risks. However, the potential benefits of administration in these patients should be carefully balanced against possible risks to the mother or offspring.

VIT-45 did not show any cross-reactivity with anti-dextran antibodies and thus can be safely administered to patients who have been previously sensitised to iron dextran. Administration of a challenge dose of VIT-45 to previously treated rats did not result in an anaphylactoid-type response, and it is considered very unlikely that VIT-45 itself is immunogenic. The carbohydrate component of VIT-45 is considered very unlikely to be immunogenic due to its composition and the ready breakdown into endogenous sugar residues.

Patient Populations and Extent of Exposure

The extent of exposure in clinical trials conducted with VIT-45 is summarised below for the pharmacology studies, and the efficacy and safety studies.

In the bioavailability study VIT-IV-CL-001 [5.3.1.1.1], and the two pharmacodynamic studies VIT-IV-CL-02 [5.3.4.2.1] and VIT-IV-CL-03 [5.3.4.2.2], a total of 80 patients were exposed to VIT-45. Safety

data are available from single-dose studies (VIT-IV-CL-001: three patients with IDA and three patients with renal anaemia; and VIT-IV-CL-02: 24 patients with mild IDA), and one multiple-dose study (VIT-IV-CL-03; 46 patients with IDA secondary to a gastrointestinal disorder).

Patients exposed in clinical pharmacology studies (Safety set)

	Diagnosis	**Patients (N) receiving at least one dose of VIT-45**
VIT-IV-CL-001 [5.3.1.1.1]	IDA or renal anaemia	6
VIT-IV-CL-02 [5.3.4.2.1]	Mild IDA	24
VIT-IV-CL-03 [5.3.4.2.2]	Moderate IDA	46
Total		**76**

In the clinical studies conducted in support of the efficacy and safety of VIT-45, a total of 819 patients have been exposed to VIT-45.

In the non-controlled study 53214 [5.3.5.2.1] conducted in haemodialysis patients, 162 patients were treated with at least one dose of VIT-45. In the controlled study VIT-IV-CL-015 [5.3.5.1.1] administration of VIT-45 (119 patients) was compared to the i.v. iron preparation Venofer® (118 patients) in haemodialysis patients. In the controlled studies VIT-IV-CL-008 [5.3.5.1.2], VIT-IV-CL-009 [5.3.5.1.3] and 1VIT03001 [5.3.5.1.4] VIT-45 was compared to oral ferrous sulphate in patients with IBD and in patients with post-partum anaemia, respectively.

Patients exposed in efficacy and safety studies (Safety set)

	Diagnosis	**Patients (N) receiving at least 1 dose of**	
	IDA associated with	**VIT-45**	**Comparator***
Study 53214[a] [5.3.5.2.1]	Chronic renal failure	162	-
VIT-IV-CL-015 [5.3.5.1.1]	Chronic renal failure	119	118
VIT-IV-CL-008[5.3.5.1.2]	IBD	137	63
VIT-IV-CL-009 [5.3.5.1.3]	Post-partum	227	117
1VIT03001 [5.3.5.1.4]	Post-partum	174	178
Total		**819**	**476**

* Venofer® in Study VIT-IV-CL-015, oral ferrous sulphate in studies VIT-IV-CL-008, -009 and 1VIT03001.

[a] 163 patients were included in the Safeyt Set, but one of these patients did not receive study medication

The current safety database includes 899 patients who received at least one dose of VIT-45. In total, 657 of 899 patients have received multiple doses of VIT-45 as summarised below.

In addition to these patients, safety was monitored for a total of 346 breast-fed infants (229 in the VIT-45 group and 117 in the ferrous sulphate group) in study VIT-IV-CL-009.

Number of patients who were treated with VIT-45 (Safety set)

Study	At least 1 dose of VIT-45	Multiple doses of VIT-45
VIT-IV-CL-001 [5.3.1.1.1]	6	-
VIT-IV-CL-02 [5.3.4.2.1]	24	-
VIT-IV-CL-03 [5.3.4.2.2.]	46	34
53214[a] [5.3.5.2.1]	162	-
VIT-IV-CL-015 [5.3.5.1.1]	119	119
VIT-IV-CL-008 [5.3.5.1.2]	137	134
VIT-IV-CL-009 [5.3.5.1.3]	227	207
1VIT03001 [5.3.5.1.4]	174	163
Total	**895**	**657**

[a] 163 patients were included in the Safety Set, but one of these patients did not receive study medication

The patients treated with VIT-45 (N = 899) were between the ages of 15 and 80 years, whereas patients treated with a comparator (Venofer® i.v. in study VIT-IV-CL-015, or oral ferrous sulphate in studies VIT-IV-CL-008, –009, and 1VIT03001) were between the ages of 15 and 79 years. Thus, patients over a wide age range were included in these clinical studies and patients included in the groups treated with VIT-45 or with the control were comparable.

Age of patients treated with VIT-45 (Safety set)

	001 N = 6	**02 N = 32**	**03 N = 46**	**53214 N = 163**	**015 N = 119**	**008 N = 137**	**009 N = 227**	**03001 N = 174**
Age [years]								
Mean (SD)	45.2 (16.1)	31.0 (8.4)	42.9 (11.0)	44.9 (12.7)	52.6 (13.3)	40.7 (13.8)	27.7 (5.5)	26.9(6.4)
Range (min, max)	28, 73	18, 45	20, 61	18, 65	22, 80	19, 78	18, 44	15, 49

Age of patients treated with comparator (Safety set)

	015 Venofer® N = 118	**008 Ferrous sulphate N = 63**	**009 Ferrous sulphate N = 117**	**03001 Ferrous sulphate N = 178**
Age [years]				
Mean (SD)	51.0 (13.6)	45.2 (16.1)	27.5 (5.4)	26.0 (5.95)
Range (min, max)	22, 79	20, 78	19, 41	15, 40

Common Adverse Events

Separated by treatment groups, between 33% and 57% of patients reported at least one treatment-emergent adverse event (TEAE) in the clinical studies (see below).

Number (percentage) of patients with at least one TEAE

	001 VIT-45	**02 VIT-45**	**03 VIT-45**	**53214 VIT-45**	**015 VIT-45**	**015 Venofer®**
At least one TEAE (%)	3/6 (50)	8/24 (33.3)	24/46 (52.1)	89/ 163 (54.6)	51/ 119 (42.9)	47/118 (39.8)
	008 VIT-45	**009 VIT-45**	**009 FS**	**03001 VIT-45**	**03001 FS**	
At least one TEAE (%)	78/137 (56.9)	70/227 (26.0)	28/ 117 (22.2)	87/174 (50.0)	97/178 (54.5)	

FS: Ferrous sulphate

In breast-fed infants of study VIT-IV-CL-009 at least one TEAE was reported for 24 (10.5%) in the VIT-45 group and for 14 (12.0%) in the ferrous sulphate group.

Study VIT-IV-CL-001 [5.3.1.1.1]
The study primarily evaluated VIT-45 iron kinetics and comprised six and four patients only. Due to the small number of patients no tendency in frequency of certain AEs could be observed.

There were no TEAEs of severe intensity.

Study VIT-IV-CL-02 [5.3.4.2.1]
The most frequently observed TEAE was headache (reported for five patients). Three adverse events with a possible relation to study drug application were reported. Two in one patient in the 100 mg group (nausea and vomiting) and one in one patient in the 1,000 mg group (headache).

There were no TEAEs of severe intensity.

Study VIT-IV-CL-03 [5.3.4.2.2]
The most frequently reported TEAEs were haematuria (five patients), C-reactive protein increased (five patients) and urticaria (two patients). All other events were reported by one patient only.

There were no TEAEs of severe intensity.

Study 53214 [5.3.5.2.1]
The most frequently reported TEAEs (≥five patients) were: hypertension (NOS) and headache (13 patients each [8.0%]), hypotension NOS and muscle cramp (eight patients each [4.9%]), respiratory tract infection viral NOS (six patients [3.7%]) and nausea (five patients [3.1%]). All other events were reported by less than five patients.

More than half (54.6%) of the patients had at least one TEAE. There were eight (4.9%) patients who had at least one severe TEAE, while 12 patients (7.4%) experienced at least one serious TEAE. Two patients (1.2%) died during the study.

Study VIT-IV-CL-015 [5.3.5.1.1]
The most frequently reported TEAEs (in ≥two patients) were: hypotension (12 patients [10.2%] in each of the treatment groups), hypertension (seven patients [5.9%] in the VIT-45 group and eight patients [6.8%] in the Venofer® group), muscle cramp (six patients [5.0%] in the VIT-45 group and five patients [4.2%] in the Venofer group), procedural hypotension (two patients [1.7%] in the VIT-45 group and one patient [0.8] in the Venofer® group), headache (three patients [2.5%] in the VIT-45 group and five patients [4.2%] in the Venofer® group), blood pressure increased (one patient [0.8%] in the VIT-45 group and four patients [3.4%] in the Venofer® group). All other events were reported by less than five patients overall.

At least one TEAE was reported by 51 patients (42.9%) in the VIT-45 group and 47 patients (39.8%) in the Venofer® group. There were five patients (4.2%) in both groups who reported at least one severe TEAE, while six patients (5.0%) in the VIT-45 group and eight patients (6.8%) in the Venofer® group reported at least one serious TEAE. One patient (0.8%) in the VIT-45 group died.

Study VIT-IV-CL-008 [5.3.5.1.2]
The most commonly reported TEAEs (in ≥three patients) were: colitis ulcerative (11 patients [8.0%] in the VIT-45 group and nine patients [14.3%] in the ferrous sulphate group), abdominal pain (seven patients [5.1%] in the VIT-45 group and two patients [3.2%] in the ferrous sulphate group), headache (eight patients [5.8%] in the VIT-45 group and one patient [1.6%] in the ferrous sulphate group), Crohn's disease, pyrexia and back pain (five patients [3.6%] in the VIT-45 group and one patient [1.6%] in the ferrous sulphate group), diarrhoea (two patients [1.5%] in the VIT-45 group and four patients [6.3%] in the ferrous sulphate group) and nausea (three patients [2.2%] in the VIT-45 group and three patients [4.8%] in the ferrous sulphate group). All other events were reported by less than six patients overall.

At least one TEAE was reported by 78 patients (56.9%) in the VIT-45 group and 27 patients (42.9%) in the ferrous sulphate group. There were eight patients (5.8%) in the VIT-45 group and 1 patient (1.6%) in the ferrous sulphate group who reported at least one severe TEAE, while nine patients (6.6%) in the VIT-45 group and no patients in the ferrous sulphate group reported at least one serious TEAE. One patient (0.7%; patient 863013) in the VIT-45 group died.

Study VIT-IV-CL-009 [5.3.5.1.3]
The most commonly reported TEAEs (in ≥three patients) were: nasopharyngitis (seven patients [3.1%] in the VIT-45 group and two patients [1.7%] in the ferrous sulphate group), constipation (one patient [0.4%] in the VIT-45 group and eight patients [6.8%] in the ferrous sulphate group), alanine aminotransferase increased (five patients [2.2%] in the VIT-45 group and three patients [2.6%] in the ferrous sulphate group), headache (six patients [2.6%] in the VIT-45 group and two patients [1.7%] in the ferrous sulphate group), infusion-site burning (five patients [2.2%] in the VIT-45 group and no patients in the ferrous sulphate group), C-reactive protein increased (four patients [1.8%] in the VIT-45 group and none in the ferrous sulphate group), uterine haemorrhage (three patients [1.3%] in the VIT-45 group and one patient [0.9%] in the ferrous sulphate group). All other TEAEs were reported by less than four patients overall.

At least one TEAE was reported by 59 patients (26.0%) in the VIT 45 group and 26 patients (22.2%) in the ferrous sulphate group. There were five patients (2.2%) in the VIT-45 group and none in the ferrous sulphate group who reported at least one severe TEAE. Serious TEAEs were reported in two patients (0.9%) in the VIT-45 group.

Subpopulation
At least one TEAE was reported in 24 breast-fed infants (10.5%) in the VIT-45 group and 14 breast-fed infants (12.0%) in the ferrous sulphate group. There were two breast-fed infants (0.9%) in the VIT-45 group and none in the ferrous sulphate group in whom at least one severe TEAE was reported, while four breast-fed infants (1.7%) in the VIT-45 group and one breast-fed infant (0.9%) in the ferrous sulphate group had at least one serious TEAE.

Study 1VIT03001 [5.3.5.1.4]
The most commonly (≥5%) experienced TEAEs by highest level term were: headaches (39 patients [22.4%] in the VIT-45 group and 32 patients [18.0%] in the ferrous sulphate group), infections with unspecified pathogen class (19 patients [10.9%] in the VIT-45 group and 20 patients [11.2%] in the ferrous sulphate group), gastrointestinal signs and symptoms (15 patients [8.6%] in the VIT-45 group and 27 patients [15.2%] in the ferrous sulphate group), gastrointestinal motility and defaecation conditions (10 patients [5.7%] in the VIT-45 group and 32 patients [18.0%] in the ferrous sulphate group), epidermal and dermal conditions (13 patients [7.5%] in the VIT-45 group and four patients [2.2%] in the ferrous sulphate group), neurological disorders (not elsewhere classified, 10 patients [5.7%] in the VIT-45 group and seven patients [3.9%] in the ferrous sulphate group).

The only TEAEs by preferred term experienced by ≥5% of subjects in the VIT-45 group were sinus headache (30 patients [17.2%]) and headache (31 patients [17.8%]; ferrous sulphate: 25 patients [14.0%]), whereas most commonly experienced TEAEs in the oral ferrous sulphate group were constipation (25 patients [14.0%]; VIT-45: 7 patients [4.0%]), sinus headache (21 patients [11.8%]), and nausea (15 patients [8.4%]; VIT-45: 3 [1.7%]).

The majority of TEAEs experienced during the study were classified by the investigator as mild or moderate. Severe TEAEs were experienced by seven subjects (4.0%) in the VIT-45 group and nine subjects (5.1%) in the ferrous sulphate group. One patient in the ferrous sulphate group experienced a life-threatening TEAE of major depression, and one patient in the VIT-45 group experienced a grade 5 TEAE which led to death.

In summary, the body systems in the clinical studies with multiple applications of VIT-45 in which the highest number of adverse events were reported are (in alphabetic order): gastrointestinal disorders, general disorders, infections, investigations, muscoloskeletal and connective tissue disorders, nervous system disorders, skin and subcutaneous tissue disorders, and vascular disorders. In the table below, those adverse events which were reported by at least five patients per preferred term in at least one study are listed. Worsening of ulcerative colitis or Crohn's disease, which was reported in the study conducted in IBD patients (VIT-IV-CL-008) was not included in this table. In the individual studies, only a few adverse events were reported for more than five patients within one group and one study.

Summary of TEAEs in patients occurring with the highest incidence per body system and preferred term as reported in clinical efficacy and safety studies

	Reported incidence by treatment groups (N of subjects, %)									
Body system / Preferred term	**003**[3]	**53214**[3]	**015**[4]		**008**[5]		**009**[5]		**03001**[6]	
	VIT-45 N = 46	**VIT-45 N = 163**	**VIT-45 N = 119**	**Venofer® N = 118**	**VIT-45 N = 137**	**FS N = 63**	**VIT-45 N = 227**	**FS N = 127**	**VIT-45 N = 174**	**FS N = 178**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Gastro-intestinal disorders	-	18 (11.0)	5 (4.2)	9 (7.6)	37 (27.0)	20 (31.7)	8 (3.5)	12 (10.3)	22 (12.6)	51 (28.7)
Abdominal pain[1]	-	5 (3.1)	-	1 (0.8)	8 (5.8)	2 (3.2)	2 (0.9)	1 (0.9)	10 (5.7)	6 (3.4)
Constipation	-	2 (1.2)	1 (0.8)	-	-	1 (1.6)	1 (0.4)	8 (6.8)	7 (4.0)	25 (14.0)
Diarrhoea	-	3 (1.8)	2 (1.7)	1 (0.8)	2 (1.5)	4 (6.3)	-	2 (1.7)	3 (1.7)	8 (4.5)
Haemato-chezia	-	-	-	-	5 (3.6)	-	-	-	-	-
Nausea	0-0	5 (3.1)	2 (1.7)	2 (1.7)	3 (2.2)	3 (4.8)	1 (0.4)	-	3 (1.7)	15 (8.4)
General disorders	2 (4.3)	7 (4.3)	5 (4.2)	6 (5.1)	11 (8.0)	3 (4.8)	14 (6.2)	-	12 (6.9)	9 (5.1)
Infusion site burning	1 (2.1)	-	-	-	-	-	5 (2.2)	-	-	-
Infections and infestations	2 (4.3)	24 (14.7)	11 (9.2)	10 (8.5)	16 (11.7)	5 (7.9)	19 (8.4)	4 (3.4)	24 (13.8)	22 (12.4)
Nasopharyn-gitis	1 (2.1)	1 (0.6)	2 (1.7)	-	3 (2.2)	2 (3.2)	7 (3.1)	2 (1.7)	1 (0.6)	3 (1.7)
Respiratory tract infection	-	10 (6.1)	-	-	-	1 (1.6)	3 (1.3)	-	4 (2.3)	1 (0.6)
Investigations	9 (19.6)	15 (9.2)	4 (3.4)	4 (3.4)	23 (16.8)	4 (6.3)	15 (6.6)	4 (3.4)	3 (1.7)	8 (4.5)
ALT increased	1 (2.1)	2 (1.2)	-	-	3 (2.2)	-	5 (2.2)	3 (2.6)	1 (0.6)	3 (1.7)
CRP increased	5 (10.9)	4 (2.5)	-	-	3 (2.2)	2 (3.2)	4 (1.8)		-	-
Musculoskeletal and connective tissue disorders	1 (2.1)	13 (8.0)	9 (7.6)	11 (9.3)	13 (9.5)	2 (3.2)	-	3 (2.6)	3 (1.7)	7 (3.9)
Back pain	-	-	2 (1.7)	-	5 (3.6)	1 (1.6)	-	1 (0.9)	1 (0.6)	2 (1.1)
Muscle cramp	-	8 (4.9)	6 (5.0)	5 (4.2)	-	-	-	-	-	1 (0.6)
Myalgia	-	1 (0.6)	-	1 (0.8)	5 (3.6)	-	-	-	-	1 (0.6)

	Reported incidence by treatment groups (N of subjects, %)									
Body system / Preferred term	**003**[3]	**53214**[3]	**015**[4]		**008**[5]		**009**[5]		**03001**[6]	
	VIT-45 N = 46	**VIT-45 N = 163**	**VIT-45 N = 119**	**Venofer® N = 118**	**VIT-45 N = 137**	**FS N = 63**	**VIT-45 N = 227**	**FS N = 127**	**VIT-45 N = 174**	**FS N = 178**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Nervous system disorders	-	15 (9.2)	3 (2.5)	8 (6.8)	9 (6.6)	1 (1.6)	7 (3.1)	3 (2.6)	39 (22.4)	32 (18.0)
Headache	-	13 (8.0)	3 (2.5)	5 (4.2)	8 (5.8)	1 (1.6)	6 (2.6)	2 (1.7)	31(17.8)	25 (14.0)
Skin and subcutaneous tissue disorders	3 (6.5)	5 (3.1)	3 (2.5)	2 (1.7)	12 (8.8)	2 (3.2)	5 (2.2)	2 (1.7)	16 (9.2)	5 (2.8)
Rash[2]	-	-	1 (0.8)	1 (0.8)	6 (4.4)	1 (1.6)	2 (0.9)	1 (0.9)	11 (6.3)	4 (2.2)
Vascular disorders	-	21 (12.9)	21 (17.6)	22 (18.6)	3 (2.2)	1 (1.7)	5 (2.2)	-	3 (1.7)	3 (1.7)
Hypertension	-	13 (8.0)	7 (5.9)	8 (6.8)	1 (0.7)	1 (1.6)	-	-	1 (0.6)	2 (1.1)
Hypotension	-	8 (4.9)	12 (10.1)	12 (10.2)	-	-	1 (0.4)	-	1 (0.6)	-

[1] including “abdominal pain upper”
[2] including ‘rash’, ‘rash erythematous’, ‘rash macular’, ‘rash maculo-papular’, ‘rash pruritic’
[3] Only body systems and events occurring in≥ 5 patients are presented.
[4] Only body systems and events occurring in ≥ 2 patients per treatment group are presented.
[5] Body systems and events occurring in≥ 3 patients in either treatment group are presented.
[6] Body systems and events occurring in≥ 5% of patients in either treatment group are presented.

Summary of adverse events in breast-fed infants
Furthermore, in Study VIT-IV-CL-009 [5.3.5.1.3] a subanalysis was performed in the breast-fed infants. At least one TEAE was reported in 24 of 229 breast-fed infants (10.5%) in the VIT-45 group and in 14 of 117 breast-fed infants (12.0%) in the ferrous sulphate group.

The most common reported (in ≥two infants) TEAEs were: constipation (three infants [1.3%] in the VIT-45 group and four infants [3.4%] in the ferrous sulphate group), erythema (five infants [2.2%] in the VIT-45 group), diarrhoea (three infants [1.3%] in the VIT 45 group), abdominal pain (one infant [0.4%] in the VIT-45 group and two infants [1.7%] in the ferrous sulphate group), nasopharyngitis (two infants [0.9%] in the VIT 45 group and one infant [0.9%] in the ferrous sulphate group), upper respiratory tract infection (one infant [0.4%] in the VIT-45 group and two infants [1.7%] in the ferrous sulphate group), pallor and flatulence (two infants [0.9%] each in the VIT-45 group). All other TEAEs were reported in less than two breast-fed infants overall.

Relationship to Study Medication

The number and percentage of patients who experienced adverse events which were judged as possibly drug-related was between 5% and 33.3% (see table below).

Number (percentage) of patients with at least one possibly drug-related adverse event

	001 VIT-45	**02 VIT-45**	**03 VIT-45**	**53214 VIT-45**	**015 VIT-45**	**015 Venofer®**
At least one possibly drug-related TEAE (%)	2/6 (33.3)	2/24 (8.3)	9/46 (19.6)	16/ 163 (9.8)	6/119 (5.0)	12/118 (10.2)
	008 VIT-45	**009 VIT-45**	**009 FS**	**03001 VIT-45**	**03001 FS**	
At least one possibly drug-related TEAE (%)	39/ 137 (28.5)	34/ 227 (15.0)	14/ 117 (12.0)	32/ 174 (18.4)	49/ 178 (27.5)	

FS Ferrous sulphate

Study VIT-IV-CL-001 [5.3.1.1.1]
Two AEs with relation to study medication were reported: One AE (dysgeusia) was considered to be possibly related and one AE (haematoma NOS) probably/likely related to study medication.

Study VIT-IV-CL-02 [5.3.4.2.1]
Three AEs with a possible relation to study drug application were reported in two patients (8.3%), one patient in the 100 mg group (nausea and vomiting) and one patient in the 1,000 mg group (moderate headache).

Study VIT-IV-CL-03 [5.3.4.2.2]
A total of four patients (20%) in Cohort 1 and four patients (15.4%) in Cohort 2 reported events of possible relationship to study medication. These events were GGT, AST and ALT increased (one patient), blood iron and transferrin abnormal (one patient), urticaria, thrombocythaemia in Cohort 1, and dermatitis allergic, urticaria, reticulocyte count increased and hyperthermia in Cohort 2. Only one patient (5.0%) in Cohort 1 reported an event of probable relationship to study medication (infusion site pain).

Study 53214 [5.3.5.2.1]
Adverse events considered to be probably related to study medication by the investigator were reported in three patients (1.8%): nausea, liver function test abnormal and headache (by one patients with five instances of probably related headache). There were 13 patients (8.0%) with TEAEs that were considered by the investigator to be possibly related to study medication.

Study VIT-IV-CL-015 [5.3.5.1.1]
In the VIT-45 group the relationship of TEAEs to study drug were as follows: only one TEAE in one patient (0.8%) was considered to be certainly related to study medication by the investigator, and this was an event of dysgeusia. There were two patients with TEAEs (1.7%) considered to be probably related to study medication by the investigator; one event of hyperthermia and one event of electrocardiogram QRS complex prolonged. There were three patients (2.5%) with TEAEs that were considered by the investigator to be possibly related to study medication. The majority of TEAEs were considered by the investigator to be unrelated (30 patients, 25.2%), or of unlikely (15 patients, 12.6%) relationship to study medication.

In the Venofer® group, the relationships of TEAEs to study drug were: two events of hypotension that were considered to be probably related to study medication. There were 10 patients (8.5%) with TEAEs that were considered by the investigator to be possibly related to study medication. The majority of TEAEs were considered by the investigator to be unrelated (24 patients, 20.3%), or of unlikely (11 patients, 9.3%) relationship to study medication.

Study VIT-IV-CL-008 [5.3.5.1.2]
In the VIT-45 group, TEAEs reported by five patients (3.6%), were considered to be certainly related to study medication by the investigator. The TEAEs reported for these patients were pruritus, rash erythematous, and urticaria. TEAEs reported by eight patients (5.8%) were considered to be probably related to study medication by the investigator (reticulocytosis, abdominal pain, diarrhoea, ALT increased, GGT increased, body temperature increased, rash erythematous, urticaria, phlebitis). TEAEs reported by 26 patients (19.0%) were considered by the investigator to be possibly related to study medication. All other TEAEs were unlikely (nine patients [6.6%]) or unrelated (30 patients [21.9%]) to study medication.

In the ferrous sulphate group, a TEAE reported by one patient (1.6%, diarrhoea) was considered by the investigator to be certainly related to study medication. There were six patients (9.5%) with TEAEs that were considered by the investigator to be probably related to study medication (reticulocytosis, diarrhoea, nausea, vomiting, colitis ulcerative, pruritus, and headache). There were seven patients each (11.1%) with TEAEs that were considered possibly and unlikely related to study medication and six patients (9.5%) with TEAEs that were considered unrelated.

Study VIT-IV-CL-009 [5.3.5.1.3]
There were 24 patients (10.6%) in the VIT-45 group and 13 patients (11.1%) in the ferrous sulphate group who reported TEAEs that were possibly, probably or certainly related to the study drug. There were four patients (1.8%) in the VIT-45 group and one patient (0.9%) in the ferrous sulphate group who withdrew study drug due to TEAEs. The 11 TEAEs which were certainly related to study drug administration concerned nine patients (4.0%) in the VIT-45 group (hepatic enzyme increased, infusion site burning, infusion site pain, rash, hyperaemia, hypersensitivity, and panic attack). In the ferrous sulphate group, there was only one TEAE certainly related to study medication (1.7%; diarrhoea). TEAEs defined as probably related to study medication occurred in one patient (0.4%; local skin reactions and constipation) in the VIT-45 group in two patients (1.7%, constipation) in the ferrous sulphate group.

In the subanalysis performed in the breast-fed infants, there was only one infant in the ferrous sulphate group who reported two episodes of constipation that were probably related to the study drug.

Study 1VIT03001 [5.3.5.1.4]
During the study, at least one drug-related TEAE (defined as probably or possibly related) was experienced by 18.4% (32/174) of the subjects in the VIT-45 group and 27.5% (49/178) of the subjects in the oral iron group. None of the TEAEs was assessed as being certainly related to either study drug. In the VIT-45 group, nine [5.2%] and 23 [13.2%] TEAEs were probably or possibly related to study medicaton, respectively. In the ferrous sulphate group, 25 patients [14.0%] and 24 patients [13.5%] with probably or possibly related TEAEs were reported, respectively. The only drug-related TEAE experienced by ≥5% of subjects in the VIT-45 group was headache (5.7%). Drug-related TEAEs experienced by ≥5% of subjects in the ferrous sulphate group were constipation (11.2%) and nausea (7.3%).

Among the drug-related TEAEs reported by ≥2% of subjects in either treatment group, those that were higher in the ferrous sulphate group than in the VIT-45 group included constipation (11.2% vs. 3.4%), nausea (7.3% vs. 1.1%), diarrhoea (3.9% vs. 0%), and hepatobiliary investigations (2.8% vs. 0.6%). The overall incidences of drug-related TEAEs that were higher in the VIT-45 group compared with the oral ferrous sulphate group included headache (5.7% vs. 2.8%), pruritus (2.3% vs. 0.0%), and rash (2.9% vs. 0.6%).

In summary, in a total of 899 patients treated with VIT-45, a total of 17 patients presented with adverse events that were judged by the investigator to be certainly related to study drug administration. A total of 25 patients reported TEAEs which were probably related to study medication. In the groups of patients treated with a comparator the following relationships were reported: in 118 patients treated with Venofer®, two adverse events were probably related to study drug administration. In 358 patients treated with oral ferrous sulphate, two patients reported TEAEs that were certainly related and 32 patients showed TEAEs that were probably related to study medication. In breast-fed infants, no TEAEs certainly or probably related to the administration of VIT-45 were reported.

In view of the high number of patients exposed to multiple doses of VIT-45, this low rate of adverse events which were assessed to be certainly or probably related to VIT-45 is a further indication of the good tolerability of VIT-45.

Moreover, VIT-45 seems to have a better tolerability than ferrous sulphate with respect to gastrointestinal side effects.

Serious Adverse Events, Withdrawals, and Deaths
Serious Adverse Events
The number and percentage of patients who experienced at least one serious adverse event (including death) and an overview of the body systems for which serious adverse events were reported in the individual studies are presented below.

Number (percentage) of patients with at least one serious adverse event

	001 VIT-45	**02 VIT-45**	**03 VIT-45**	**53214 VIT-45**	**015 VIT-45**	**015 Venofer®**
At least one serious TEAE (%)	0	0	0	12/163 (7.4)	6/119 (5.0)	8/118 (6.8)
	008 VIT-45	**008 FS**	**009 VIT-45**	**009 FS**	**03001 VIT-45**	**03001 FS**
At least one serious TEAE (%)	9/137 (6.6)	0	2/227 (0.9)	0	4/174 (2.3)	4/178 (2.2)

FS Ferrous sulphate

There were no serious adverse events in studies VIT-IV-CL-001 [5.3.1.1.1], VIT-IV-CL-02 [5.3.4.2.1] and VIT-IV-CL-03 [5.3.4.2.2].

Study 53214 [5.3.5.2.1]:
There were 12 patients (7.4%) who reported serious TEAEs, including the two patients (1.2%) who died. Renal transplantation was reported by three patients (1.9%). Only two patients experienced more than one serious TEAE (one patient experienced three serious adverse events and one experienced six serious adverse events). All other serious TEAEs were reported by only one patient each.

None of the serious TEAEs were considered by the investigator to be related to study medication.

Study VIT-IV-CL-015 [5.3.5.1.1]:
Fourteen patients (six treated with VIT-45 [5.0%] and 8 treated with Venofer® [6.8%]) reported serious TEAEs, including one patient in the VIT-45 group who died. Myocardial infarction (VIT-45 group), gastrointestinal haemorrhage, melaena (both events in the Venofer® group), arteriovenous fistula thrombosis and haematoma (one patient in each group for both events) were reported by two patients each. None of the serious TEAEs were considered by the investigator to be related to study medication.

Study VIT-IV-CL-008 [5.3.5.1.2]:
There were nine patients (6.6%) who reported serious TEAEs; all patients received VIT-45. Anaemia was the only serious TEAE reported by more than one patient. None of the serious TEAEs were considered by the investigator to be related to study medication.

Study VIT-IV-CL-009 [5.3.5.1.3]:
Serious TEAEs were reported in two patients (three events each), who received VIT-45. None of the serious TEAEs were considered by the investigator to be related to study drug. The following events were reported: endometritis decidual, pyrexia and metrorrhagia (one patient), uterine haemorrhage, vaginal hysterectomy and sepsis (one patient). All events were resolved.

In the subanalysis, four breast-fed infants (1.7%) in the VIT-45 group and one (0.9%) in the ferrous sulphate group experienced eight serious TEAEs (six VIT-45 and two ferrous sulphate). None of these TEAEs were considered by the investigator to be related to study drug. Two of the TEAEs in the VIT-45 group were of severe intensity, and in both cases the TEAEs resolved without sequelae. Two TEAEs (epilepsy and convulsion) in one breast-fed infant in the VIT-45 group and one TEAE of a cerebral cyst in the ferrous sulphate group resolved with sequelae. Both TEAEs were unlikely or unrelated to study drug.

Study 1VIT03001 [5.3.5.1.4]:
During the study, four (2.3%) subjects in the VIT-45 group, including the one subject who died, and four (2.2%) subjects in the ferrous sulphate group experienced at least one serious adverse event during the study, none of which was considered by the investigator to be related to study medication. The patients receiving VIT-45 experienced appendicitis, cholecystitis, postoperative infections and peripartum cardiomyopathy with cardiac failure leading to death. Patients treated with ferrous sulphate showed congestive cardiac failure, cholelithiasis, major depression and thrombophlebitis.

Serious adverse events by body system

Body system / preferred term (N, %)	53214 VIT-45 (N = 163)	015 VIT-45 (N = 119)	015 Venofer® (N = 118)	008 VIT-45 (N = 137)	009 VIT-45 (N = 227)	1VIT03001 VIT-45 (N = 174)	1VIT03001 FS (N = 174)
At least one serious TEAE	12 (7.4)	6 (5.0)	8 (6.8)	9 (6.6)	2 (0.9)	4 (2.3)	4 (2.2)
Blood and lymphatic system disorders	-	-	-	2 (1.5)	-	-	-
Cardiac disorders	1 (0.6)	2 (1.7)	1 (0.8)	2 (1.5)	-	1 (0.6)	1 (0.6)
Gastrointestinal disorders	3 (1.8)	-	2 (1.7)	4 (2.9)	-	-	-
General disorders and administration site conditions	1 (0.6)	1 (0.8)	-	-	1 (0.4)	-	-
Hepatobiliary disorders	-	-	-	1 (0.7)	-	1 (0.6)	1 (0.6)
Infections and infestations	4 (2.5)	1 (0.8)	2 (1.7)	-	2 (0.9)	2 (1.1)	-
Injury, poisoning and procedural complications	-	1 (0.8)	2 (1.7)	-	-	-	-
Metabolism and nutrition disorders	-	-	-	1 (0.7)	-	-	-
Neoplasms	-	-	-	1 (0.7)	-	-	-
Nervous system disorders	-	-	1 (0.8)	-	-	-	-
Psychiatric disorders	1 (0.6)	-	-	-	-	-	1 (0.6)
Reproductive system and breast disorders					2 (0.9)	-	-
Respiratory, thoracic, and mediastinal disorders	1 (0.6)	-	-	-	-	-	-
Surgical and medical procedures	3 (1.8)	2 (1.7)	-	-	1 (0.4)	-	-
Vascular disorders	2 (1.2)	1 (0.8)	3 (2.5)	1 (0.7)	-	-	1 (0.6)

In summary, serious adverse events were reported for many different body systems and no accumulation in one or more body systems became obvious. As none of the serious adverse events was considered to be

related to study medication, it can be assumed that treatment with VIT-45 is not causally related with the occurrence of serious adverse events.

Withdrawals
In Studies VIT-IV-CL-001 [5.3.1.1.1] and VIT-IV-CL-02 [5.3.4.2.1] all patients completed the study. In the other studies between 7.6 and 28.3% of patients discontinued prematurely.

None of the patients discontinued participation in the study due to lack of efficacy.

Study discontinuation due to TEAS

Study	Treatment	Total withdrawals N (%)	Study discontinuation due to TEAEs N (%)
VIT-IV-CL-003 [5.3.4.2.2]	VIT-45	13 (28.3)	3 (6.5)
No. 53214 [5.3.5.2.1]	VIT-45	13 (8.0)	5 (3.1)
VIT-IV-CL-015 [5.3.5.1.1]	VIT-45	9 (7.6)	2 (1.7)
VIT-IV-CL-015 [5.3.5.1.1]	Venofer®	16 (13.6)	5 (4.2)
VIT-IV-CL-008 [5.3.5.1.2]	VIT-45	12 (8.8)	2 (1.5)
VIT-IV-CL-008 [5.3.5.1.2]	Ferrous sulphate	11 (17.5)	5 (7.9)
VIT-IV-CL-009 [5.3.5.1.3]	VIT-45	29 (12.8)	3 (1.3)
VIT-IV-CL-009 [5.3.5.1.3]	Ferrous sulphate	15 (12.8)	1 (0.9)
1VIT03001 [5.3.5.1.4]	VIT-45	9 (5.2)	2 (1.1)
1VIT03001 [5.3.5.1.4]	Ferrous sulphate	16 (9.0)	4 (2.2)
All Trials		**143/900 (15.9)**	**32/899 (3.6)**

In summary, the number (and percentage) of patients treated with VIT-45 who withdrew due to adverse events was low (3.6 % overall). Thus, there is no hint that treatment with VIT-45 might result in safety problems in patients with IDA.

Deaths
An overview of the number of deaths reported for the individual studies is presented below.

Listing of deaths

	001 VIT-45	**02 VIT-45**	**03 VIT-45**	**53214 VIT-45**	**015 VIT-45**	**015 Venofer®**
Deaths, N (%)	0	0	0	2/163 (1.2)	1/118 (0.8)	0
	008 VIT-45	**009 VIT-45**	**009 FS**	**03001 VIT-45**	**03001 FS**	
Deaths, N (%)	1/137 (0.7)	0	0	1/174 (0.6)	0	

FS Ferrous sulphate

Study 53214 [5.3.5.2.1]:
There were two patients who died(one had pulmonary tuberculosis and one had cardiac failure acute). Both TEAEs were serious, severe in intensity and unrelated to study medication.

Study VIT-IV-CL-015 [5.3.5.1.1]:
One patient (0.8%) in the VIT-45 group died. This patient had acute anterior myocardial infarction, which was serious, severe in intensity and unlikely to be related to study medication. The patient died more than a week after study medication was withdrawn due to another, non-serious TEAE.

Study VIT-IV-CL-008 [5.3.5.1.2]:
One death was reported in this study. This patient in the VIT-45 group experienced a cardiac arrest, which was serious, severe in intensity and unrelated to study medication.

Study 1VIT03001 [5.3.5.1.4]:
There was one patient in the VIT-45 group who died during the study. They experienced peripartal cardiomyopathy with heart failure, which was serious, severe in intensity and unrelated to study medication.

In summary, only single fatalities occurred and none of them was considered to be related to study medication. Out of a total of 899 patients exposed to VIT-45, five patients died. Taking into consideration that the patient populations included in these studies consisted of chronically ill persons and that patients up to the age of 80 years were included, the unrelated death of five patients cannot be considered unexpected.

Clinical Laboratory Evaluations
There were no consistent trends in safety laboratory abnormalities. Only very occasionally, individual cases of increases in liver function tests (GGT, ALT, or AST) or of an elevated CRP value were reported. For haematocrit and red blood cells, mean values increased from baseline and, therefore, showed an improvement during study participation. An increase in reticulocyte count was experienced in Study VIT-IV-008 at the early timepoints in the VIT-45 group. As a result of treatment, serum ferritin and TfS levels above the normal ranges were measured in individual patients.

Similarities and Differences in Results Among Studies
In Studies VIT-IV-CL-008 and 1VIT03001, a higher rate of pruritus, rash and urticaria was reported in patients treated with VIT-45 if compared to patients treated with oral ferrous sulphate.

A comparison between the number and percentage of patients experiencing these adverse events during the clinical development of VIT-45 is presented below. In the single-dose pharmacology studies, VIT-IV-CL-001, –02, and VIRD-VIT-45-IM, no such adverse events were reported, thus these studies were not included in the table.

Comparison of adverse events

	003	53214	015	015	008	008	009	009	03001	03001
	VIT-45 N=45	VIT-45 N=163	VIT-45 N=119	Venofer® N=118	VIT-45 N=137	FS N=63	VIT-45 N=229	FS N=117	VIT-45 N=174	FS N=178
Pruritus[1]	0	2 (1.2)	1 (0.8)	2 (1.7)	2 (1.5)	1 (1.6)2	0	0	4 (2.3)	-
Rash[2]	0	0	1 (0.8)	1 (0.8)	6 (4.4)	1 (1.6)	2 (0.9)	1 (0.9)	11 (6.3)	4 (2.2)
Urticaria	2 (4.3)	0	0	0	3 (2.2)	0	-	-	1 (0.6)	1 (0.6)

[1] including “pruritus generalised”

[2] including ‘rash’, ‘rash erythematous’, ‘rash macular’, ‘rash maculo-papular’, ‘rash pruritic’

As can be seen, individual reports of pruritus, rash and urticaria were received in every study. These events occurred in patients treated with VIT-45 and in patients treated with the comparator Venofer® or oral ferrous sulphate.

In Study VIT-IV-CL-008, three patients experienced four events of urticaria. The intensity of urticaria was assessed as mild in three cases and moderate in one case (a second event experienced by one patient, which was unrelated to study drug) by the investigator. All three patients were re-challenged with a second dose of VIT-45 and the events did not recur. It can be concluded that the events were not due to immunological reactions after receiving study medication.

Summary and Conclusion
In the clinical studies performed, VIT-45 was well-tolerated by patients with IDA of different aetiology.

In the different studies, up to 56.9% of the patients reported at least one TEAE, which is not unusual in chronically ill patients and post partum women suffering from anaemia. An analysis of the TEAEs reported revealed no accumulation in one or more body systems, and the majority of adverse events were reported for single patients. The only adverse events which were experienced by more than 10% of the patients were headache in Study 1VIT03001 and hypotension in Study VIT-IV-CL-015. However, each of the two adverse events occurred in the parallel treatment groups of each study (headache 17.2% in the VIT-45 group and 11.8% in the ferrous sulphate group, hypotension 10.1% in the VIT-45 group and 10.2% in the Venofer® group), thus being not specifically imputed to VIT-45 (hypotensive periods are frequent in dialysis patients).

From the TEAEs reported in the clinical studies, there were no reported hypersensitivity reactions after treatment with VIT-45.

Serious adverse events were reported for up to 7.4% of the patients in the efficacy and safety studies (no reports of serious adverse events were received in the pharmacology studies). None of these events was considered to be related to the study medication.

In total, only a very low number of adverse events were judged to be related to treatment by the investigators.

The number of patients who discontinued study medication due to adverse events was low.

In total, nine studies have been completed, in which a total of 899 patients were treated with VIT-45. Five patients died and none of these fatalities was considered to be related to study medication.

CONCLUSIONS AND RISK:BENEFIT ASSESSMENT
Pharmacokinetic evaluation of VIT-45 using the PET technique showed a rapid distribution in the circulation. During the study period of 8 hours, the majority of the injected dose was cleared from the circulation and distributed in the liver, spleen, and bone marrow. The relative distribution of iron as VIT-45 showed a much higher uptake by the bone marrow in relation to spleen and liver. Red blood cell utilisation increased rapidly during the first 6 to 9 days indicating the potential efficacy of VIT-45 in iron replacement therapy.

The distribution volume of iron polymaltose complexes almost corresponds to that of plasma. In two Phase I/II studies in patients with mild to moderate IDA, pharmacokinetic analysis revealed increases in exposure roughly proportional with the iron dose administered with VIT-45.

The carbohydrate part of VIT-45 is metabolised by means of the glycolytic pathway. Degradation products of VIT-45 are iron(III), the (α 1→4)-linked glucose dimer maltose and oligomers maltotriose and maltotetraose, respectively.

VIT-45 demonstrated a monoexponential elimination pattern with a $t_{½}$ in the range of 10 to 18 hours. There was negligible renal elimination. Taking into consideration the predetermined limits set in the clinical study protocols dose and dosage schedules, no accumulation of iron with repeated study drug administration was observed.

Specific drug interactions for VIT-45 are not known.

All pharmacodynamic parameters investigated in Phase I/II studies, i.e. haemoglobin and iron storage variables, showed the expected response to i.v. iron replacement therapy. Serum ferritin values together with TfS values following repeated VIT-45 infusions demonstrated a clinically effective replenishment of depleted iron stores. Transiently elevated TfS also indicated that iron binding capacity is almost fully utilised following VIT-45 infusion. Undesired high levels of serum ferritin or TfS indicating iron intoxication were avoided. In the multiple-dose study, the gradual decrease in transferrin over time also indicated successful iron replacement. The treatment responses in parameters of iron metabolism led to a clinical response of rising haemoglobin in more than 97% of the participating patients.

In the pivotal clinical studies conducted in support of the efficacy and safety of VIT-45, all primary and secondary therapeutic response parameters confirmed that administration of VIT-45 was effective in treating IDA due to various aetiologies.

Haemoglobin levels were raised to expected and clinically meaningful levels.

In Study VIT-IV-CL-015, the primary response rate for haemodialysis patients, defined as an increase in haemoglobin of at least 10 g/L 4 weeks after baseline, was 46.4% in the VIT-45 group and 37.2% in the Venofer® group. In Studies VIT-IV-CL-008, -009, and 1VIT03001, based on the primary efficacy variable (increase in haemoglobin from baseline to Week 12 or increase of ≥20 g/L anytime during the 6-week study period, respectively), VIT-45 was non-inferior to ferrous sulphate in patients with IDA secondary to IBD and in patients with post partum anaemia, respectively.

The values of serum ferritin and TfS demonstrated a successful repletion of the iron stores in patients treated with VIT-45. Serum ferritin levels were increased rapidly by treatment with VIT-45, and the pre-defined target range for serum ferritin was reached by the majority of patients treated with VIT-45.

In the studies in which VIT-45 was compared to oral ferrous sulphate treatment (VIT-IV-CL-008, -009, and 1VIT03001), the increase of serum ferritin was significantly higher at all visits in patients treated with VIT-45 than in patients treated with ferrous sulphate.

TfS levels moved from suboptimal levels to the clinically accepted target range (20-50%) within 2 weeks after start of treatment with VIT-45.

No clinically significant new or unexpected safety concerns were found during the clinical development of VIT-45.

In the different studies up to 56.9% of the patients reported at least one TEAE, which is not unusual in chronically ill patients and postpartum women suffering from anaemia. An analysis of the TEAEs reported revealed no accumulation in one or more body systems, and the majority of adverse events were reported for single patients. Moreover, only a very low number of adverse events were judged to be related to treatment by the investigators, and the number of patients who discontinued study medication due to adverse events was low.

From the TEAEs reported in the clinical studies there was no indication that treatment with VIT-45 might result in hypersensitivity reactions. Polysaccharide complexes such as VIT-45 containing mainly α 1→4 glycoside linkages that can be readily hydrolysed by endogenous amylases are generally not immunogenic. In pre-clinical studies, VIT-45 neither induced any anaphylactoid-type reactions by itself nor showed any cross-reactivity with anti-dextran antibodies leading to dextran-induced anaphylactic shock reactions. Consequently, VIT-45 can be safely administered to patients who have been previously sensitised to iron dextran.

Serious adverse events were reported for up to 7.4% of the patients in the efficacy and safety studies (no reports of serious adverse events were received in the pharmacology studies). In all nine studies completed to date, in which a total of 899 patients were treated with VIT-45, five patients died. None of the serious adverse events or deaths was considered to be related to the study medication.

Clinical studies performed with VIT-45 have demonstrated an effective and safe ferric carboxymaltose complex for delivery of iron to target tissues in the treatment of patients with anaemia due to chronic renal failure, irritable bowel syndrome and anaemia post partum. Assessment of the benefits and risks of the use of VIT-45 in the treatment of iron deficiency in these patient groups demonstrates a favourable benefit-risk profile.

V USER CONSULTATION

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Ferinject 50mg Iron/ml Solution for Injection/Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

Preclinical studies were carried out in accordance with Good Laboratory Practice (GLP), and in accordance with recognised guidelines. No toxicity was demonstrated, and no new toxicological problems for these products were found.

EFFICACY

The clinical studies performed with VIT-45 have demonstrated that it is an effective and safe ferric carboxymaltose complex for delivery of iron to target tissues in the treatment of patients with iron deficiency.

No significant new or unexpected safety concerns were found during the clinical development.

PRODUCT LITERATURE

The summary of product characteristics, patient information leaflet and labelling are appropriate for a product of this type.

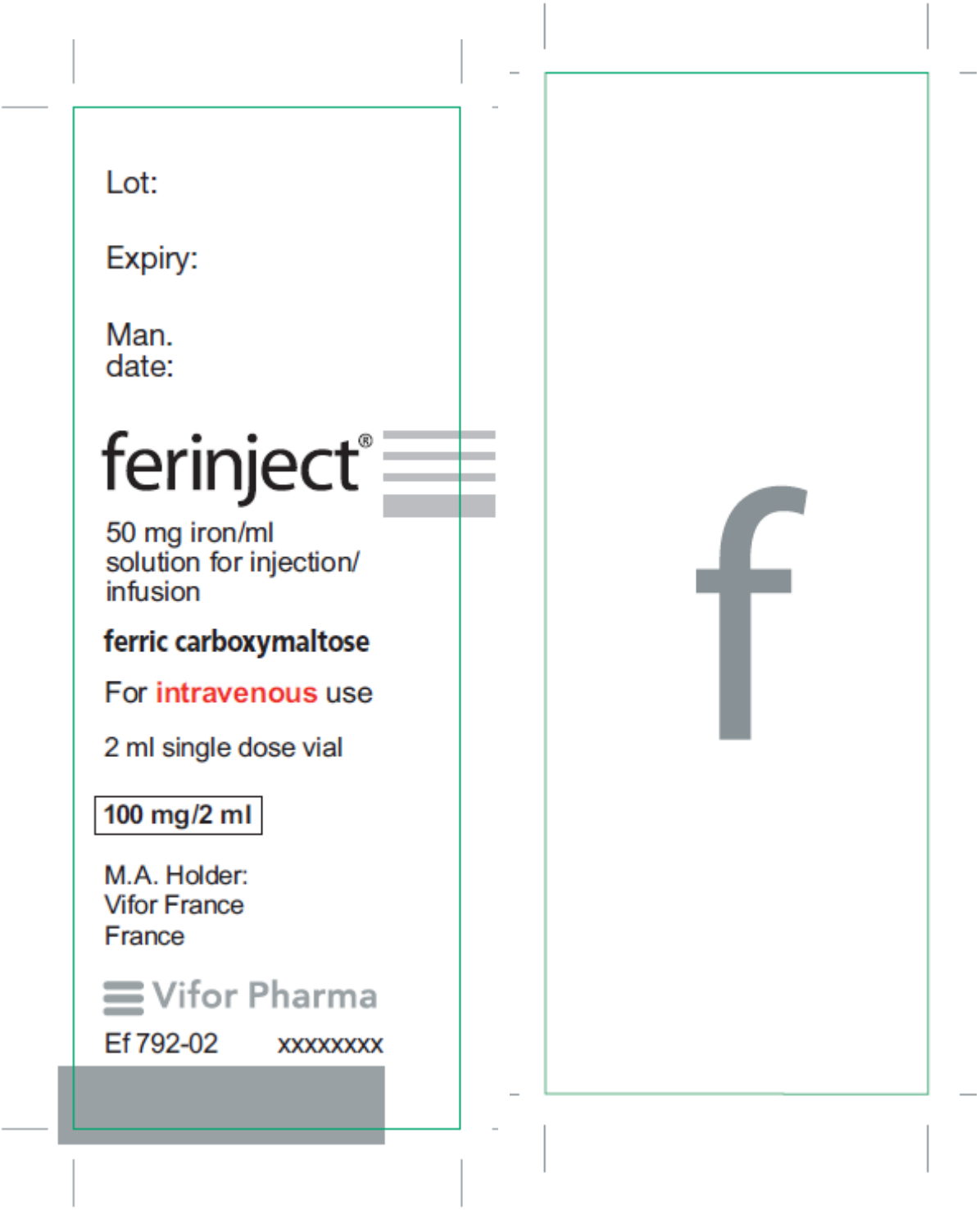
RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

Clinical studies performed with the product have demonstrated it to be an effective and safe ferric carboxymaltose complex for delivery of iron to target tissues in the treatment of patients with anaemia due to chronic renal failure, irritable bowel syndrome and anaemia post partum.

Assessment of the benefits and risks for its use in the treatment of iron deficiency in these patient groups demonstrates a favourable benefit-risk profile.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:

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Man.
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ferinject®
50 mg iron/ml
solution for injection/
infusion
ferric carboxymaltose
For intravenous use
2 ml single dose vial
100 mg/2 ml
M.A. Holder:
Vifor France
France
Vifor Pharma
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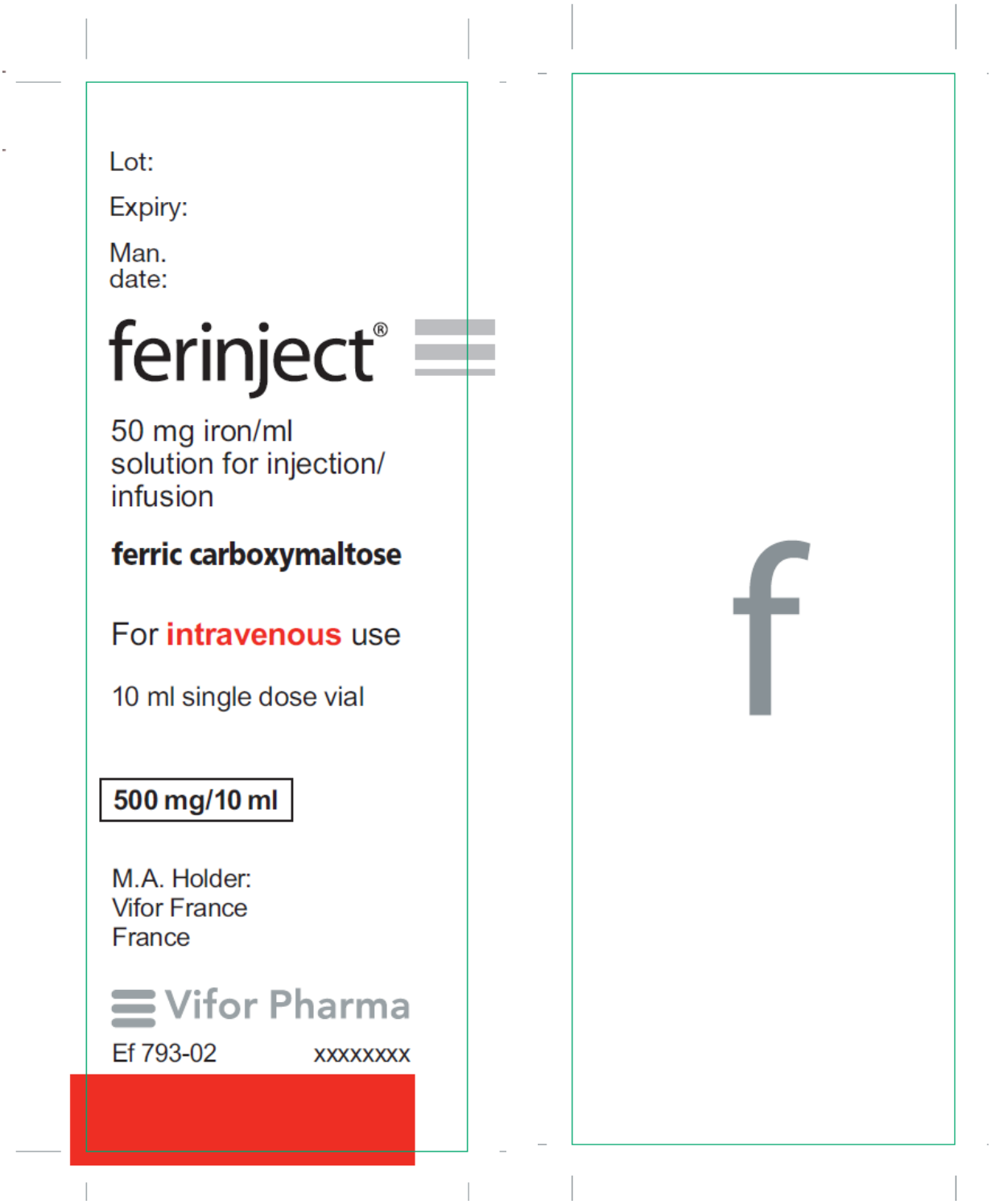
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solution for injection/
infusion
ferric carboxymaltose
For intravenous use
10 ml single dose vial
500 mg/10 ml
M.A. Holder:
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Vifor Pharma
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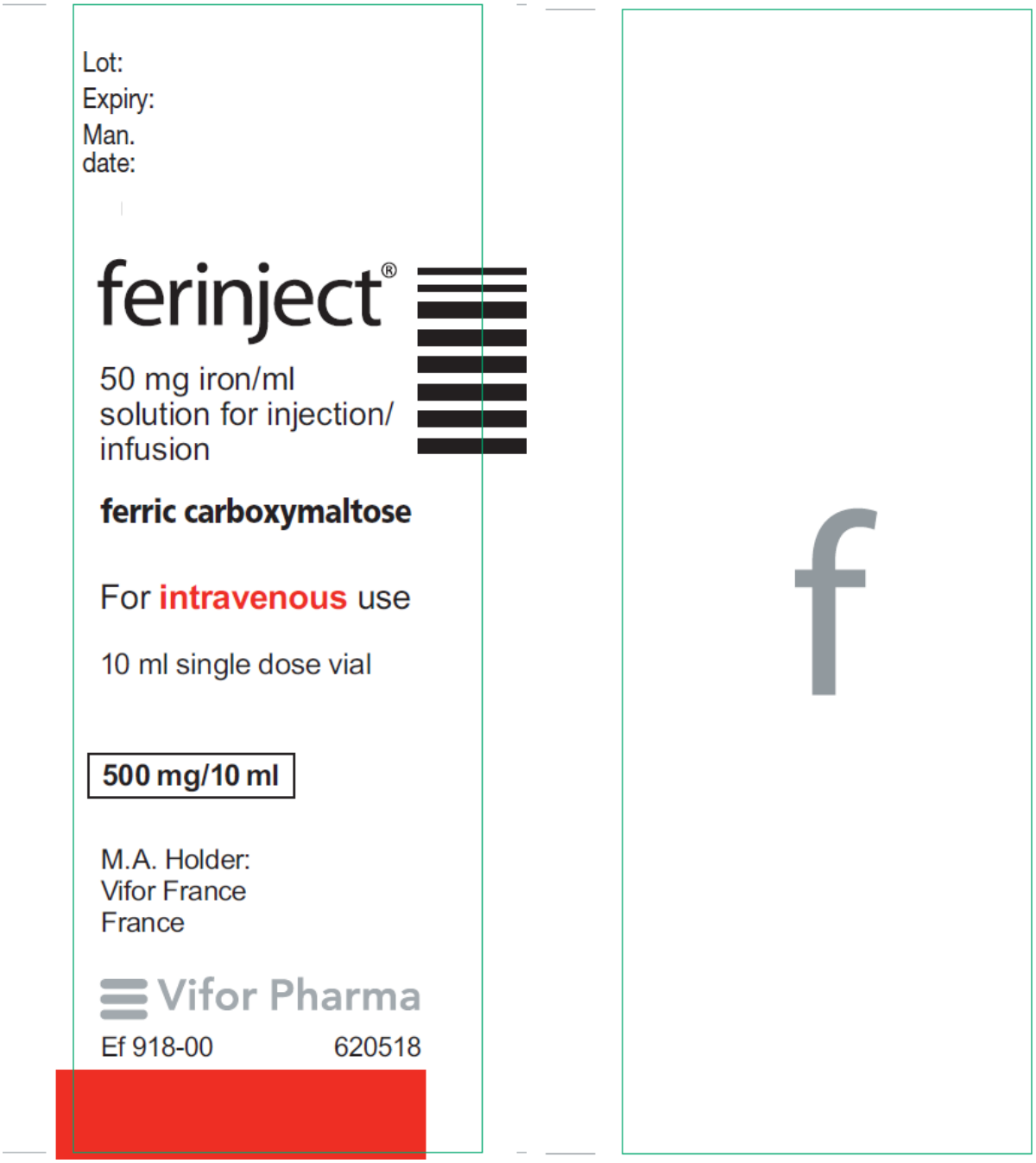
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Expiry:
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ferinject®
50 mg iron/ml solution for injection/ infusion
ferric carboxymaltose
For intravenous use
10 ml single dose vial
500 mg/10 ml
M.A. Holder:
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France
Vifor Pharma
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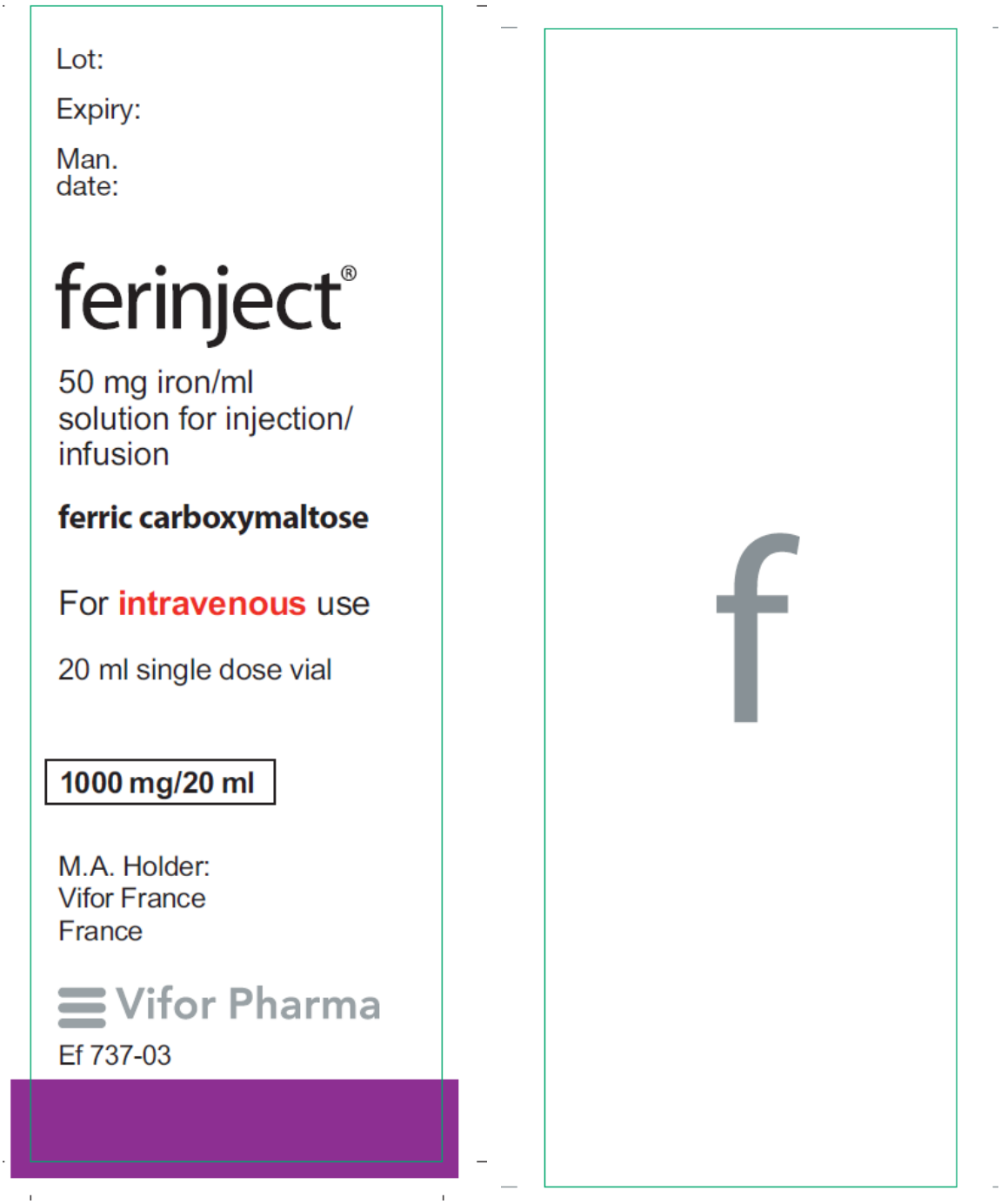
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Expiry:
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ferinject®
50 mg iron/ml solution for injection/ infusion
ferric carboxymaltose
For intravenous use
20 ml single dose vial
1000 mg/20 ml
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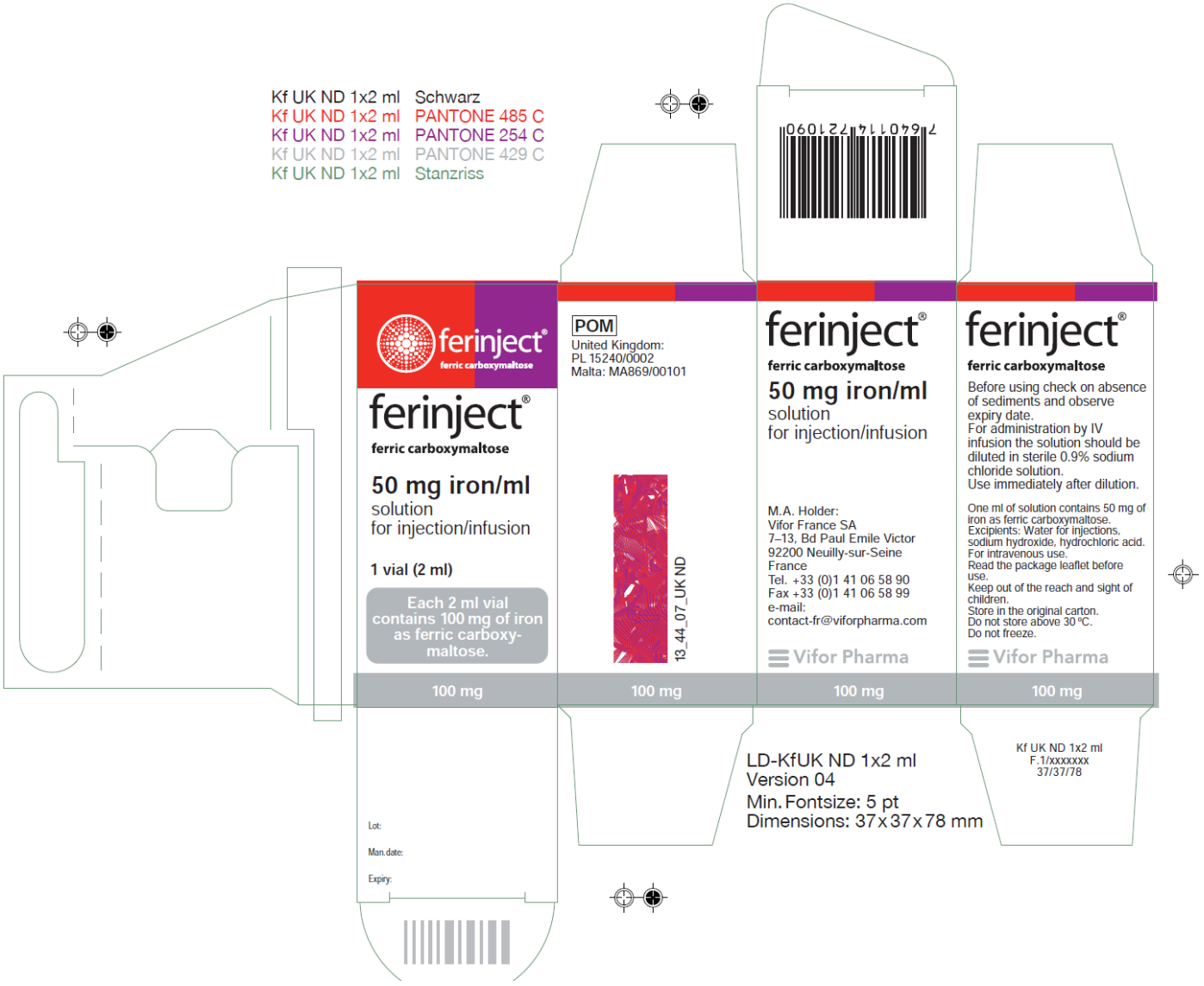
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Kf UK ND 1x2 ml PANTONE 485 C
Kf UK ND 1x2 ml PANTONE 254 C
Kf UK ND 1x2 ml PANTONE 429 C
Kf UK ND 1x2 ml Stanzriss
ferinject®
ferric carboxymaltose
50 mg iron/ml
solution
for injection/infusion
1 vial (2 ml)
Each 2 ml vial contains 100 mg of iron as ferric carboxy-maltose.
POM
United Kingdom:
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Malta: MA869/00101
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M.A. Holder:
Vifor France SA
7–13, Bd Paul Emile Victor
92200 Neuilly-sur-Seine
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
e-mail:
contact-fr@viforpharma.com
Vifor Pharma
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
One ml of solution contains 50 mg of iron as ferric carboxymaltose.
Excipients: Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original carton.
Do not store above 30 °C.
Do not freeze.
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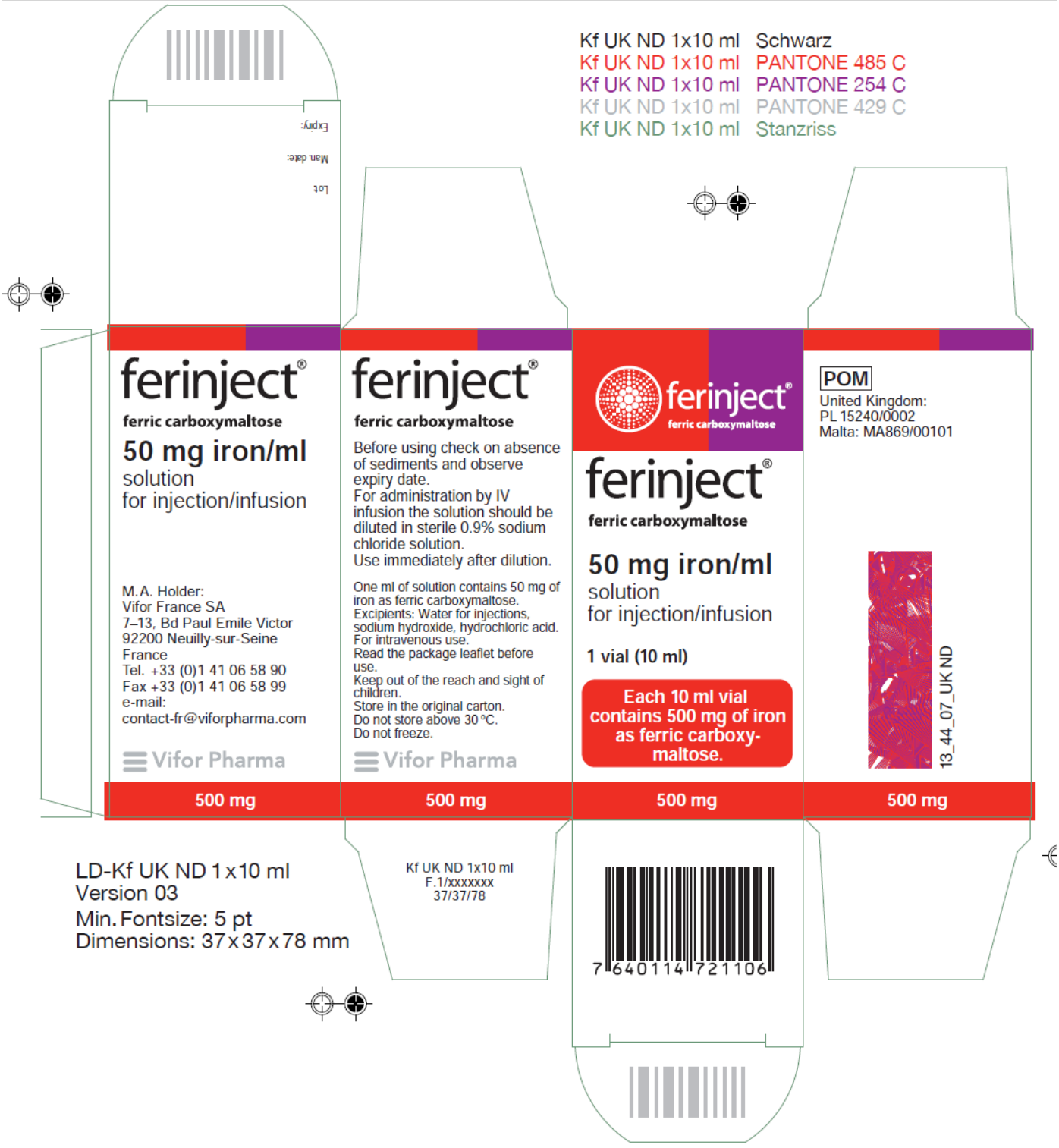
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ferinject®
ferric carboxymaltose
50 mg iron/ml
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for injection/infusion
M.A. Holder:
Vifor France SA
7–13, Bd Paul Emile Victor
92200 Neuilly-sur-Seine
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
e-mail:
contact-fr@viforpharma.com
Vifor Pharma
500 mg
ferinject®
ferric carboxymaltose
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
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Vifor Pharma
500 mg
ferinject®
ferric carboxymaltose
ferinject®
ferric carboxymaltose
50 mg iron/ml
solution
for injection/infusion
1 vial (10 ml)
Each 10 ml vial contains 500 mg of iron as ferric carboxy-maltose.
500 mg
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Malta: MA869/00101
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Min. Fontsize: 5 pt
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Expiry:
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ferinject®
ferric carboxymaltose
50 mg iron/ml
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for injection/infusion
M.A. Holder:
Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
e-mail:
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Store in the original carton in order to protect from light.
Do not store above 30 °C.
Do not freeze.
Vifor Pharma
1000 mg
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ferinject®
ferric carboxymaltose
ferinject®
ferric carboxymaltose
50 mg iron/ml
solution
for injection/infusion
1 vial (20 ml)
Each 20 ml vial contains 1000 mg of iron as ferric carboxymaltose.
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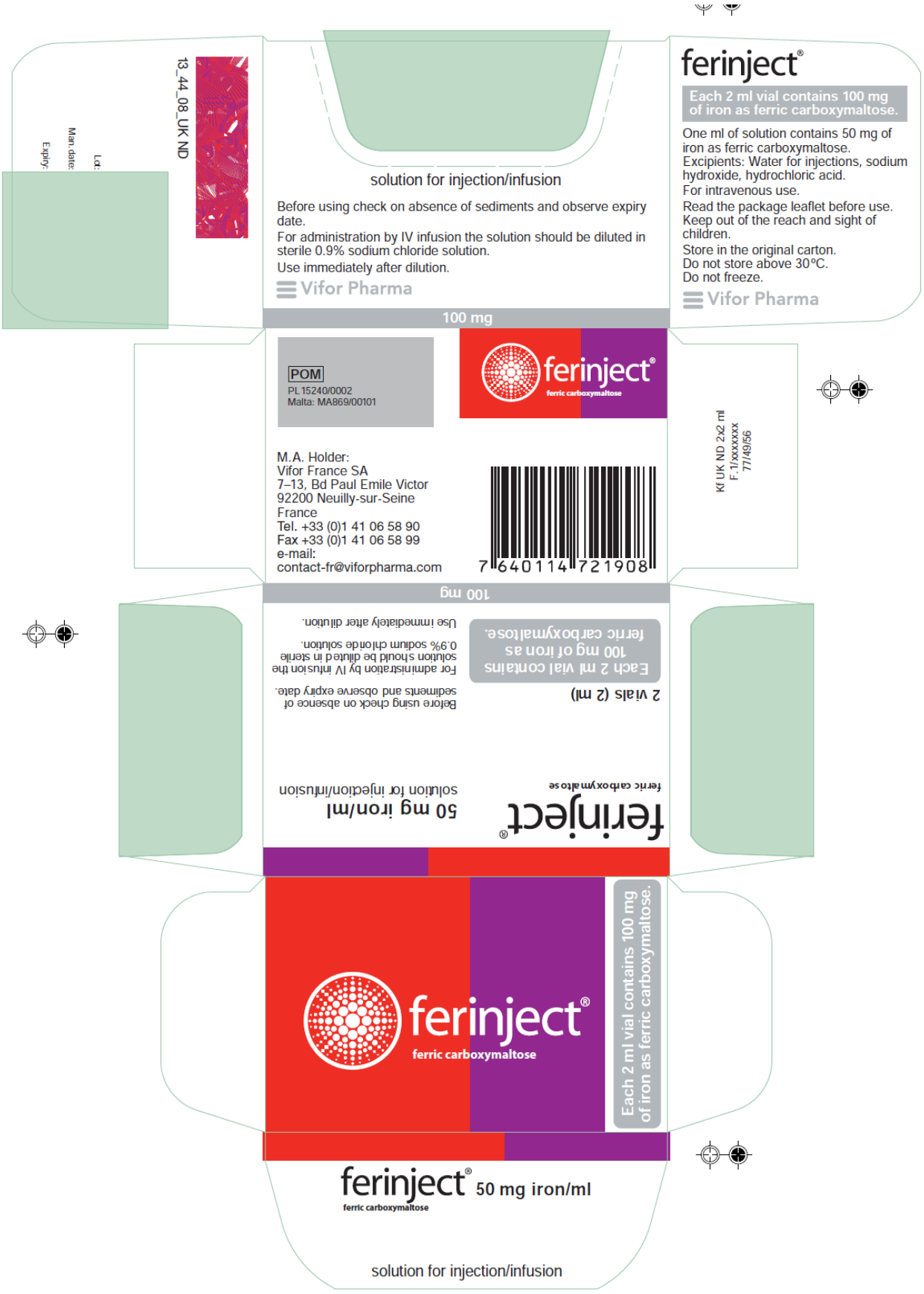
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solution for injection/infusion
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
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Vifor Pharma
ferinject®
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
One ml of solution contains 50 mg of iron as ferric carboxymaltose.
Excipients: Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
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Vifor Pharma
100 mg
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Malta: MA869/00101
ferinject®
ferric carboxymaltose
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7–13, Bd Paul Emile Victor
92200 Neuilly-sur-Seine
France
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Fax +33 (0)1 41 06 58 99
e-mail:
contact-fr@viforpharma.com
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Kf UK ND 2x2 ml
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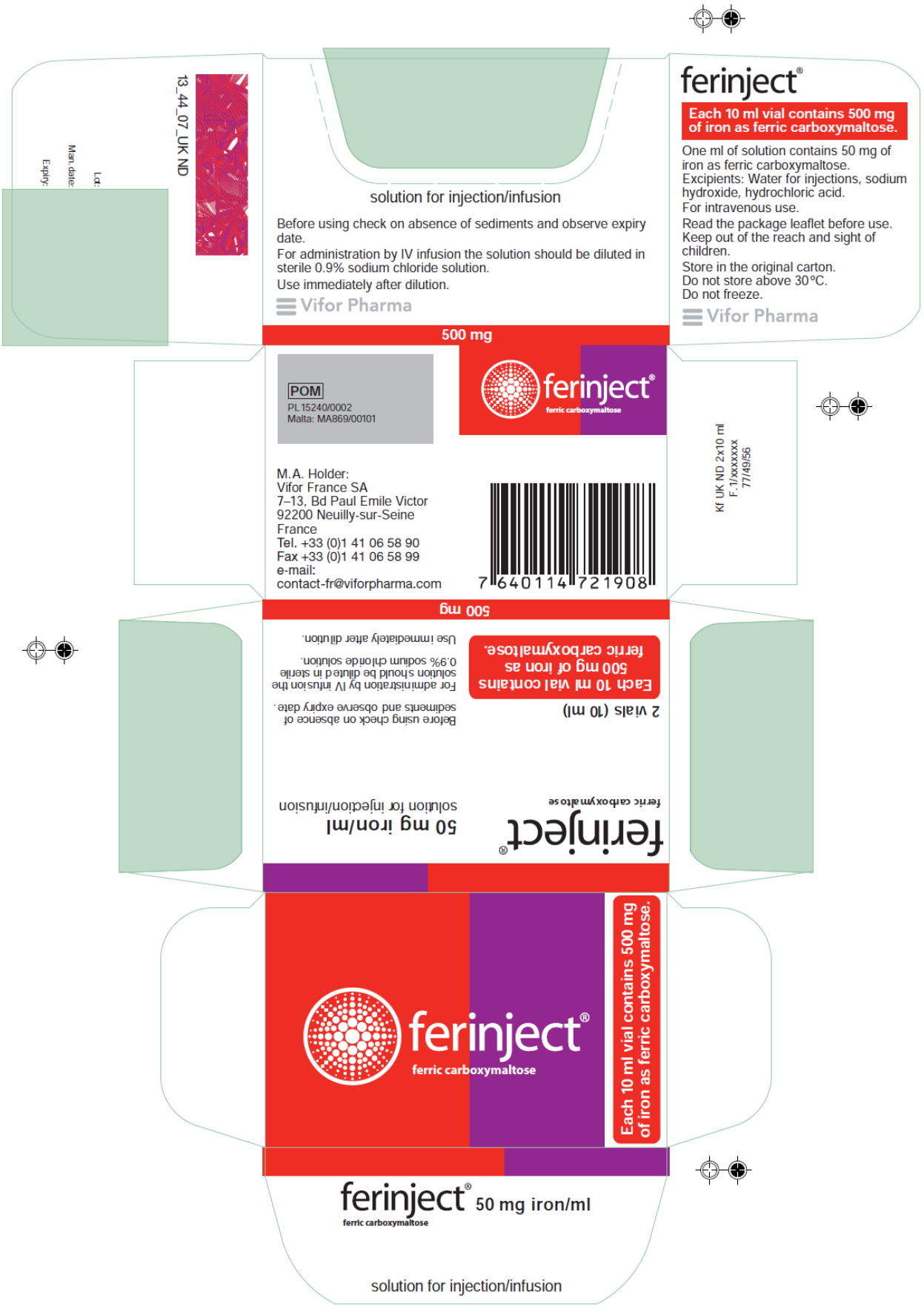
100 mg
2 vials (2 ml)
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
ferinject®
ferric carboxymaltose
50 mg iron/ml
solution for injection/infusion
ferinject®
ferric carboxymaltose
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
ferinject® 50 mg iron/ml
ferric carboxymaltose
solution for injection/infusion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Use immediately after dilution.
Vifor Pharma
ferinject®
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
One ml of solution contains 50 mg of iron as ferric carboxymaltose.
Excipients: Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
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Vifor Pharma
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Kf UK ND 2x10 ml
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500 mg
2 vials (10 ml)
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ferric carboxymaltose
50 mg iron/ml
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ferinject® 50 mg iron/ml
ferric carboxymaltose
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
ferinject®
ferric carboxymaltose
50 mg iron/ml solution for injection/infusion
5 vials (2 ml)
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
Before using check on absence of sediments and observe expiry date.
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100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
e-mail: contact-fr@viforpharma.com
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ferinject®
ferric carboxymaltose
100 mg
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
Kf 1128-00 620519 39/44.5/112.5
solution for injection/infusion
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Expiry:
Man. date:
ferinject®
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
One ml of solution contains 50 mg of iron as ferric carboxymaltose.
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Do not freeze.
Vifor Pharma


ferinject®
ferric carboxymaltose
50 mg iron/ml
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
ferinject® 50 mg iron/ml solution for injection/infusion
ferric carboxymaltose
5 vials (10 ml)
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
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Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
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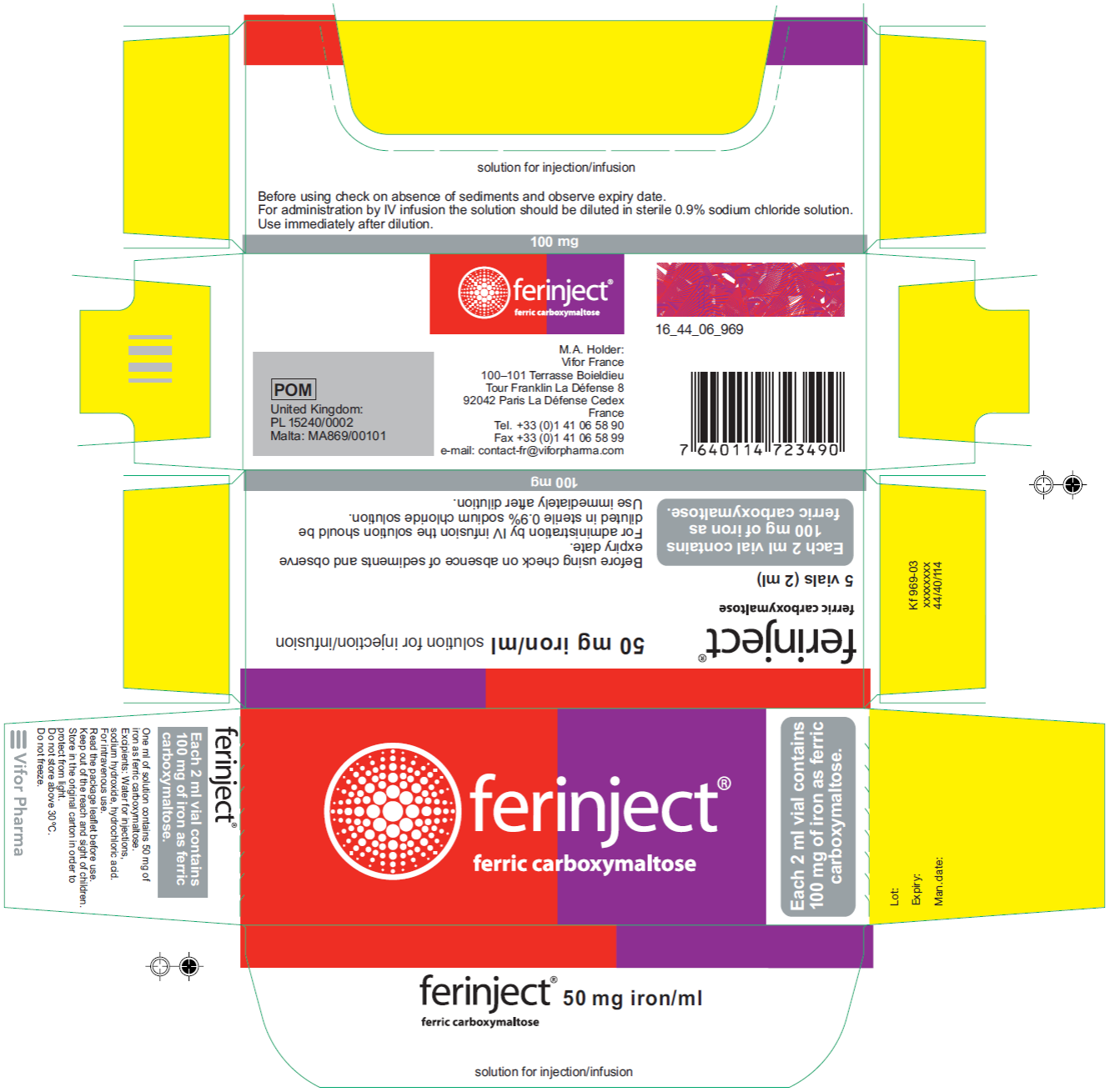
Man. date:
Vifor Pharma


solution for injection/infusion
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
100 mg
ferinject®
ferric carboxymaltose
16_44_06_969
POM
United Kingdom:
PL 15240/0002
Malta: MA869/00101
M.A. Holder:
Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
e-mail: contact-fr@viforpharma.com
7 640114 723490
100 mg
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
5 vials (2 ml)
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
ferinject®
ferric carboxymaltose
50 mg iron/ml solution for injection/infusion
Kf 969-03
xxxxxxxx
44/40/114
Vifor Pharma
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
One ml of solution contains 50 mg of iron as ferric carboxymaltose.
Excipients: Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original carton in order to protect from light.
Do not store above 30°C.
Do not freeze.
ferinject®
Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
ferinject®
ferric carboxymaltose
Lot:
Expiry:
Man.date:
ferinject® 50 mg iron/ml
ferric carboxymaltose
solution for injection/infusion


solution for injection/infusion
5 vials (10 ml)
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
500 mg
ferinject
ferric carboxymaltose
16_44_06_970
M.A. Holder:
Vifor France
100–101 Terrasse Boieldieu
Tour Franklin La Défense 8
92042 Paris La Défense Cedex
France
Tel. +33 (0)1 41 06 58 90
Fax+33 (0)1 41 06 58 99
e-mail: contact-fr@viforpharma.com
POM
United Kingdom:
PL 15240/0002
Malta: MA869/00101
7 640114 723506
ferinject
ferric carboxymaltose
50 mg iron/ml solution for injection/infusion
5 vials (10 ml)
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
Vifor Pharma
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.
Lot:
Expiry:
Man. date:
ferinject
ferric carboxymaltose
50 mg iron/ml
solution for injection/infusion

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists non-safety updates to the Marketing Authorisation for this product that have been approved by the MHRA since the DCP. The updates have been added as annexes to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of the procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
To change the storage conditions from "Do not refrigerate or freeze" to "Do not freeze". Consequently, section 6.4 (Special storage precautions) of the SPC, PIL and label have been updated	**UK/H/0894/001/IB/014**	SmPC PIL, Labelling	13/12/2010	13/01/2011	Approval	Yes (Annex 1.6)
To update Section 4.2 (Posology and administration) of the SPC with a new Ferinject standardised dosing regime which is superior to the current individually calculated dosage regimes of Venofer in correcting IDA in patients with mild IBD or IBD in remission. Consequential updates are made to the PIL.	**UK/H/0894/001/II/011**	SmPC PIL	13/12/2010	10/07/2011	Approval	Yes (Annex 1.6)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached Y/N (version)
To update Section 4.2 (Posology and administration) of the SPC by increasing the dose of iron that can be given as an IV injection to 1000mg: FERINJECT may be administered by intravenous injection using undiluted solution up to 1000 mg. For doses greater than 200 and up to 500 mg iron, FERINJECT should be administered at a rate of 100 mg/mm. For doses greater than 500 and up to 1000 mg iron, FERINJECT should be administered over 15 minutes. Consequential updates have been made to the labels and PIL	**UK/H/0894/001/II/012**	SmPC PIL, Labelling	13/12/2010	10/07/2011	Approval	Yes (Annex 1.6)
To update the SPC in line with a post-approval commitment with consequential updates to the PIL and labelling following discussions with the MHRA.	**UK/H/0894/001/II/010**	SmPC PIL, Labelling	13/12/2010	03/10//2011	Approval	Yes (Annex 1.6)
To update Section 4.2 of the SmPC by amending the wording to increase the maximum amount of iron that may be administered per kg body weight from 15mg to 20mg. Consequential updates are made to the PIL.	**UK/H/0894/001/II/013**	SmPC PIL	13/12/2010	10/07/2011	Approval	Yes (Annex 1.6)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached Y/N (version)
To change the storage conditions from "Do not refrigerate or freeze" to "Do not freeze". Consequently, section 6.4 (Special storage precautions) of the SmPC, PIL and label have been updated.	**UK/H/0894/001/IB/014**	SmPC PIL Labelling	13/12/2010	13/01/2011	Aprroval	No
To register an additional pack sizes of 2x2ml vials and 2x10 ml vials to the currently approved pack sizes (1x2ml, 1x10ml, 5x2ml and 5x10ml).	UK/H/0894/001/IA/018	SmPC PIL	13/09/2011	11/10/2011	Approval	No
To add a pack size of 20 ml.	UK/H/0894/001/II/027	SmPC PIL Labelling	19/04/2013	14/10/2013	Approval	No
To update sections 1, 2, 4.2 - 4.4, 4.6 - 4.9, 5.1 - 5.3 and 6.5 of the SPC in line with clinical trial data from a number of relevant studies. Changes to the adverse drug reaction table in section 4.8 are made as a result of additional clinical trial data being made available. Additional QRD updates have been made. Consequently the Leaflet has been updated UK/H/0894/001/II/026	UK/H/0894/001/II/026	SmPC PIL	07/01/2013	27/09/2013	Approval	No

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached Y/N (version)
To update Section 4.6 (Fertility, Lactation and Pregnancy) and Section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SmPC) and consequentially the leaflet with new study data about the indication of the product on cardiology and women's health. To also update Section 4.8 (Undesirable effects) of the SmPC, and consequentially the leaflet in line with recent Company Core Data Sheet (CCDS) and Quality Review of Documents (QRD) template.	**UK/H/0894/II/035/G**	SmPC PIL	16/05/2016	29/03/2017	Approval	Yes (Annex 1.7)

Annex 1.1

Reference: **PL 15240/0002; UK/H/0894/001/IB/014**

Product: FERINJECT 50 mg iron/ml solution for injection/infusion

MAH: **Vifor France SA**

Active Ingredient: **Ferric carboxymaltose**

Reason:
To change the storage conditions from "Do not refrigerate or freeze" to "Do not freeze". Consequently, section 6.4 (Special storage precautions) of the SPC, PIL and label have been updated.

Conclusion:
Satisfactory stability data, and updated SmPC fragments and PIL, were submitted in support of this variation application. The variation was approved on 13 January 2011 and the following updated SmPC fragments and PIL have been incorporated into this Marketing Authorisation.

Summary of Product Characteristics - updated

The fragments updated in view of the stated variation are reproduced below:

6.4 Special precautions for storage

Store in the original package. Do not store above 30 °C. Do not freeze.

10 DATE OF REVISION OF THE TEXT

13/01/2011

Annex 1.2

Reference: **PL 15240/0002; UK/H/0894/001/II/011**

Product: FERINJECT 50 mg iron/ml solution for injection/infusion

MAH: **Vifor France SA**

Active Ingredient: **Ferric carboxymaltose**

Reason:
To update Section 4.2 (Posology and administration) of the SPC with a new Ferinject standardised dosing regime which is superior to the current individually calculated dosage regimes of Venofer in correcting IDA in patients with mild IBD or IBD in remission. Consequential updates are made to the PIL.

Evaluation:
See Assessment Report (Annex 1.6)

Conclusion:
This variation was approved on 13 July 2011.

Annex 1.3

Reference: **PL 15240/0002; UK/H/0894/001/II/012**

Product: FERINJECT 50 mg iron/ml solution for injection/infusion

MAH: **Vifor France SA**

Active Ingredient: **Ferric carboxymaltose**

Reason:
To update Section 4.2 (Posology and administration) of the SPC by increasing the dose of iron that can be given as an IV injection to 1000mg:

FERINJECT may be administered by intravenous injection using undiluted solution up to 1000 mg. For doses greater than 200 and up to 500 mg iron, FERINJECT should be administered at a rate of 100 mg/mm. For doses greater than 500 and up to 1000 mg iron, FERINJECT should be administered over 15 minutes. Consequential updates have been made to the labels and PIL.

Evaluation:
See Assessment Report (Annex 1.6)

Conclusion:
This variation was approved on 13 July 2011.

Annex 1. 4

Reference: **PL 15240/0002; UK/H/0894/001/II/010**

Product: FERINJECT 50 mg iron/ml solution for injection/infusion

MAH: **Vifor France SA**

Active Ingredient: **Ferric carboxymaltose**

Reason:
To update the SPC in line with a post-approval commitment, with consequential updates to the PIL and labelling following discussions with the MHRA.

Evaluation:
See Assessment Report (Annex 1.6)

Conclusion:
This variation was approved on 03 October 2011.

Annex 1.5

Reference: **PL 15240/0002; UK/H/0894/001/II/013**

Product: FERINJECT 50 mg iron/ml solution for injection/infusion

MAH: **Vifor France SA**

Active Ingredient: **Ferric carboxymaltose**

Reason:
To update Section 4.2 of the SPC by amending the wording to increase the maximum amount of iron that may be administered per kg body weight from 15mg to 20mg. Consequential updates are made to the PIL.

Evaluation:
See Assessment Report (Annex 1.6)

Conclusion:
This variation was approved on 03 October 2011.

Annex 1. 6

Reference: **PL 15240/0002; UK/H/0894/001/II/010,**
PL 15240/0002; UK/H/0894/001/II/011
PL 15240/0002; UK/H/0894/001/II/012
PL 15240/0002; UK/H/0894/001/II/013

Final Variation Assessment Report (FVAR) for the stated variations.

Mutual Recognition Procedure

Type II variation
Final Variation Assessment Report

Ferinject 50 mg iron/ml solution for injection/infusion
Ferric Carboxymaltose

UK/H/0894/001/II/010-013

Marketing Authorisation Holder: Vifor France SA

Date: 12 July 2011

ADMINISTRATIVE INFORMATION

Name of the medicinal product(s) in the RMS	Ferinject 50 mg iron/ml solution for injection/infusion
INN (or common name) of the active substance(s)	Ferric Carboxymaltose
Pharmaco-therapeutic group (ATC code)	B03AC, Iron trivalent, parenteral preparations
Pharmaceutical form(s) and strength(s)	Solution For Injection/Infusion, 50 mg/ml

Reference Number for the Mutual Recognition Procedure	UK/H/0894/001/II/010-013
Member States concerned	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovak Republic, Spain and Sweden.

In the Reference Member State:

Marketing authorisation holder's name and address	Vifor France SA, 7-13 Boulevard Paul Emile Victor, F-92200 Neuilly-sur-Seine, France
Date of first authorisation	19 July 2007
Marketing authorisation number	PL 15240/0002

Variation Procedure Start Date	13 December 2010
Date of Preliminary Variation Assessment Report	22 January 2011
Day 60	10 June 2011
Day 90	10 July 2011

Nature of changes requested	- To update the SPC in line with a post-approval commitment (removal of contraindication in first trimester of pregnancy) - Introduction of a simplified dose determination to replace the Ganzoni formula - Increase the dose of Ferinject that can be administered as an IV bolus injection - Increase the maximum dose of iron that may be administered per kg bodyweight

I LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
ADR	Adverse Drug Reaction
AE	Adverse Event
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante
ALT	Alanine transaminase
ALP	Alkaline phosphatase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
BMI	Body Mass Index
CAI	Colitis Activity Index
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document
ECG	Electrocardiogram
EMEA	European Medicines Agency
ESA	Erythropoiesis Stimulating Agent
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
FCM	Ferric Carboxymaltose
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
Hb	Haemoglobin
Hct	Haematocrit
HD	Haemodialysis
HUB	Heavy uterine bleeding
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Conference on Harmonisation
IDA	Iron Deficiency Anaemia
ITT	Intention-To-Treat
IV	Intravenous
KDOQI	Kidney Disease Outcomes Quality Initiative
LDH	lactate dehydrogenase
LOCF	Last Observation Carried forward
MAA	Marketing Authorisation Application
MCH	Mean Corpuscular Haemoglobin

MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NACB	National Academy of Clinical Biochemistry
NCI-CTC	National Cancer Institute common toxicity criteria
NDD	Non dialysis-dependent
NICE	National Institute for Health and Clinical Excellence
NOAEL	No-observed-adverse-effect level
PIL	Patient Information Leaflet
PD	Pharmacodynamics
PK	Pharmacokinetics
PPS	Per-Protocol Set
PSRPH	Potential Serious Risk to Public Health
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent Adverse Event
TIBC	Total Iron Binding Capacity
TID	Three times daily
TNF	Tumour Necrosis Factor
TfS	Transferrin Saturation
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
WBC	White Blood Cell

II RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variation applications UK/H/0894/001/II/010-013 for Ferinject 50 mg iron/ml solution for injection/infusion (ferric carboxymaltose), in the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used, for the following proposed changes

- **UK/H/0894/001/II/010**
  To update the SPC in line with a post-approval commitment (including removal of contraindication in first trimester of pregnancy)
- **UK/H/0894/001/II/011**
  Introduction of a simplified dose determination to replace the Ganzoni formula
- **UK/H/0894/001/II/012**
  Increase the dose of Ferinject that can be administered as an IV bolus injection
- **UK/H/0894/001/II/013**
  Increase the maximum of iron that may be administered per kg bodyweight

are approvable.

III SCOPE OF THE VARIATIONS

This assessment report concerns Ferinject 50 mg iron/ml solution for injection/infusion, ferric carboxymaltose (FCM). This was initially licensed in the UK and several member states (AT, CZ, DE, DK, EE, EL, ES, FI, IE, LT, LU, LV, NL, PL, PT, SE, and SK) in a decentralised procedure that concluded on 19 July 2007. An MRP/Repeat-Use Procedure (UK/H/0894/001/E/01/MR) with Belgium, Bulgaria, Cyprus, France, Hungary, Iceland, Italy, Malta, Norway, Romania and Slovenia as new CMSs ended successfully on 9 March 2010.

During this MRP some CMSs had comments on the SPC, however since no changes were allowed during the procedure the applicant committed to a submission of a post-procedural variation in order to address these comments. These comments principally relate to removal of the contraindication for use in the first trimester of pregnancy. (**UK/H/0894/001/II/010**)

In addition to this post-procedural variation, the sponsor proposes the following additional revisions to the SPC section 4.2.

- Introduction of a simplified dose determination to replace the Ganzoni formula (**UK/H/0894/001/II/011**)
- Increase the dose of Ferinject that can be administered as an IV bolus injection (**UK/H/0894/001/II/012**)
- Increase the maximum dose of iron that may be administered per kg bodyweight (**UK/H/0894/001/II/013**)

These 4 Type II variations have been discussed in a single assessment report for convenience, and because they are relevant to each other.

IV SCIENTIFIC DISCUSSION

IV.1 UK/H/0894/001/II/010

IV.1.1 Introduction

During an MRP/Repeat-Use Procedure (UK/H/0894/001/E/01/MR) for Ferinject which ended successfully on 9 March 2010, France and Romania requested that the contraindication for use in the first trimester of pregnancy be removed from Section 4.3 of the SPC. Since no changes were allowed during the procedure the applicant committed to a submission of a post-procedural variation in order to address these comments.

In support of this variation the applicant has submitted an addendum to the CTD Module 2.4 (Nonclinical Overview) for Ferinject (VIT-45), that was previously submitted in March 2006. This addendum comprises a reappraisal of the nonclinical information relating to embryo-foetal toxicity of VIT-45, and takes into account the CHMP guidance on risk assessment of medicinal products on human reproduction and lactation (EMEA/CHMP/203927/2005), which came into effect in January 2009.

IV.1.2 Non clinical aspects

The scope of this change is based on an expert statement provided in the addendum to the non-clinical overview and reassessment of the relevant non-clinical studies. During procedure UK/H/0894/001/E/01/MR a number of CMSs requested a removal of the contraindication for use in the first trimester and this request has been based upon the recommendations of the Guideline On Risk Assessment Of Medicinal Product On Human Reproduction And Lactation: From Data To Labelling' (EMEA/CHMP/203927/2005).

A brief review of the embryo-fetal studies in rats and rabbits has been provided and they are summarised below:

Study no. VFR048/002163: Embryo-fetal toxicity study in rats:
GLP compliant embryo-fetal toxicity studies were performed in the rat (doses of 3, 9 and 30 mg Fe/kg/day). Clear signs of maternal toxicity were seen at 30 mg and 9 mg Fe/kg/day.

There were no adverse effects on embryo-fetal survival or growth although a small number of fetuses were found to have thickened/kinked ribs in the 30 mg Fe/kg/day group at the detailed skeletal examination, an effect that was considered treatment related. The expert has argued that rib abnormalities are common finding in studies at dosages that cause maternal toxicity. Nevertheless at a dose of 9 mg Fe/kg/day, no effects on fetal rib morphology were seen and this was considered to be the No-observed-adverse-effect level (NOAEL) for embryo-fetal development.

Study no. VFR049/004349: Embryo-fetal toxicity study in rabbits
Embryo-fetal toxicity studies were performed in the rabbit (doses of 4.5, 9, 13.5 and 18 mg Fe/kg/day), signs of maternal toxicity was seen at doses of 18 and 13.5 mg Fe/kg/day.

There was an increase in pre-implantation loss with a resultant reduction in the mean number of implantations and live young in the 18 mg Fe/kg/day group. No effects on embryo-fetal survival were seen at the lower doses. Embryo-fetal abnormalities were noted in all treatment groups and consisted of domed cranium (18, 13.5 and 9 mg Fe/kg/day) flexed bilateral forepaw/limb (18 mg Fe/kg/day), hydrocephaly, incomplete ossification of cranial centres, enlarged fontanel, unossified phalanges and cervical ribs (13.5

mg Fe/kg/day). The only effect noted in the 4.5 mg Fe/kg/day group was an increased incidence of unossified phalanges. The expert has stated that this could be a result of slight delay in maturity of the fetal skeleton, possibly secondary to iron overload in the parent animals, and did not represent a permanent adverse effect on the fetus. They have also argued that, based on historical control animal data at the time of the studies, there is no difference in the incidence of unossified phalanges in the 4.5 mg Fe/kg/day group and controlled litters. As a result the applicant proposes a NOAEL of 4.5 mg Fe/kg/day.

Assessor's Comment
It is clear that the rabbit developmental effects are seen on all doses and a clear NOAEL in the rabbit cannot be established. The applicant should provide historical data for the incidence of unossified phalanges in control animals in studies conducted at the time of study no. VFR049/004349 to fully support their argument for the dose level of 4.5 mg Fe/kg/day.

Study no. VFR 050/004685: Fertility and early embryonic development
Effects of Ferinject on fertility and early embryonic development were assessed in a GLP compliant study in rats with male and female animals dosed with 3, 9 and 30 mg Fe/kg three times per week by one hour intravenous infusions (i.e. 9, 27 and 90 mg Fe/kg/week). Signs of toxicity due to iron overload were apparent in adults in the 27 and 90 mg Fe/kg/week groups. Indices of fertility and early embryonic development were unaffected. The NOAEL for fertility and early embryonic development was considered to be 90 mg Fe/kg/week. It is concluded that Ferinject had no effect on animal fertility.

Risk Assessment
A number of GLP complaint studies have been completed for Ferinject to explore the effects on fertility and early embryonic development (rat), embryo-fetal development (rat and rabbit) and peri-post natal effects (rat). Changes to fetal skeletal development have been observed in the rat (at the high dose only) and for the rabbit (effects seen at all doses). Similar alterations in fetal skeletal parameters have been observed in embryo-fetal toxicity studies conducted on other parenteral iron products, such as iron sucrose (Venofer) and iron-poly(sorbitol-gluconate), secondary to iron overload in treated pregnant animals.

The expert is therefore suggesting a class effect for these products and has also supplied some argumentation for fetal protection against excessive iron exposure from the maternal circulation. Placental transfer of iron from radio-labelled Ferinject was found to be low in a study conducted in pregnant rats, with low transfer across the human placenta being observed in an *in vitro* study. It is implied that the placenta plays a role in facilitating appropriate iron supply to the developing fetus, and also serving as a protective barrier against excessive iron transfer and iron overload. The conclusion of the expert is that the fetus is well protected against excessive iron exposure as a result.

There is some data from animal studies that suggests embryo-fetal development effects during exposure to rabbits and rats. From these studies NOAEL for fetal development (9 mg Fe/kg/day or 63 mg Fe/kg/week in rats, 4.5 mg Fe/kg/day or 31.5 mg Fe/kg/week in rabbits) provide a 1.5 fold (rabbit) and 3 fold (rat) margins of safety over the maximum weekly human dosage of 20 mg Fe/kg (applicant is proposing an increase in dose from 15 mg Fe/kg to 20 mg Fe/kg).

The risk assessment process outlined in the EMEA/CHMP/203927/2005 guideline has been applied to the animal data for Ferinject. The expert has stated that the effects seen are likely to be a non-specific consequence of maternal toxicity, and are reversible, since ossification irregularities usually indicate a temporary delay in skeletal maturation periods. He has also concluded that in the case of the rabbit studies, the higher doses are harder to evaluate and the effects observed may be secondary to poor maternal

condition. They also acknowledge that in Section 6.2 of the guidance document that in cases of developmental effects, that true teratogenic (malformative) effects, associated with exposure in the first trimester, can result in embryonic loss. No effects of Ferinject on embryo-fetal losses were observed in any of the reproductive toxicity studies that were performed, covering all phases of the reproductive cycle. Based on this argumentation the expert concludes that relevant risks can be concluded from the non-clinical studies and that as no significant risk has been identified there is no justification to contraindicate in pregnancy. Proposals to amend sections 4.3, 4.6 and 5.3 with appropriate warnings have been supplied:

The proposal states:

Section 4.3:

4.3 Contraindications

The use of FERINJECT is contraindicated in cases of:
- *known hypersensitivity to FERINJECT or to any of its excipients*
- *anaemia not attributed to iron deficiency, e.g. other microcytic anaemia*
- *evidence of iron overload or disturbances in utilisation of iron*
- ***~~pregnancy in the first trimester~~***

Section 4.6:

4.6 Pregnancy and lactation

There are no or limited amount of data from the use of FERINJECT in pregnant women. *A careful risk/benefit evaluation is required before use during pregnancy****, especially during the first trimester****.*

Pre-clinical data indicate *that iron released from FERINJECT can cross the placenta* ***in limited, controlled amounts. Treatment of pregnant animals with FERINJECT at maternal non-toxic doses resulted in no adverse effects on embryos or foetuses (see section 5.3).***

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible (≤1%). Based on limited data on nursing women it is unlikely that FERINJECT represents a risk to the nursing child.

Section 5.3:

5.3 Pre-clinical safety data

Pre-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity. ***Pre-clinical*** *studies indicate that iron released from FERINJECT does cross the placental barrier and is excreted in milk* ***in limited, controlled amounts****. In reproductive toxicology studies using iron replete animals FERINJECT was associated with minor skeletal abnormalities in the fetus,* ***but only at dosages that cased maternal toxicity****. No long-term studies in animals have been performed to evaluate the carcinogenic potential of FERINJECT. No evidence of allergic or immunotoxic potential has been observed. A controlled in-vivo test demonstrated no cross-reactivity of FERINJECT with anti-dextran antibodies. No local irritation or intolerance was observed after intravenous administration.*

Conclusions

The applicant has readdressed the findings first presented in the initial application for Ferinject and has re-examined the developmental skeletal effects observed in the embryo-fetal studies in rats and rabbits. The skeletal changes observed in two species reflect growth retardation that can in cases of the rat be attributed to a consequence of maternal toxicity. However the effects such as delayed ossification in the rabbit occur at 4.5 mg Fe/kg/day and was not associated with maternal toxicity. The argumentation to remove the contraindication is not conclusive and there is sufficient evidence to suggest treatment related delayed ossification in rabbits.

In addition the applicant is proposing to increase the maximum tolerated single dose to 1000 mg of iron (20 ml) per day or 20 mg of iron (0.4 ml) per kg body weight (previously was 15 mg of iron per kg body weight). This would also be the maximum dose of iron permitted to be administered over a week.

At present there is insufficient experience in human exposure to warrant removal of the pregnancy contraindication, and the findings of the non-clinical studies further support continued caution to be applied for the use of this product during pregnancy.

IV.1.3 Clinical aspects

In addition to the changes to Sections 4.3, 4.6 and 5.3, the applicant has proposed several other changes to the SPC, arising from comments raised by CMSs during the MRP/Repeat-Use Procedure (UK/H/0894/001/E/01/MR) which ended successfully on 9 March 2010. These other changes are acceptable.

IV.2 UK/H/0894/001/II/011

IV.2.1 Introduction

In the current Ferinject SPC the cumulative dose required for repletion of iron stores is calculated using the Ganzoni formula. The applicant proposes that the Ganzoni formula is complex and errors may be made in calculating the required dose. The Ganzoni formula may also underestimate the storage iron depot, and patients may receive unsuitable doses.

The applicant has conducted a clinical study (**FER-IBD-COR**) with the aim to evaluate the efficacy and safety of a new standardised dosage regimen of Ferinject compared to individually calculated dosage regimens of Venofer (iron sucrose) in the correction of iron deficiency anaemia (IDA) in patients with inflammatory bowel disease (IBD) in remission.

IV.2.2 Study FER-IBD-COR

IV.2.2.1 Methods

This was a multi-centre, randomised, prospective, open-label study to investigate the efficacy and safety of a standardised correction dosage regimen of intravenous ferric carboxymaltose (Ferinject) versus iron sucrose (Venofer) for treatment of IDA in patients with IBD.

Baseline assessments were planned for Day 1, prior to the first dose of study drug. Subjects randomised to Ferinject were to be dosed up to three times (Days 1, 8 and 15) depending on their weight and Hb level at baseline. Subjects randomised to Venofer were to receive up to 11 infusions twice a week (for example, Days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32 and 35), depending on the individual dose regimen calculated using their iron deficit at baseline. All subjects were to return for safety, efficacy assessments at Weeks 4, 8 and 12. Subjects who were not anaemic at Week 12 were invited to continue to participate in the maintenance study.

- **Study Participants**

Subjects were considered eligible if they were suffering from mild IBD or in remission, with a Hb of 7 to 12 g/dL (female) or 7 to 13 g/dL (male), and ferritin <100 µg/L, and normal levels of vitamin B_{12} and folic acid. Exclusion criteria included history of erythropoietin, IV or oral iron therapy, or blood transfusion in the 4 weeks prior to screening.

Assessor's comment:
This study has been conducted in a population with mild IBD or IBD in remission, yet the proposed variation is intended to change the posology of Ferinject for the more general population of iron deficiency anaemia of any cause. A justification for this strategy has not been provided and is required.

Justification is required for the inclusion criterion of serum ferritin <100 µg/L. The British Society of Gastroenterology cites a level of <12-15 µg/L in a normal population, and < 50 µg/L in those with co-existent disease. Given that the study population comprised only patients with either mild IBD or those in remission, a level of <100 µg/L may be considered inappropriately high and may have resulted in the inclusion of patients who were not iron deficient.

- **Treatments**

Subjects were randomised in a 1:1 ratio to Ferinject or Venofer and were dosed as follows:

- **Ferinject**

Subjects were to receive up to three infusions (on Days 1, 8 and 15) according to their Hb and body weight, as summarised in the table below. The total weekly dose was not to exceed 1000 mg for any subject, regardless of their body weight.

Hb (g/dL)	Dosage of FERINJECT® for subjects with body weight <70 kg	Dosage of FERINJECT® for subjects with body weight ≥70 kg
<10	1500 mg	2000 mg
≥10	1000 mg	1500 mg

Subjects with body weight below 67 kg were to receive a single dose of 500 mg Ferinject as an infusion.

Subjects with body weight below 70 kg and with Hb baseline below 10 g/dL were to receive 1500 mg in total, whereby subjects with a body weight below 67 kg were to receive 500 mg on Days 1, 8, and 15 and subjects with a body weight between 67 kg and 70 kg were to receive 1000 mg on Day 1 and 500 mg on Day 8.

Subjects with body weight of 70 kg and above and with Hb baseline below 10 g/dL were to receive 2000 mg in total: 1000 mg on Days 1 and 8.

Subjects with body weight below 70 kg and with Hb baseline of 10 g/dL or higher were to receive 1000 mg in total whereby subjects with a body weight below 67 kg were to receive 500 mg on Days 1 and 8 and subjects with body weight between 67 kg and 70 kg were to receive 1000 mg on Day 1.

Subjects with body weight of 70 kg and above and with Hb baseline of 10 g/dL or higher were to receive 1500 mg in total: 1000 mg on Day 1 and 500 mg on Day 8.

Ferinject was to be diluted in sterile 0.9% sodium chloride solution as follows:

FERINJECT®	Iron	Maximum amount of sterile 0.9% sodium chloride solution	Minimum administration time
10 to 20 mL	500 to 1000 mg	250 mL	15 minutes

- **Venofer**

For subjects in the individually calculated Venofer dosage regimen group, the individual iron deficit was to be calculated using the modified formula of Ganzoni:

Cumulative iron deficit [mg] = body weight [kg] x (target Hb* - actual Hb) [g/dL]** x 2.4*** + iron storage depot [500 mg]

*Target Hb for body weight >35 kg = 15 g/dL, respectively 9.3 mmol/L
**To convert mmol/L to g/dL: multiply Hb (mmol/L) by the factor 1.61145
***Factor 2.4 = 0.0034 (iron content Hb = 0.34%) x 0.07 (blood volume = 7% of bw) x 10000 (conversion g/dL to mg/L)

If a subject's body mass index (BMI) was >25 (BMI = weight [kg]/height [m] x height [m]), a normalised weight was to be used for the calculation of iron deficit (Normalised weight = 25 x height [m] x height [m]).

Subjects were to receive up to 11 Venofer infusions twice a week, for example, on Days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, and 35, depending on their calculated iron deficit. The total single dose was not to exceed 200 mg of iron given not more than 3 times per week. If the total necessary dose exceeded the maximum allowed single dose, the dose (administration) was to be split.

Venofer was to be diluted in sterile 0.9% sodium chloride solution as follows: 10 mL Venofer (200 mg iron) in maximum 200 mL sterile 0.9% sodium chloride solution. Dilution was to be done immediately prior to infusion and the solution was to be administered via IV drip infusion by designated staff in at least 30 minutes.
The first 25 mL of iron (ie, 25 mL of solution) was to be infused as a test dose over a period of 15 minutes. If no adverse reactions were observed during this time, the remaining portion of the infusion was allowed to be given at an infusion rate of not more than 50 mL in 15 minutes.

Assessor's comment:
The treatment regime for Ferinject is consistent with the posology proposed in these variations. Furthermore the regime appears simple, and limits the number of infusions to 3. However it appears that heavier patients (≥85 kg) with more severe anaemia would receive lower doses of iron under this proposed regime than under the previous regime. The applicant should comment on the relevance of this.

The treatment regime for Venofer is consistent with the standard (licensed) posology for Venofer and Ferinject; however it is unclear why Venofer was chosen for the control group, rather than standard dosing with Ferinject, which would allow a more direct comparison of the safety and efficacy of the treatment regimes alone without the influence of the active substances themselves. The applicant should provide an explanation.

- **Objectives**

The primary objective of this study was to evaluate the non-inferiority in efficacy of the standardised dosage regimen of Ferinject compared to individually calculated dosage regimens of Venofer in the correction of IDA in patients with IBD in remission.

The secondary objective was to evaluate the safety and tolerability of the standardised correction dose regimen of Ferinject.

Assessor's comment:
As mentioned above, the relevance of the primary objective of this study is unclear.

- **Outcomes/endpoints**

Outcomes measured included:

- Changes in haemoglobin and ferritin
- Health-related quality of life (SF-36)
- CDAI (Crohn's disease activity index), CAI (colitis activity index), and CRP (C-reactive protein) were assessed to determine disease activity

- Standard laboratory parameters
- Adverse events

- **Sample size**

Sample sizes of 183 in both the Ferinject dosage group and the Venofer group were sufficient and the sample size calculation was acceptable.

- **Randomisation**

Randomisation was performed based on a pre-defined, computer-generated randomisation list. The randomisation was satisfactory.

- **Statistical methods**

- Analysis populations

The following 3 definitions of analysis populations were used for the data analysis and tabulations.

- **Safety Set**: All randomised subjects who received at least 1 dose of study treatment. Subjects were included in the analysis according to the treatment received.
- **Full Analysis Set (FAS)**: All randomised subjects who received at least 1 dose of study drug and who attended at least one post baseline visit, following the principle of intention-to-treat (ITT). Subjects were included in the analysis according to the treatment to which they were randomised.
- **Per-Protocol Set (PPS)**: All randomised subjects who were compliant with the study protocol, ie, who did not experience any major protocol deviations.

- Efficacy Evaluation

The primary endpoint was the number of responders as defined by an increase in Hb of at least 2 g/dL at Week 12 as compared to baseline. Evaluation was done by a one-sided 97.5% CI evaluated by a non-inferiority margin of 7%.

Secondary endpoints were:

- Proportion of subjects who achieved either an Hb increase ≥2 g/dL or Hb gender specific normal range at Week 12 (female ≥12, male ≥13 g/dL)
- Proportion of non-anaemic subjects at Week 12.
- Proportion of subjects with a ferritin measurement >100 µg/L at Week 12.
- Proportion of subjects with a TfS (transferring saturation) score of between 20 and 50% at Week 12.
- Proportion of non-anaemic subjects with a ferritin measurement >100 µg/L at Week 12.
- Hb, ferritin and TfS adjusted for baseline measurement at subsequent visits (Week 1 to Week 12).
- Health-related QoL as measured by SF-36 version 2 adjusted for baseline score at Week 12.
- IBDQ adjusted for baseline score at Week 12.

Effect of treatment on the above endpoints was tested using logistic regression with responder status as dependent variable, treatment as a factor and baseline score as covariate. Interaction between

treatment and baseline score were further investigated in a separate model. Continuous variables for analysis were: Hb as recorded at all time points during study conduct, ferritin as recorded at all time points during study conduct, TfS as recorded at all time points during study conduct.

- Missing data

The analyses have been based on observed cases (ie, no replacement of missing data). For the primary endpoint last observation carried forward (LOCF) data has also been presented (where at least one post baseline score is present), as has 'worst case' data (if a subject has a missing response at Week 12 then the response is taken to be non-responder).

Assessor's comment:
A clinical justification for the non-inferiority margin has not been provided. This is required.

The use of observed cases is not an acceptable method for dealing with missing data. Worst case data is the most conservative method, and will be used together with per protocol data, for the assessment of efficacy.

IV.2.2.2 Results

- **Participant flow**

A total of 880 subjects were screened, of whom 485 were randomised (244 subjects to Ferinject group and 241 to Venofer group). Main reasons for screening failures were not meeting inclusion criteria such as required Hb, ferritin, vitamin B12, and/or folic acid levels.

The majority of subjects (483/485) were treated with study drug; 2 subjects in the Venofer group were lost to follow-up after randomisation and received no treatment. A total of 48/485 (9.9%) subjects withdrew prematurely (22/244 [9.0%] in the Ferinject group and 26/241 [10.8%] in the Venofer group). The percentage of subjects withdrawing prematurely was similar in the two treatment groups.

Subject disposition is summarised in the table below.

	FERINJECT® (N = 244) n (%)	VENOFER® (N = 241) n (%)	Total (N = 485) n (%)
Screened	-	-	880
Screening failures	-	-	395
Randomised	244 (100)	241 (100)	485 (100)
Treated	244 (100)	239 (99.2)	483 (99.6)
Withdrawn	22 (9.0)	26 (10.8)	48 (9.9)
Completed	222 (91.0)	215 (89.2)	437 (90.1)

The reasons for premature discontinuation are summarised in the table below.

	FERINJECT® (N = 244) n (%)	VENOFER® (N = 241) n (%)	Total (N = 485) n (%)
Subjects discontinued	22 (9.0)	26 (10.8)	48 (9.9)
Reasons for discontinuation:			
Excessive acute bleeding* or surgery with expected relevant blood loss	0 (0.0)	2 (0.8)	2 (0.4)
Intolerable AE	8 (3.3)	4 (1.7)	12 (2.5)
Withdrawal of consent	5 (2.0)	8 (3.3)	13 (2.7)
Intercurrent illness, condition or procedural complication	0 (0.0)	3 (1.2)	3 (0.6)
Subject's best interest (investigator's opinion)	1 (0.4)	0 (0.0)	1 (0.2)
Intake of iron preparations other than study drug	0 (0.0)	2 (0.8)	2 (0.4)
Non-compliance with study procedures because of AE due to i.v. infusion	0 (0.0)	2 (0.8)	2 (0.4)
Non-compliance with study procedures due to numerous visits in the hospital	0 (0.0)	3 (1.2)	3 (0.6)
Withdrawal due to numerous infusions of VENOFER®	0 (0.0)	4 (1.7)	4 (0.8)
Other	10 (4.1)	6 (2.5)	16 (3.3)

Assessor's comment:
Subject discontinuation data is acceptable. It is noted that significantly more subjects discontinued in the Venofer arm due to issues related to the number of IV infusions.

- **Conduct of the study**

Among all randomised subjects, there were 67/485 (13.8%) subjects with at least one major protocol deviation (7.0% in the Ferinject group and 20.7% in the Venofer group). The most common major protocol deviation overall was "compliance to study drug is unequal to 100% ± 10%" which was reported in 63/485 (13.0%) subjects overall, 7.0% in the Ferinject group and 19.1% in the Venofer group.

A summary of major protocol deviations is shown in the table below.

Type of deviation	FERINJECT® (N = 244) n (%)	VENOFER® (N = 241) n (%)	Total (N = 485) n (%)
Any subjects with major protocol deviation	17 (7.0)	50 (20.7)	67 (13.8)
Violation of inclusion/exclusion criteria	0 (0.0)	2 (0.8)	2 (0.4)
Intake of prohibited medication	0 (0.0)	1 (0.4)	1 (0.2)
Compliance to study drug is unequal to 100% ± 10%	17 (7.0)	46 (19.1)	63 (13.0)
Drug treatment despite safety stopping rule conditions	0 (0.0)	2 (0.8)	2 (0.4)

Assessor's comment:
Protocol amendments and deviations are acceptable.

- **Baseline data**

Subject demographic data is shown in the table below.

	FERINJECT® (N = 244)	VENOFER® (N = 239)	Total (N = 483)
Age (years)			
Mean (SD)	39.68 (13.74)	39.55 (14.38)	39.61 (14.05)
Median (Range)	39.50 (18.0, 81.0)	38.00 (18.0, 78.0)	39.00 (18.0, 81.0)
Height (cm)			
Mean (SD)	170.0 (8.9)	169.7 (8.9)	169.8 (8.9)
Median (Range)	169.0 (149, 192)	169.0 (151, 198)	169.0 (149, 198)
Weight (kg)			
Mean (SD)	68.40 (14.53)	68.04 (13.96)	68.22 (14.24)
Median (Range)	66.60 (39.0, 137.0)	66.30 (40.0, 118.0)	66.50 (39.0, 137.0)
Sex (n [%])			
Male	98 (40.2)	101 (42.3)	199 (41.2)
Female	146 (59.8)	138 (57.7)	284 (58.8)
Ethnic origin (n [%])			
White	239 (98.0)	231 (96.7)	470 (97.3)
Black	1 (0.4)	1 (0.4)	2 (0.4)
Asian	2 (0.8)	5 (2.1)	7 (1.4)
Other	2 (0.8)	2 (0.8)	4 (0.8)

The incidence and history of Crohn's disease, ulcerative colitis and anaemia are summarised in the table below.

	FERINJECT® (N = 244)	VENOFER® (N = 239)	Total (N = 483)
Diagnosis (n [%])			
Crohn's disease	86 (35.2)	74 (31.0)	160 (33.1)
Ulcerative colitis	158 (64.8)	165 (69.0)	323 (66.9)
Anaemia	244 (100.0)	239 (100.0)	483 (100.0)
Duration of Crohn's disease (months)			
n	86	74	160
Mean (SD)	100.73 (101.06)	90.69 (88.01)	96.09 (95.08)
Median (Range)	68.32 (1.3, 503.3)	65.49 (0.3, 347.6)	66.83 (0.3, 503.3)
Duration of ulcerative colitis (months)			
n	158	165	323
Mean (SD)	74.20 (79.08)	72.41 (77.72)	73.29 (78.27)
Median (Range)	49.86 (0.3, 320.9)	41.10 (0.2, 407.2)	43.50 (0.2, 407.2)
Duration of anaemia (months)			
n	244	239	483
Mean (SD)	29.12 (49.46)	28.70 (45.67)	28.91 (47.58)
Median (Range)	6.39 (0.0, 320.9)	9.10 (-0.1, 264.9)	8.05 (-0.1, 320.9)

Assessor's comment:
Baseline data for haemoglobin and ferritin status should be provided.

- **Outcomes and estimation**

  - Primary Endpoint

    The table below shows the results for the primary endpoint, the proportion of subjects with an increase in Hb of at least 2 g/dL at Week 12 compared to baseline.

	FAS (observed case)		PPS	
	FERINJECT® (N = 240)	**VENOFER® (N = 235)**	**FERINJECT® (N = 227)**	**VENOFER® (N = 189)**
Number of observations	228	220	218	181
Responder (n [%])	150 (65.8)	118 (53.6)	144 (66.1)	98 (54.1)
Non-responder (n [%])	78 (34.2)	102 (46.4)	74 (33.9)	83 (45.9)
% of subjects responding	65.79	53.64	66.06	54.14
Difference[1] in % (FERINJECT®-VENOFER®)	12.15		11.91	
95% CI	(3.07, 20.97)		(2.28, 21.31)	
p-value[2]	0.004		0.008	
	FAS (LOCF)		**FAS (worst case)**	
	FERINJECT® (N = 240)	**VENOFER® (N = 235)**	**FERINJECT® (N = 227)**	**VENOFER® (N = 189)**
Number of observations	239	234	239	234
Responder (n [%])	156 (65.3%)	124 (53.0%)	150 (62.8%)	118 (50.4%)
Non-responder (n [%])	83 (34.7%)	110 (47.0%)	89 (37.2%)	116 (49.6%)
% of subjects responding	65.27	52.99	62.76	50.43
Difference[1] in % (FERINJECT®-VENOFER®)	12.28		12.33	
95% CI	(3.42, 20.88)		(3.40, 21.00)	
p-value[2]	0.003		0.003	

Assessor's comment:
The significance of a response rate of 63% for the endpoint of increase in Hb of at least 2 g/dL at Week 12 in the Ferinject is questioned. This is on the basis that in one of the original Ferinject licensing studies (1VIT03001, 6 week study in women with postpartum anaemia) a similar primary endpoint was used (percentage of patients achieving an increase in Hb of at least 2 g/dL at any time after baseline). In this study the responder rate was 96%. In contrast, at no point in the current study did the responder rate rise above 72% (achieved at Week 8). Furthermore, in a study by Kulnigg et al. (Am J Gastroenterol 2008; 103: 1182-1192), in which an IBD population was assessed and FCM dose was calculated using the Ganzoni formula, the responder rate at 12 weeks was 77%. This calls into question the external validity of the study.

Superiority has been adequately demonstrated for Ferinject over Venofer with a 12% difference in the proportion of subjects with an increase in Hb of at least 2 g/dL at Week 12.

- Secondary Endpoints
    - Proportion of Subjects who Achieved either an Hb Increase ≥2 g/dL or Hb Gender Specific Normal Range at Week 12
        - Ferinject - 79.9%; Venofer 71.4% (full analysis set, worst case)
        - 8.55% difference in proportion (95% CI 0.81 – 16.18)
    - Proportion of Non-anaemic Subjects at Week 12
        - Ferinject - 72.8%; Venofer 61.8% (full analysis set)
        - Odds ratio 1.65 (95% CI 1.10 – 2.46)
    - Proportion of Subjects with a Ferritin Measurement >100 µg/L at Week 12
        - Ferinject – 42.5%; Venofer – 22.3% (full analysis set)
        - Odds ratio 1.95 (95% CI 1.30 – 2.92)
    - Proportion of Subjects with a TfS Score of between 20 and 50%
        - Ferinject – 52.7%; Venofer – 36.4% (full analysis set)
        - Odds ratio 2.05 (95% CI 1.37 – 3.06)
    - Proportion of Non-anaemic Subjects with a Ferritin Measurement >100 µg/L at Week 12
        - Ferinject – 31.1%; Venofer – 16.7% (full analysis set)
        - Odds ratio 2.23 (95% CI 1.40 – 3.53)
    - Change from baseline in Hb, Ferritin and TfS
        - Hb (g/dL)

	FERINJECT® (N = 240)	VENOFER® (N = 235)	p-values
Change from baseline to: [1]			
Week 1	0.45	0.41	0.550
Week 2	1.34	0.90	<0.001
Week 4	2.32	1.88	<0.001
Week 8	2.81	2.27	<0.001
Week 12	2.81	2.36	0.002

- Ferritin (µg/L)

	FERINJECT® (N = 240)	VENOFER® (N = 235)	p-values
Change from baseline to: [1]			
Week 1	315.17	126.99	<0.001
Week 2	343.29	173.62	<0.001
Week 4	205.69	160.09	<0.001
Week 8	115.87	94.08	0.015
Week 12	93.94	72.01	0.007

- Transferrin saturation (%)

	FERINJECT® (N = 240)	VENOFER® (N = 235)	p-values
Change from baseline to: [1]			
Week 1	10.11	4.96	<0.001
Week 2	15.22	9.22	<0.001
Week 4	15.96	11.64	<0.001
Week 8	14.39	10.47	<0.001
Week 12	15.03	9.24	<0.001

- Quality of Life Questionnaire SF-36 version 2 & Intestinal Bowel Disease Questionnaire
  - Results numerically in favour of Ferinject, but not statistically significant.

Treatment compliance (based on the accurate computer-generated total dose calculated from Ganzoni formula) in the Ferinject group was 92.5% as compared to 79.1% in the Venofer group. Even where the Ganzoni formula was calculated correctly by the investigator compliance was still lower in the Venofer group, presumably due to the large number of infusions required.

Assessor's comment:
Superiority of Ferinject over Venofer is supported by the secondary endpoint, and compliance was significantly higher in the Ferinject arm.

In one of the efficacy studies submitted as part of the original licensing application for Ferinject (VIT-IV-CL-008, involving subjects with IDA secondary to IBD) the primary endpoint was change from baseline level of Hb at Week 12. A result of 3.6 g/dL was obtained for the Ferinject group (3.3 g/dL for the ferrous sulphate control group). A similar result was obtained in study VIT-IV-CL-009, in women with post-partum anaemia. As mentioned above, the absence of a placebo arm makes the external validity of this present study difficult to judge, but the difference of nearly 30% in change from baseline of Hb at Week 12 between this current study and one of the original Ferinject efficacy studies is of concern and should be explained by the applicant

- Subgroup analyses

Subgroup analyses were performed to control for baseline Hb status, and concomitant use of TNF alpha blockers. The results are shown in the table below.

	FERINJECT® (N = 240)		VENOFER® (N = 235)	
Haemoglobin [g/dL] at baseline	**n**	**%**	**n**	**%**
≥7 and <10	86		84	
Responder	78	(90.7%)	66	(78.6%)
Non-responder	8	(9.3%)	18	(21.4%)
≥10 and ≤12 for females (≤13 for males)	129		122	
Responder	66	(51.2%)	49	(40.2%)
Non-responder	63	(48.8%)	73	(59.8%)
TNF alpha blockers as concomitant medication	**n**	**%**	**n**	**%**
With TNF alpha blockers	23		20	
Responder	12	(52.2%)	12	(60.0%)
Non-responder	11	(47.8%)	8	(40.0%)
Without TNF alpha blockers	205		200	
Responder	138	(67.3%)	106	(53.0%)
Non-responder	67	(32.7%)	94	(47.0%)

Assessor's comment:
The group using TNF alpha blockers as a concomitant medication is the only group in which Ferinject was not superior to Venofer. The significance of this should be discussed by the applicant.

Further to previous comment regarding heavier patients potentially receiving lower doses of iron under the proposed regime the applicant should present a subgroup analysis for the primary and secondary endpoints stratified by patient weight.

- **Safety Evaluation**
  - Adverse Events

The percentage of subjects experiencing any treatment emergent adverse event (TEAE) was similar in the two groups (50% Ferinject, 46.9% Venofer). The most common TEAEs (occurring in >1% subjects) are detailed in the table below.

System Organ Class Preferred term	FERINJECT® (N = 244) n (%) E	VENOFER® (N = 239) n (%) E	Total (N = 483) n (%) E
Subjects with any event	**122 (50.0) 305**	**112 (46.9) 276**	**234 (48.4) 581**
Blood and lymphatic system disorders	**4 (1.6) 4**	**2 (0.8) 3**	**6 (1.2)7**
Cardiac disorders	**7 (2.9) 11**	**3 (1.3) 4**	**10 (2.1) 15**
Tachycardia	3 (1.2) 3	1 (0.4) 1	4 (0.8) 4
Gastrointestinal disorders	**45 (18.4) 66**	**43 (18.0) 66**	**88 (18.2) 132**
Colitis ulcerative	14 (5.7) 17	6 (2.5) 8	20 (4.1) 25
Nausea	8 (3.3) 10	10 (4.2) 12	18 (3.7) 22
Abdominal pain	7 (2.9) 9	8 (3.3) 9	15 (3.1) 18
Diarrhoea	2 (0.8) 2	6 (2.5) 7	8 (1.7) 9
Crohn's disease	4 (1.6) 4	3 (1.3) 3	7 (1.4) 7
Flatulence	3 (1.2) 3	3 (1.3) 3	6 (1.2) 6
Haematochezia	2 (0.8) 2	4 (1.7) 4	6 (1.2) 6
Vomiting	1 (0.4) 1	3 (1.3) 4	4 (0.8) 5
General disorders and administration site conditions	**13 (5.3) 16**	**14 (5.9) 22**	**27 (5.6) 38**
Fatigue	4 (1.6) 4	5 (2.1) 10	9 (1.9) 14
Pyrexia	5 (2.0) 6	2 (0.8) 2	7 (1.4) 8
Infections and infestations	**41 (16.8) 56**	**27 (11.3) 31**	**68 (14.1) 87**
Nasopharyngitis	13 (5.3) 14	8 (3.3) 10	21 (4.3) 24
Influenza	8 (3.3) 8	3 (1.3) 3	11 (2.3) 11
Pneumonia	2 (0.8) 2	3 (1.3) 4	5 (1.0) 6
Respiratory tract infection viral	5 (2.0) 5	0 (0.0) 0	5 (1.0) 5
Urinary tract infection	4 (1.6) 4	1 (0.4) 1	5 (1.0) 5
Bronchitis	1 (0.4) 1	3 (1.3) 3	4 (0.8) 4
Respiratory tract infection	3 (1.2) 4	1 (0.4) 1	4 (0.8) 5
Injury, poisoning and procedural complications	**3 (1.2) 4**	**5 (2.1) 6**	**8 (1.7) 10**
Investigations	**27 (11.1) 40**	**25 (10.5) 44**	**52 (10.8) 84**
Alanine aminotransferase increased	3 (1.2) 3	6 (2.5) 6	9 (1.9) 9
C-reactive protein increased	4 (1.6) 4	5 (2.1) 5	9 (1.9) 9
Serum ferritin increased	7 (2.9) 7	1 (0.4) 1	8 (1.7) 8
Blood phosphorus decreased	7 (2.9) 7	0 (0.0) 0	7 (1.4) 7
Red blood cell sedimentation rate increased	3 (1.2) 3	3 (1.3) 3	6 (1.2) 6
Aspartate aminotransferase increased	3 (1.2) 3	2 (0.8) 2	5 (1.0) 5
Blood folate decreased	2 (0.8) 2	3 (1.3) 3	5 (1.0) 5
Haemoglobin decreased	1 (0.4) 1	3 (1.3) 3	4 (0.8) 4
Red blood cell decreased	0 (0.0) 0	3 (1.3) 4	3 (0.6) 4
Metabolism and nutrition disorders	**5 (2.0) 8**	**6 (2.5) 6**	**11 (2.3) 14**
Iron overload	1 (0.4) 1	3 (1.3) 3	4 (0.8) 4
Musculoskeletal and connective tissue disorders	**21 (8.6) 25**	**11 (4.6) 17**	**32 (6.6) 42**
Arthralgia	9 (3.7) 10	4 (1.7) 6	13 (2.7) 16
Back pain	3 (1.2) 3	3 (1.3) 3	6 (1.2) 6
Nervous system disorders	**20 (8.2) 28**	**17 (7.1) 31**	**37 (7.7) 59**
Headache	11 (4.5) 13	8 (3.3) 13	19 (3.9) 26
Dizziness	4 (1.6) 5	6 (2.5) 7	10 (2.1) 12
Paraesthesia	3 (1.2) 3	0 (0.0) 0	3 (0.6) 3
Renal and urinary disorders	**3 (1.2) 3**	**5 (2.1) 7**	**8 (1.7) 10**
Respiratory, thoracic and mediastinal disorders	**6 (2.5) 9**	**6 (2.5) 11**	**12 (2.5) 20**
Respiratory disorder	2 (0.8) 2	3 (1.3) 3	5 (1.0) 5
Skin and subcutaneous tissue disorders	**19 (7.8) 20**	**12 (5.0) 14**	**31 (6.4) 34**
Rash	5 (2.0) 5	2 (0.8) 2	7 (1.4) 7
Pruritus	3 (1.2) 3	2 (0.8) 2	5 (1.0) 5
Erythema	3 (1.2) 3	1 (0.4) 1	4 (0.8) 4
Vascular disorders	**4 (1.6) 4**	**5 (2.1) 6**	**9 (1.9) 10**
Hypertension[1]	3 (1.2) 3	0 (0.0) 0	3 (0.6) 3

E = number of events; N = number of subjects in group; n = number of subjects with observations;

There were no deaths during the study. 22 (4.6%) subjects had serious adverse events (SAEs). The incidence of SAEs was similar between the treatment groups.

- Clinical Laboratory Assessments

The following haematology parameters were measured: Hb, Hct, RBC count, platelet, MCV, MCH, WBC count, lymphocytes, monocytes, neutrophils, eosinophils, basophils, reticulocytes and ESR. Descriptive statistics for these parameters are provided in the clinical study report. No specific safety concerns are raised by the results of these assessments.

The following clinical chemistry parameters were measured: phosphate, sodium, potassium, albumin, ALT, AST, creatinine, LDH, CRP, vitamin B12 and folic acid. Descriptive statistics for these parameters are provided in the clinical study report. A transient decrease in serum phosphate is known to occur with ferric carboxymaltose, but not with iron sucrose. This phenomenon was seen in the Ferinject group through to Week 8, though values appeared to have normalised by the end of the study. No such decrease occurred in the Venofer group.

Ferritin, transferrin and TfS scores were measured to evaluate the iron status of the subjects. Descriptive statistics for these parameters are provided in the clinical study report. Serum ferritin levels increased markedly in the Ferinject group from Week 1 to Week 4 to mean levels above 300 µg/L. This increase was less pronounced in the Venofer group.

Assessor's comment:
As a different product was used as an active comparator it is difficult to assess the significance of the decrease in serum phosphate. The applicant should present comparative data from other trials with Ferinject (which used the standard dosing regime) and discuss the potential clinical relevance of this issue.

The applicant should discuss why gamma-glutamyltransferase was not included in the battery of clinical chemistry tests, since an increase in this enzyme is a known (though rare) risk of IV iron carboxymaltose therapy.

The applicant is requested to discuss the potential for iron overload with the proposed Ferinject regime, given that serum ferritin levels were twice as high as those in the Venofer group until Week 4.

IV.2.3 Conclusions

Whilst it is accepted that the current method for calculating the required cumulative dose of iron using the Ganzoni formula is not ideal, insufficient evidence has been presented to support the safety and efficacy of the proposed regime.

The study presented has been conducted in a population with IDA secondary to inflammatory bowel disease, and the applicant has failed to discuss how this is generalisable to the wider population of IDA due to other causes. In addition, there are concerns regarding one of the inclusion criteria, which may affect the validity of the study.

There is a serious concern about the active comparator used in this study. Iron sucrose has been compared to ferric carboxymaltose, therefore the significance of the efficacy and safety findings are difficult to interpret.

Results for the primary efficacy endpoint and one of the secondary endpoints were lower than expected from previous studies with ferric carboxymaltose in a similar patient population – this raises a concern over the external validity of the study.

IV.3 UK/H/0894/001/II/012

IV.3.1 Introduction

The current SPC states that for IV bolus injection, "Ferinject may be administered by IV injection up to a maximum single dose of 4 mL (200 mg of iron) per day but not more than three times a week". This variation proposes to increase the dose of Ferinject that can be administered as an undiluted bolus IV injection up to 1000 mg iron.

In support of this the applicant has conducted 3 clinical studies, in patients with IDA due to heavy uterine bleeding, childbirth, and non-dialysis-dependent chronic kidney disease, aimed at demonstrating the efficacy and safety of IV bolus doses of ferric carboxymaltose up to a maximum of 1,000 mg administered over 15 minutes.

IV.3.2 Study 1VIT07017

IV.3.2.1 Methods

This was an open-label, multicentre, randomised study to assess the safety and tolerability of intravenous Ferinject in comparison to standard medical care for heavy uterine bleeding (HUB) and postpartum subjects with iron deficiency anaemia.

The study had a Treatment Phase (Day 0), an End of Study Visit (Day 30), and a follow-up phone call 30 days after the last dose of study for Group A subjects that early terminated and all Group B subjects. Eligible subjects were randomised in a 1:1 ratio to Ferinject (Group A) vs. standard medical care for IDA (Group B) on Day 0. Subjects were stratified by the aetiology of their IDA (postpartum vs. HUB), baseline haemoglobin (≤8, 8.1 to 9.5, ≥9.6 g/dL), cardiac risk (category 1 vs. 2, as defined below), and by past response to oral iron (poor/yes or poor/no, as defined below). All subjects were to return to the clinic at Day 30 (End of Study Visit). Follow-up calls were made for Group A subjects who early terminated and all Group B subjects to assess adverse events 30 days after the last dose of study drug.

- **Study Participants**

Subjects were considered eligible if they were suffering from IDA and

- Cohort I
  - postpartum
  - with a screening visit haemoglobin ≤11 g/dL obtained ≥18 hours post delivery
- Cohort II
  - a history of HUB within the past 6 months, defined as any one of the following:
    - inability to control flow with tampons alone;
    - use of more than 12 pads per period or 4 tampons per day, unless subject was unusually fastidious;
    - passage of clots, especially if they were larger than approximately 2 cm in diameter or if they persisted after the first day;
    - d. period duration exceeding 7 days;
  - screening visit haemoglobin using point of care testing ≤11.5 g/dL
  - screening visit central laboratory haemoglobin ≤11 g/dL

Exclusion criteria included any history of anaemia (haemolytic, macrocytic, hypoplastic, or sideroblastic) other than anaemia due to pregnancy/delivery and HUB, current or recent history (within past 3 months) of gastrointestinal bleeding or greater than minor acute blood loss (other than blood loss due to delivery), received IV iron, red blood cell transfusion(s) or erythropoiesis stimulating agents within the month prior to or during screening, myelosuppressive therapy, active infection requiring ongoing antibiotics or antivirals, and receiving treatment for asthma.

- **Treatments**

Subjects randomised to Group A received an undiluted dose of iron as FCM (15 mg/kg up to a maximum of 1000 mg) over 15 minutes as a slow IV injection on Day 0. Pre-pregnancy weight was to be used if the subject was postpartum. This single dose was based on data from four Phase 3 studies in women with IDA (3 postpartum and 1 HUB) in which 90% of the 773 patients were found to have a total iron requirement of ≤1600 mg, meaning that 1 or 2 doses of 15 mg/kg (maximum 1000 mg) FCM would likely treat IDA in most postpartum and HUB patients.

Subjects randomised to Group B received standard medical care for the treatment of the subject's IDA as determined by the Investigator from Day 0 through Day 30. This may have included no treatment.

Assessor's comment:
The treatment regime for Ferinject is not in accordance with the updated proposed regime, in which most women with a haemoglobin of ≤10 g/dL would receive a cumulative dose of 1500 mg iron. However since this study has been submitted to demonstrate the safety of a single IV dose of 1000 mg, the treatments administered are acceptable.

- **Objectives**

The primary objective of this study was to evaluate the safety of IV bolus doses of FCM up to 1000 mg compared to standard medical care in the treatment of IDA in HUB and postpartum subjects.

The secondary objective of this study was to further support the efficacy of FCM compared to oral iron (ferrous sulfate) in patients with postpartum IDA or IDA secondary to HUB.

- **Outcomes/endpoints**

Safety variables included adverse events, and laboratory evaluations (haematology, chemistry, and iron indices).

Efficacy variables included number and proportion of postpartum subjects in the modified intent-to-treat (mITT) population with a haemoglobin value of >12 g/dL anytime between baseline and end of study or time of intervention, number and proportion of HUB subjects in the mITT population achieving a haemoglobin increase of ≥2 g/dL anytime between baseline and end of study or time of intervention, and mean change from baseline to the highest post-randomisation haemoglobin, ferritin, serum iron, total iron binding capacity (TIBC), and TSAT value.

- **Sample size**

At least 1500 (up to 2000) subjects were to be randomised in a 1:1 ratio to FCM or standard medical care. Based on the oral iron group in all active-controlled multicenter studies as summarised in the latest safety

update, approximately 2.5% of subjects receiving standard medical care were expected to experience a serious adverse event.

- **Randomisation**

Subjects were randomised in a 1:1 ratio to either FCM (Group A) or standard medical care for treatment of IDA (Group B).

Subjects were stratified by the aetiology of their IDA (postpartum or HUB), baseline haemoglobin (≤8, 8.1 to 9.5, ≥9.6 g/dL), cardiac risk (category 1, category 2), and by past response to oral iron (poor/yes or poor/no).

- **Statistical methods**

- Analysis populations

  The following definitions of analysis populations were used for the data analysis and tabulations. With the exception of adverse events and potentially clinically significant (PCS) results, all analyses were performed with the mITT population.
  - **Safety Set**: all Group A subjects who received a dose of randomised FCM treatment on Day 0 and all Group B subjects prescribed standard medical care (including subjects who received no treatment) for IDA on Day 0.
  - **Modified Intent to Treat population (mITT)**: subjects from the safety population who were randomised to Group A (FCM) or Group B and prescribed oral iron as the standard medical care for treating IDA, had 2 baseline haemoglobin values (with a <1 g difference between the 2) and at least 1 post-baseline haemoglobin assessment.

- Efficacy Evaluation

  There was no primary efficacy endpoint for this study. The primary endpoint was a safety endpoint. Secondary efficacy endpoints were:
  - The number and percentage of postpartum subjects achieving a haemoglobin of >12 g/dL anytime between baseline and the end of the study or between baseline and the time of intervention. Fisher's exact test was performed to compare these values across the treatment groups.
  - The number and percentage of HUB subjects achieving a haemoglobin increase of ≥2 g/dL anytime between baseline and the end of study or between baseline and the time of intervention. Fisher's exact test was performed to compare these values across the treatment groups.
  - The mean change from baseline to highest post-randomisation haemoglobin, ferritin, serum iron, TIBC, and TSAT was summarised for the safety population and compared across treatment groups using an analysis of variance (ANOVA) with a factor for randomised treatment group.

- Safety Evaluation

  The primary safety endpoint of this study was the incidence of treatment-emergent serious adverse events, overall and related from Day 0 through 30 days after the last dose of study drug. Secondary safety endpoints included incidence and severity of adverse events, and incidence of treatment-emergent abnormal clinical laboratory values.

Assessor's comment:
The statistical methods are considered acceptable for the stated objectives of the study.

IV.3.2.2 Results

- **Participant flow**

2045 subjects were randomised to receive FCM (1023 subjects) or standard medical care (1022 subjects). Of these 2045 subjects, 27 randomised to FCM were discontinued from the study prior to dosing. Therefore, a total of 996 subjects were treated in the FCM group and 1022 were treated in the standard medical care group. 860 (84.1%) of the 996 subjects in the FCM group and 847 (82.9%) of the 1022 subjects in the standard medical care group completed the study.

A summary of subject disposition and study termination is presented in the table below.

	FCM (N=1023)	SMC[a] (N=1022)	Total (N=2045)
Subjects Enrolled[b]	1023 (100.0%)	1022 (100.0%)	2045 (100.0%)
Subjects Treated	996 (97.4%)	1022 (100.0%)	2018 (98.7%)
Required Intervention	5 (0.5%)	5 (0.5%)	10 (0.5%)
Received blood transfusion	1 (0.1%)	0	1 (<0.1%)
Received non-study oral iron	1 (0.1%)	0	1 (<0.1%)
Surgical procedure[c]	3 (0.3%)	5 (0.5%)	8 (0.4%)
Subjects Discontinued[d]	158 (15.4%)	170 (16.6%)	328 (16.0%)
Adverse event	3 (0.3%)	5 (0.5%)	8 (0.4%)
Selection criteria/study compliance	115 (11.5%)	128 (12.5%)	243 (12.0%)
Lost to follow-up	9 (0.9%)	25 (2.4%)	34 (1.7%)
Subject request	15 (1.5%)	3 (0.3%)	18 (0.9%)
Physician decision	1 (0.1%)	0	1 (<0.1%)
Other	15 (1.5%)	9 (0.9%)	24 (1.2%)
Subjects Completed Study	860 (84.1%)	847 (82.9%)	1707 (83.5%)

Assessor's comment:
Subject discontinuation data is acceptable.

- **Conduct of the study**

Six subjects in the FCM group and 7 subjects in the standard medical care group had significant protocol violations. The most common violation noted was subject not meeting Screening Visit central haemoglobin criterion (value exceeded 11 g/dL).

Assessor's comment:
Protocol amendments and deviations are not considered to have impacted significantly on the study results.

- **Baseline data**

Subject demographic data and baseline characteristics are shown in the table below.

Demographic Characteristic	FCM (N=996)	SMC (N=1022)
Age (years)		
Mean (SD)	31.2 (9.36)	31.4 (8.98)
Median	30.0	31.0
Minimum – Maximum	15, 65	14, 56
Race		
African American	391 (39.3%)	387 (37.9%)
Asian	5 (0.5%)	8 (0.8%)
Caucasian	457 (45.9%)	477 (46.7%)
Hispanic	122 (12.2%)	135 (13.2%)
Other	21 (2.1%)	15 (1.5%)
Height (cm)	(N=996)	(N=1019)
Mean (SD)	163.4 (6.93)	163.1 (7.07)
Median	162.6	162.6
Minimum – Maximum	137.2, 182.9	137.2, 186.7
Weight (kg)	(N=992)	(N=1013)
Mean (SD)	82.0 (21.71)	82.8 (21.64)
Median	78.1	78.9
Minimum – Maximum	41.3, 180.5	44.9, 168.3
Weight, pre-pregnancy[a] (kg)	(N=609)	(N=625)
Mean (SD)	72.4 (19.96)	73.3 (19.85)
Median	68.0	70.3
Minimum – Maximum	40.8, 166.9	40.4, 152.0
BMI (kg/m^2)	(N=992)	(N=1012)
Mean (SD)	30.7 (7.66)	31.1 (7.66)
Median	29.8	29.7
Minimum – Maximum	15.9, 66.3	17.4, 67.7
Etiology		
Postpartum	606 (60.8%)	623 (61.0%)
HUB	390 (39.2%)	399 (39.0%)
Cardiac Risk Factor[a]		
Category 1	709 (71.2%)	723 (70.7%)
Category 2	287 (28.8%)	299 (29.3%)
Prior Iron Treatment		
Yes	252 (25.3%)	283 (27.7%)
No	744 (74.7%)	739 (72.3%)
Poor Response to Oral Iron	(N=548)	(N=568)
Yes	236 (43.1%)	252 (44.4%)
No	312 (56.9%)	316 (55.6%)
Hemoglobin	(N=994)	(N=1019)
Mean (SD)	9.9 (1.32)	9.8 (1.29)
Median	10.0	10.0
Minimum – Maximum	5.0, 12.9	4.5, 13.2

Assessor's comment:
Baseline data is comparable for the two groups.

The mean weight for patients seems high, with mean BMI >30 (ie, obese). The applicant is requested to comment on this.

- **Outcomes and estimation**

- Efficacy Endpoints

  - Postpartum subjects achieving a haemoglobin of >12 g/dL anytime between baseline and the end of the study or between baseline and the time of intervention.

	Number (%) Subjects		
	FCM n/N (%)	Oral Iron n/N (%)	Fisher's Exact p-value
Hemoglobin >12 g/dL Anytime Between Baseline and End of Study or Time of Intervention	233/342 (68.1%)	181/357 (50.7%)	<0.001

- HUB subjects achieving a haemoglobin increase of ≥2 g/dL anytime between baseline and the end of study or between baseline and the time of intervention.

	Number (%) Subjects		
	FCM n/N (%)	Oral Iron n/N (%)	Fisher's Exact p-value
Hemoglobin Increase ≥2 g/dL Anytime Between Baseline and End of Study or Time of Intervention	195/331 (58.9%)	108/329 (32.8%)	<0.001

- Mean change from baseline to highest post-randomisation haemoglobin, ferritin, serum iron, TIBC, and TSAT.

	FCM (N=606)	SMC (N=623)	p-value[a]
Hemoglobin (g/dL)			
Baseline			0.194
N	606	623	
Mean (SD)	10.20 (1.161)	10.11 (1.191)	
Median	10.35	10.30	
Minimum, Maximum	6.7, 12.9	6.1, 13.2	
Change to Highest Result			<0.001
N	590	595	
Mean (SD)	2.35 (1.225)	1.86 (1.267)	
Median	2.30	1.80	
Minimum, Maximum	-0.4, 6.2	-1.9, 5.9	
Ferritin (ng/mL)			
Baseline			0.679
N	606	623	
Mean (SD)	25.99 (22.730)	26.55 (24.973)	
Median	19.75	20.10	
Minimum, Maximum	3.2, 163.3	1.7, 260.7	
Change to Highest Result			<0.001
N	597	599	
Mean (SD)	155.03 (90.692)	-2.32 (22.698)	
Median	140.80	-0.70	
Minimum, Maximum	-34.6, 499.0	-222.8, 103.3	
Serum Iron (µg/dL)			
Baseline			0.173
N	606	623	
Mean (SD)	39.89 (33.485)	37.78 (19.031)	
Median	35.00	35.00	
Minimum, Maximum	7.0, 734.0	8.0, 318.0	
Change to Highest Result			0.551
N	596	596	
Mean (SD)	40.51 (40.149)	38.74 (60.071)	
Median	41.00	22.00	
Minimum, Maximum	-640.0, 152.0	-99.0, 390.0	
TIBC (µg/dL)			
Baseline			0.207
N	606	623	
Mean (SD)	381.02 (65.166)	376.31 (65.512)	
Median	377.50	373.00	
Minimum, Maximum	188.0, 776.0	187.0, 586.0	
Change to Highest Result			<0.001
N	596	593	
Mean (SD)	-128.60 (68.857)	-64.92 (56.822)	
Median	-131.00	-62.00	
Minimum, Maximum	-490.0, 367.0	-233.0, 110.0	
TSAT (%)			
Baseline			0.607
N	606	623	
Mean (SD)	10.50 (5.908)	10.33 (5.395)	
Median	9.00	9.00	
Minimum, Maximum	2.0, 95.0	2.0, 77.0	
Change to Highest Result			<0.001
N	596	593	
Mean (SD)	22.43 (11.845)	14.08 (16.884)	
Median	22.00	9.00	
Minimum, Maximum	-62.0, 69.0	-24.0, 94.0	

a p-value for comparison between treatment groups using analysis of variance

Assessor's comment:
The primary objective of this study was to evaluate the safety of high dose IV boluses of Ferinject, and indeed the dose of Ferinject was not optimised to demonstrate efficacy. With this in mind, a response rate of 68% for women with a haemoglobin of at least 12 g/dL during the study in the Ferinject group seems acceptable. The other efficacy measures also appear acceptable in comparison to standard medical care.

- **Safety Evaluation**

  - Extent of Exposure

Mean exposure to FCM and standard medical care are shown in the tables below.

Summary of Extent of Exposure for Subjects Receiving FCM

Total Iron Received (mg) by Population	FCM (N=996)
Safety Population	
Mean (SD)	943.6 (102.33)
Median	1000.0
Minimum, Maximum	250.0, 1660.0
Postpartum Population	(N=606)
Mean (SD)	926.4 (106.86)
Median	1000.0
Minimum, Maximum	250.0, 1000.0
HUB Population	(N=390)
Mean (SD)	970.4 (88.55)
Median	1000.0
Minimum, Maximum	350.0, 1660.0

Standard Medical Care Treatment Record

Safety Population	Day 0 Treatment Prescribed (N=1022) n (%)	Treatment at Day 30	
		Unchanged (N=932) n (%)	Changed (N=59) n (%)
No Treatment	25 (2.4%)	23 (2.5%)	11 (18.6%)
Oral Iron	950 (93.0%)	867 (93.0%)	31 (52.5%)
Blood Transfusion	1 (0.1%)	0	2 (3.4%)
Other	64 (6.3%)	58 (6.2%)	18 (30.5%)
Postpartum Population	**(N=623)**	**(N=580)**	**(N=26)**
No Treatment	22 (3.5%)	22 (3.8%)	6 (23.1%)
Oral Iron	573 (92.0%)	533 (91.9%)	15 (57.7%)
Blood Transfusion	1 (0.2%)	0	2 (7.7%)
Other	43 (6.9%)	40 (6.9%)	4 (15.4%)
HUB Population	**(N=399)**	**(N=352)**	**(N=33)**
No Treatment	3 (0.8%)	1 (0.3%)	5 (15.2%)
Oral Iron	377 (94.5%)	334 (94.9%)	16 (48.5%)
Blood Transfusion	0	0	0
Other	21 (5.3%)	18 (5.1%)	14 (42.4%)

Assessor's comment:
It appears that a single patient in the HUB group received an overdose of 1660 mg FCM in error.

Summary data for the number of subjects receiving the maximum dose of 1000 mg FCM should be provided.

Although a figure of 95% is quoted for mean compliance (number of pills taken/number of pills prescribed) in the standard medical care treatment group, it is difficult to determine from the clinical study report exactly how much oral iron was prescribed for these subjects during the study. Summary data should be provided for doses of oral iron prescribed in the standard medical care group.

- Adverse Events

During the study for postpartum and HUB subjects combined, at least 1 treatment-emergent adverse event (TEAE) was experienced by 27.3% (272/996) of the subjects in the FCM group and 26.9% (275/1022) of the subjects in the standard medical care group. The most commonly (≥2%) experienced TEAEs in the FCM group were headache (2.5%) and injection site extravasation (2.4%). The most commonly experienced TEAEs in the standard medical care group were constipation (7.7%), nausea (3.4%), and diarrhoea (2.0%). This is summarised in the table below.

TEAEs Experienced by ≥2% of Subjects in Either Group or With a Statistically Significant Difference between the FCM or Standard Medical Care Group – Postpartum and HUB Subjects Combined

MedDRA SOC[a] Preferred Term	FCM (N=996) n (%)	SMC (N=1022) n (%)	p-value[b]
At Least 1 Treatment-Emergent Adverse Event	**272 (27.3%)**	**275 (26.9%)**	**0.841**
Gastrointestinal Disorders	34 (3.4%)	137 (13.4%)	<0.001*
Constipation	9 (0.9%)	79 (7.7%)	<0.001*
Diarrhoea	9 (0.9%)	20 (2.0%)	0.060
Nausea	8 (0.8%)	35 (3.4%)	<0.001*
Vomiting	2 (0.2%)	13 (1.3%)	0.007*
General Disorders and Administration Site Conditions	87 (8.7%)	12 (1.2%)	<0.001*
Injection site extravasation	24 (2.4%)	0	<0.001*
Injection site pain	12 (1.2%)	1 (0.1%)	0.002*
Injection site bruising	11 (1.1%)	0	<0.001*
Injection site irritation	8 (0.8%)	0	0.003*
Injection site paraesthesia	6 (0.6%)	0	0.014*
Injection site coldness	5 (0.5%)	0	0.029*
Immune System Disorders	5 (0.5%)	0	0.029*
Investigations	25 (2.5%)	11 (1.1%)	0.018*
ALT Increased	18 (1.8%)	6 (0.6%)	0.013*
Metabolism and Nutrition Disorders	8 (0.8%)	1 (0.1%)	0.020*
Hypophosphataemia	6 (0.6%)	0	0.014*
Nervous System Disorders	49 (4.9%)	21 (2.1%)	<0.001*
Headache	25 (2.5%)	15 (1.5%)	0.110
Dysgeusia	7 (0.7%)	0	0.007*

During the study for postpartum and HUB subjects combined, at least 1 drug-related TEAE (defined as possibly or probably related) was experienced by 12.8% (127/996) of the subjects in the FCM group and 11.8% (121/1022) of the subjects in the standard medical care group. Proportions were comparable between FCM and standard medical care for the postpartum and HUB groups.

Drug-Related TEAEs Experienced by ≥0.5% of Subjects in Either Group or With a Statistically Significant Difference Between the FCM or Standard Medical Care Group – Postpartum and HUB Subjects Combined

MedDRA SOC[a] Preferred Term	FCM (N=996) n (%)	SMC (N=1022) n (%)	p-value[b]
At Least 1 Treatment-Emergent Adverse Event	**127 (12.8%)**	**121 (11.8%)**	**0.542**
Gastrointestinal Disorders	13 (1.3%)	103 (10.1%)	<0.001*
Abdominal pain upper	2 (0.2%)	7 (0.7%)	0.179
Constipation	5 (0.5%)	70 (6.8%)	<0.001*
Diarrhoea	2 (0.2%)	9 (0.9%)	0.065
Nausea	3 (0.3%)	26 (2.5%)	<0.001*
Vomiting	0	6 (0.6%)	0.031*
General Disorders and Administration Site Conditions	61 (6.1%)	4 (0.4%)	<0.001*
Injection site extravasation	23 (2.3%)	0	<0.001*
Injection site pain	9 (0.9%)	0	0.002*
Injection site bruising	6 (0.6%)	0	0.014*
Injection site irritation	5 (0.5%)	0	0.029*
Pyrexia	5 (0.5%)	2 (0.2%)	0.282
Investigations	17 (1.7%)	6 (0.6%)	0.020*
ALT increased	13 (1.3%)	4 (0.4%)	0.028*
AST increased	12 (1.2%)	5 (0.5%)	0.091
Metabolism and Nutrition Disorders	7 (0.7%)	0	0.007*
Hypophosphataemia	6 (0.6%)	0	0.014*
Nervous System Disorders	25 (2.5%)	5 (0.5%)	<0.001*
Headache	9 (0.9%)	3 (0.3%)	0.088
Dysgeusia	7 (0.7%)	0	0.007*
Dizziness	6 (0.6%)	1 (0.1%)	0.067
Skin and Subcutaneous Tissue Disorders	15 (1.5%)	4 (0.4%)	0.011*
Urticaria	6 (0.6%)	2 (0.2%)	0.174

The majority of the TEAEs experienced during the study were classified by the Investigator as Grade 1 or Grade 2 severity. Grade 3 treatment-emergent adverse events were experienced by 17 subjects (1.7%) in the FCM group (6 postpartum and 11 HUB subjects) and 22 subjects (2.2%) in the standard medical care group (9 postpartum and 13 HUB). Two subjects (0.2%) in the FCM group (both postpartum) and 2 subjects (0.2%) in the standard medical care group (1 postpartum and 1 HUB subject) experienced TEAEs classified by the Investigator as Grade 4 severity. No subjects in either the FCM or standard medical care group experienced treatment-emergent adverse events classified by the Investigator as Grade 5 severity. Seven of the HUB subjects and 1 of the postpartum subjects in the FCM group and 1 postpartum subject in the standard medical care group experienced Grade 3 treatment-emergent adverse events that were considered by the Investigator to be study drug-related.

No subjects died during the study. A total of 6 (0.6%) subjects in the FCM group and 22 (2.2%) subjects in the standard medical care group experienced at least 1 serious adverse event during the study, none of which were considered by the Investigator to be related to study medication. Six of the 7 subjects in the FCM group and 14 of the 22 subjects in the standard medical care group who prematurely discontinued study drug experienced adverse events that were considered to have probable or possible relationships to study drug by the Investigator.

Subjects Who Experienced Adverse Events That Led to Premature Discontinuation of Study Drug

Subject Number	Age/Race/Type	Preferred Term	Onset Date	Res Date	Severity	Causality[a]	Treatment
FCM							
10411	36/C/HUB	Injection site extravasation	12Mar08		Grade 1	Probable	None
11509	30/C/PP	Injection site bruising	03Oct08	04Oct08	Grade 1	Probable	None
		Injection site extravasation	03Oct08	04Oct08	Grade 1	Probable	None
11649	29/C/PP	Hypersensitivity	30Oct08	30Oct08	Grade 1	Probable	None
10916	43/AA/HUB	Injection site bruising	18Jun08	19Jun08	Grade 1	None	None
11811	20/AA/PP	Injection site extravasation[b]	25Nov08	25Nov08	Grade 2	Probable	Other
10881	20/AA/HUB	Injection site extravasation	13Jun08	13Jun08	Grade 1	Probable	Other
11407	30/C/PP	Injection site extravasation	18Sep08		Grade 2	Possible	None
Standard Medical Care							
10435	32/C/PP	Abdominal pain	06Apr08	10Apr08	Grade 1	Probable	None
10715	37/H/PP	Abdominal pain	13May08	17May08	Grade 1	Unlikely	None
10060	32/C/PP	Constipation	08Dec07	21Dec07	Grade 1	Probable	Medication
10509	28/AA/PP	Postpartum haemorrhage[b,c]	06Apr08	06Apr08	Grade 4	None	Surgical
10311	20/C/PP	Nausea	13Mar08	17Mar08	Grade 1	Possible	None
10404	38/AA/HUB	Constipation	16Mar08		Grade 1	Possible	None
10507	29/C/PP	Abdominal discomfort[b]	05Apr08	11Apr08	Grade 2	Probable	None
11072	22/AA/PP	Nausea	15Aug08	15Aug08	Grade 1	Possible	None
12025	45/C/HUB	Menorrhagia[c]	19Jan09	29Jan09	Grade 3	None	Surgical
10944	24/H/PP	Nausea	25Jun08	09Jul08	Grade 1	Possible	None
		Constipation	30Jun08		Grade 1	Probable	None
10113	40/C/HUB	Abdominal pain[b]	08Jan08	11Jan08	Grade 2	None	Medication
11795	54/C/HUB	Uterine haemorrhage	10Dec08	19Dec08	Grade 3	None	Surgical
10352	48/AA/HUB	Nausea	29Feb08	07Mar08	Grade 1	Probable	None
11593	49/C/HUB	Uterine haemorrhage[b,c]	07Nov08	18Nov08	Grade 1	None	Surgical
10831	38/AA/HUB	Constipation	03Jun08	06Jun08	Grade 1	Probable	None
		Nausea	03Jun08	09Jun08	Grade 1	Probable	None
11611	21/H/PP	Abdominal pain upper	24Oct08	17Nov08	Grade 1	Probable	None
10529	36/C/HUB	Small intestinal obstruction[b,c]	22Apr08	01May08	Grade 3	None	Surgical
		Abdominal hernia[b,c]	22Apr08	01May08	Grade 3	None	Surgical
		Abdominal adhesions[b,c]	22Apr08	01May08	Grade 3	None	Surgical
10770	35/AA/HUB	Nausea	19May08	07Jun08	Grade 1	Unlikely	None
		Vomiting	19May08	07Jun08	Grade 1	Unlikely	None
11137	25/C/PP	Drug exposure via breast milk	07Aug08	29Aug08	Grade 3	Probable	None
11901	43/C/HUB	Vomiting	10Dec08	17Dec08	Grade 1	Probable	None
11569	35/AA/HUB	Vulvovaginal pruritus	25Oct08	30Oct08	Grade 1	None	Medication
		Constipation	31Oct08	02Nov08	Grade 1	Possible	None
11141	42/C/HUB	Abdominal pain	06Aug08	16Aug08	Grade 2	Probable	None
		Constipation	06Aug08	16Aug08	Grade 1	Probable	None

Four subjects in the FCM group (2 postpartum and 2 HUB) experienced hypersensitivity reactions during the study. Each of the hypersensitivity events was classified by the Investigator as Grade 1 in severity. 23 subjects in the FCM group (11 postpartum and 12 HUB) and 16 subjects in the standard medical care group (8 postpartum and 8 HUB) experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including rash, pruritus, urticaria, acne, angioedema, dry skin, erythema, erythema multiforme, hyperhidrosis, pruritus generalised, rash papular, skin exfoliation, swelling face, alopecia, dermal cyst, eczema, and night sweats. The majority of these events were classified by the Investigator as either Grade 1 or Grade 2 in severity and considered not related to study drug.

- Clinical Laboratory Assessments

When treatment-emergent abnormal clinical chemistry values were analysed for postpartum and HUB subjects combined, a statistically significantly greater proportion of subjects in the FCM group reported phosphorus abnormal (9.0% for the FCM group and 0% for the standard medical care group). When treatment-emergent abnormal clinical chemistry values were analyzed for HUB subjects, a statistically significantly greater proportion of subjects in the FCM group reported phosphorus abnormal (21.3% for the FCM group and 0% for the standard medical care group). In other FCM clinical trials, 8% of postpartum patients (N=316) and 70% of HUB patients (N=224) experienced reduced serum phosphate. In these trials, no adverse events due to symptoms of low phosphate were reported and no patient discontinued therapy secondary to the low phosphate levels. There was no consistent relationship between dose of FCM and the frequency or degree of low serum phosphate. The effects of FCM on serum phosphate are transient and appear not to be associated with other clinically significant events.

The applicant states that no statistically significant differences were observed between the FCM and standard medical care groups for any of the other treatment-emergent abnormal clinical chemistry values. However, when laboratory investigations were considered as adverse events, a significant difference between the postpartum and HUB groups was observed. In the HUB group 0.3% (1/390) of subjects in the FCM group experienced an increase in ALT, AST, and GGT. However these figures were markedly higher in the postpartum group, with 2.8% (17/606) experiencing an increase in ALT, 2.3% (14/606) experiencing an increase in AST, and 0.5% (3/606) experiencing an increase in GGT. Figures for raised ALT and AST were also higher for postpartum patients receiving standard medical care than HUB patients receiving standard medical care.

Adverse event data were generally as expected in the FCM and standard medical care groups, with the commonest AEs in the Ferinject group being headache and injection site reactions, whilst in the standard medical care group gastrointestinal events were commonest.

The applicant should comment on the frequency of injection site reactions observed in this study compared to that observed with lower bolus doses of IV FCM.

In HUB and postpartum patients combined 1.2% of subjects in the Ferinject group experienced an AE of increased aspartate aminostransferase (categorised as 'uncommon' in the SPC). This appears to be attributable to the postpartum group, in whom increases in AST and ALT were more pronounced. An explanation should be provided for this.

Summary data on adverse events and clinical laboratory assessments should be provided for subjects who received the maximum dose of 1000 mg of FCM, as compared with those who received lower doses. In addition, similar summary data should be provided for subjects according to baseline stratification categories (baseline haemoglobin (≤8, 8.1 to 9.5, ≥9.6 g/dL), cardiac risk (category 1, category 2), and past response to oral iron).

IV.3.3 Study 1VIT07018

IV.3.3.1 Methods

This was an open-label, multicentre, randomised study to assess the safety and tolerability of intravenous Ferinject in comparison to standard medical care for non dialysis-dependent (NDD) and haemodialysis (HD)-dependent chronic kidney disease (CKD) subjects with iron deficiency anaemia.

The study had a Treatment Phase (Day 0), an End of Study Visit (Day 30), and a follow-up phone call 30 days after the last dose of study drug for Group A subjects that terminated early and all Group B subjects. Subjects were stratified to FCM vs. standard medical care by the aetiology of their IDA (NDD- and HD-CKD), baseline haemoglobin (<9, 9.1 to 11, >11 g/dL), age (≤65, 66 to 75, 76 to 85), and current use of erythropoiesis stimulating agent (ESA; yes/no). Eligible subjects were randomised in a 1:1 ratio to FCM (Group A) vs. standard medical care for IDA (Group B) on Day 0.

- **Study Participants**

Subjects were considered eligible if they were suffering from IDA and

- Cohort I (NDD-CKD)
  - Screening Visit (central labs):
    - Haemoglobin ≤11.5 g/dL
    - TSAT ≤30%
    - Ferritin ≤300 ng/mL
  - Subject had not received IV iron within 1 month prior to Day 0 Visit
  - Subject had at least a 3-month history of NDD-CKD
- Cohort II (HD-CKD)
  - Screening Visit (central labs):
    - Haemoglobin ≤12.5 g/dL
    - TSAT ≤30%
    - Ferritin ≤500 ng/mL
  - Subject had at least a 6-month history on HD
  - Subject did not anticipate need for iron repletion therapy (>200 mg of IV iron) during the 30-day study period

Exclusion criteria included any history of anaemia (haemolytic, macrocytic, hypoplastic, or sideroblastic) other than anaemia due to CKD or iron deficiency, current or recent history (within past 3 months) of gastrointestinal bleeding or greater than minor acute blood loss, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 1.5 times the upper limit of normal, myelosuppressive therapy, active infection requiring ongoing antibiotics or antivirals, and receiving treatment for asthma.

Assessor's comment:
Once again justification is required for the serum ferritin inclusion criteria. Guidelines issued by the UK Renal Association in 2010 (available from www.renal.org/guidelines) and NICE in 2006 on the management of anaemia in CKD refer to lower ferritin levels in the diagnosis of IDA in both non-dialysis and haemodialysis dependent patients with CKD. Furthermore, in the original Ferinject studies in patients with CKD (Study 53214 and Study VIT-IV-CL-015) a serum ferritin of less than 200 µg/L was used as an inclusion criterion.

- **Treatments**

Subjects randomised to Group A received either an undiluted dose of iron as FCM IV (15 mg/kg up to a maximum of 1000 mg) over 15 minutes as a slow IV injection (Cohort I – NDD-CKD), or 200 mg of FCM IV push undiluted directly into the venous line of the dialyser (Cohort II – HD-CKD). For Group A subjects, erythropoietin stimulating agent (ESA) treatment was to remain stable during the Treatment Phase unless a dose reduction was required as per label for safety reasons.

Subjects randomised to Group B received standard medical care for the treatment of the subject's IDA as determined by the Investigator from Day 0 through Day 30. This may have included no treatment.

Assessor's comment:
The justification for the lower dose in haemodialysis-dependent CKD patients is accepted. This is reflected in the proposed posology for Ferinject in Section 4.2 of the SPC.

- **Objectives**

The primary objective of this study was to further evaluate the safety of the maximum administered dose of IV FCM compared to standard medical care in the treatment of IDA in NDD- and HD-CKD subjects.

- **Outcomes/endpoints**

No evaluation of efficacy was planned for this study. However, the final statistical analysis plan included analysis of efficacy data.

Safety variables included adverse events, and laboratory evaluations (haematology, chemistry, and iron indices).

- **Sample size**

A maximum of 500 subjects were to be randomised into this study. No formal sample size calculation was performed.

- **Randomisation**

Subjects who had met all of the inclusion criteria and none of the exclusion criteria were randomised to either Group A or Group B. Subjects were stratified by the aetiology of their IDA (NDD- and HD-CKD), baseline haemoglobin (<9, 9.1 to 11, >11 g/dL), age (≤65, 66 to 75, 76 to 85) and current use of ESA (yes/no), and randomised in a 1:1 ratio (FCM to standard medical care for treatment of IDA).

- **Statistical methods**

- Analysis populations
  The following definitions of analysis populations were used for the data analysis and tabulations.
  - **Safety Set**: all Group A subjects who received a dose of randomised FCM treatment on Day 0 and all Group B subjects prescribed standard medical care for IDA on Day 0. All safety analyses were performed with the Safety Population.

- **Modified Intent to Treat population (mITT)**: all subjects in the Safety Population with a haemoglobin measured at baseline and at least once after randomisation. All efficacy analyses were performed with the mITT Population.

- Efficacy Evaluation
  There was no primary efficacy endpoint for this study. The primary endpoint was a safety endpoint. Secondary efficacy endpoints were:
  - Proportion of subjects achieving an increase in haemoglobin of 1.0 g/dL at any time between baseline (Day 0) and Day 30.
  - Proportion of subjects achieving a haemoglobin >12.0 g/dL at any time between baseline (Day 0) and Day 30.
  - Mean change in haemoglobin, ferritin and TSAT from baseline (Day 0) to Day 30 (or end of study for subjects who prematurely discontinued).

  The FCM group was compared to each of the following control groups.
  - All subjects in Group B (standard medical care).
  - Subjects in Group B who received IV iron (Venofer, iron dextran, or Ferrlecit) as approximately 5 doses of 200 mg each or as 10 doses of 100 mg each. Subjects who received high doses of IV iron, such as iron dextran at individual doses of 1000 mg, were excluded.
  - Subjects in Group B who received Venofer or Ferrlecit as approximately 5 doses of 200 mg each or as 10 doses of 100 mg each.
  - Subjects in Group B who received Venofer as approximately 5 doses of 200 mg each or as 10 doses of 100 mg each.

- Safety Evaluation
  The primary safety endpoint of this study was the incidence of treatment-emergent serious adverse events, overall and related from Day 0 through 30 days after the last dose of study drug. Secondary safety endpoints included incidence and severity of adverse events, and incidence of treatment-emergent abnormal clinical laboratory values or vital sign values.

Assessor's comment:
The statistical methods are considered acceptable for the stated objectives of the study.

IV.3.3.2 Results

- **Participant flow**

517 subjects were randomised at 56 centres to receive FCM (258 subjects) or standard medical care (259 subjects). Of these 517 subjects, 4 randomised to FCM were discontinued from the study prior to dosing. Reasons for discontinuation included selection criteria/study compliance (3 subjects) and subject request (1 subject). Therefore, a total of 254 subjects were treated in the FCM group and 259 were treated in the standard medical care group.

251 (98.8%) of the 254 subjects in the FCM group and 250 (96.5%) of the 259 subjects in the standard medical care group completed the study. Of the 3 subjects in the FCM group who did not complete the study, 1 discontinued due to adverse events, 1 was lost to follow-up, and 1 discontinued due to subject request. Of the 9 subjects in the standard medical care group who did not complete the study, 4 discontinued due to adverse events, 3 were lost to follow-up, and 2 discontinued due to selection criteria/compliance.

A summary of subject disposition and study termination is presented in the table below.

	Group A: FCM	Group B: SMC	Total
Subjects Randomized	258	259	517
Safety Population[a]	254	259	513
mITT Population[b]	249 (98.0%)	249 (96.1%)	498 (97.1%)
Group B Subset Populations[c]			
Received IV iron	NA	159 (61.4%)	159 (31.0%)
Received IV iron of Venofer or Ferrlecit	NA	157 (60.6%)	157 (30.6%)
Received IV iron of Venofer	NA	127 (49.0%)	127 (24.8%)
Subjects Did Not Complete Study	3 (1.2%)	9 (3.5%)	12 (2.3%)
Adverse event	1 (0.4%)	4 (1.5%)	5 (1.0%)
Selection criteria/compliance	0	2 (0.8%)	2 (0.4%)
Lost to follow-up	1 (0.4%)	3 (1.2%)	4 (0.8%)
Subject request	1 (0.4%)	0	1 (0.2%)
Subjects Completed Study	251 (98.8%)	250 (96.5%)	501 (97.7%)

Assessor's comment:
Subject discontinuation data is acceptable.

- **Conduct of the study**

One amendment was made to the protocol. This amendment involved mainly clarification of the inclusion and exclusion criteria. 28 subjects in the FCM group and 29 subjects in the standard medical care group had violations of inclusion/exclusion criteria.

Assessor's comment:
Protocol amendments and deviations are not considered to have impacted significantly on the study results.

- **Baseline data**

Subject demographic data and baseline characteristics are shown in the table below.

Demographic Characteristic	Group A: FCM (N=254)	Group B: SMC (N=259)
Age (years)		
Mean (SD)	62.5 (12.81)	63.1 (12.11)
Median	65	65
Minimum – Maximum	26, 85	23, 85
≤65	139 (54.7%)	133 (51.4%)
66-75	81 (31.9%)	91 (35.1%)
76-85	34 (13.4%)	35 (13.5%)
Gender		
Female	159 (62.6%)	153 (59.1%)
Male	95 (37.4%)	106 (40.9%)
Race		
African American	84 (33.1%)	76 (29.3%)
Asian	4 (1.6%)	5 (1.9%)
Caucasian	129 (50.8%)	128 (49.4%)
Hispanic	31 (12.2%)	43 (16.6%)
Other	6 (2.4%)	7 (2.7%)
Weight (kg)		
Mean (SD)	92.03 (25.537)	89.41 (23.863)
Median	89.1	86.6
Minimum – Maximum	38.1, 181.4	41.3, 191.0
Height (cm)		
Mean (SD)	166.06 (9.147)	166.21 (10.214)
Median	165.1	165.1
Minimum – Maximum	139.7, 193.0	132.1, 193.0
BMI (kg/m^2)		
Mean (SD)	33.28 (8.480)	32.30 (7.859)
Median	31.9	31.4
Minimum – Maximum	14.4, 64.2	16.1, 58.7
Cohort		
I (NDD)	204 (80.3%)	212 (81.9%)
II (HD)	50 (19.7%)	47 (18.1%)
Current ESA Use		
No	148 (58.3%)	148 (57.1%)
Yes	106 (41.7%)	111 (42.9%)
Iron Intolerance		
No	235 (92.5%)	246 (95.0%)
Yes	19 (7.5%)	13 (5.0%)
Previous Iron Therapy		
No	93 (36.6%)	103 (39.8%)
Yes	161 (63.4%)	156 (60.2%)
Drug Allergy		
No	140 (55.1%)	141 (54.4%)
Yes	114 (44.9%)	118 (45.6%)
Days Since Last Dose of Iron[a]		
N	151	149
Mean (SD)	88.1 (169.38)	104.1 (212.02)
Median	14	12
Minimum – Maximum	1, 1190	-29, 1757
Screening Hemoglobin (g/dL)		
Mean (SD)	10.55 (0.859)	10.43 (0.920)
Median	10.7	10.6
Minimum – Maximum	6.9, 12.4	7.7, 12.5
Hemoglobin Category		
≤9.0 g/dL	15 (5.9%)	18 (6.9%)
9.1-11.0 g/dL	161 (63.4%)	166 (64.1%)
≥11.1 g/dL	78 (30.7%)	75 (29.0%)
Screening TSAT (%)		
Mean (SD)	19.76 (5.807)	19.60 (6.490)
Median	20	20
Minimum – Maximum	4, 31	4, 39
<20	120 (47.2%)	125 (48.3%)
Screening Ferritin (ng/mL)		
Mean (SD)	125.53 (109.292)	120.08 (114.450)
Median	86.1	86.2
Minimum – Maximum	4.1, 499.4	3.6, 796.5
<100	139 (54.7%)	142 (54.8%)

Assessor's comment:
Baseline data is comparable for the two groups.

The mean weight for patients seems high, with mean BMI >30 (ie, obese). The applicant is requested to comment on this.

- **Outcomes and estimation**
  - Efficacy Endpoints
    - Proportion of subjects achieving an increase in haemoglobin of ≥1.0 g/dL at any time between baseline (Day 0) and Day 30.
    - Proportion of subjects achieving a haemoglobin >12.0 g/dL at any time between baseline (Day 0) and Day 30.

	Number (%) Subjects		Treatment Group Difference	
	Group A: FCM N=249 n/N (%)	Group B: SMC N=249 n/N (%)	Fisher's Exact p-value	95% CI
Increase in Hemoglobin ≥1.0 g/dL Anytime Between Baseline (Day 0) and Day 30	64 (25.7%)	55 (22.1%)	0.401	-0.12, 0.04
Achievement of Hemoglobin >12.0 g/dL Anytime Between Baseline (Day 0) and Day 30	36 (14.5%)	32 (12.9%)	0.696	-0.08, 0.05

    - Mean change in haemoglobin, ferritin and TSAT from baseline (Day 0) to Day 30 (or end of study for subjects who prematurely discontinued).

	Group A: FCM	Group B: SMC	p-value[a]	95% CI[a]
Hemoglobin (g/dL)				
Baseline for Day 30			0.096	-0.03, 0.32
N	246	240		
Mean (SD)	10.59 (0.940)	10.45 (0.996)		
Median	10.5	10.5		
Minimum, Maximum	6.7, 12.8	6.9, 12.9		
Change to Day 30			0.061	-0.01, 0.31
N	246	240		
Mean (SD)	0.49 (0.923)	0.33 (0.877)		
Median	0.5	0.2		
Minimum, Maximum	-2.2, 3.3	-2.3, 4.4		
Baseline for End of Study			0.104	-0.03, 0.31
N	248	248		
Mean (SD)	10.60 (0.937)	10.45 (0.995)		
Median	10.6	10.5		
Minimum, Maximum	6.7, 12.8	6.9, 12.9		
Change to End of Study			0.057	-0.00, 0.31
N	248	248		
Mean (SD)	0.48 (0.914)	0.33 (0.881)		
Median	0.5	0.2		
Minimum, Maximum	-2.2, 3.3	-2.3, 4.4		
Ferritin (ng/mL)				
Baseline for Day 30			0.920	-19.58, 21.68
N	248	241		
Mean (SD)	122.87 (110.917)	121.82 (121.187)		
Median	89.4	79.1		
Minimum, Maximum	4.8, 717.5	3.2, 799.9		
Change to Day 30			<0.001	110.19, 168.63
N	248	241		
Mean (SD)	242.58 (180.534)	103.17 (145.990)		
Median	241.5	58.8		
Minimum, Maximum	-275.4, 895.9	-373.7, 861.0		
Baseline for End of Study			0.841	-18.32, 22.50
N	249	248		
Mean (SD)	122.48 (110.867)	120.39 (120.515)		
Median	88.2	78.2		
Minimum, Maximum	4.8, 717.5	3.2, 799.9		
Change to End of Study			<0.001	110.72, 168.25
N	249	248		
Mean (SD)	242.23 (179.473)	102.75 (145.011)		
Median	240.4	58.7		
Minimum, Maximum	-275.4, 895.9	-373.7, 861.0		
TSAT (%)				
Baseline for Day 30			0.509	-2.12, 1.05
N	248	238		
Mean (SD)	20.70 (8.756)	21.23 (9.043)		
Median	20	20		
Minimum, Maximum	5, 92	5, 81		
Change to Day 30			<0.001	1.40, 5.63
N	248	238		
Mean (SD)	8.61 (10.757)	5.10 (12.937)		
Median	8	5		
Minimum, Maximum	-71, 33	-65, 54		
Baseline for End of Study			0.545	-2.06, 1.09
N	249	244		
Mean (SD)	20.65 (8.775)	21.13 (8.977)		
Median	20	20		
Minimum, Maximum	5, 92	5, 81		
Change to End of Study			<0.001	1.43, 5.63
N	249	244		
Mean (SD)	8.57 (10.853)	5.05 (12.817)		
Median	8	4		
Minimum, Maximum	-71, 33	-65, 54		

Assessor's comment:
The primary objective of this study was to evaluate the safety of high dose IV boluses of Ferinject, and the dose of Ferinject was not optimised to demonstrate efficacy. However, the efficacy of the FCM regime appears comparable to that of standard medical care.

- **Safety Evaluation**

  - Extent of Exposure

    Mean exposure to FCM and standard medical care are shown in the tables below.

    Summary of Extent of Exposure for Subjects Receiving FCM

Total Dose of Iron (mg) Received	**NDD**	**HD**	**Total**
	(N=204)	(N=50)	(N=254)
Mean (SD)	975.7 (74.52)	200.0 (0.00)	823.0 (316.15)
Median	1000	200	1000
Minimum - Maximum	500, 1000	200, 200	200,1000

    Standard Medical Care Treatment Record

	NDD (N=212) n (%)	**HD (N=47) n (%)**	**Total (N=259) n (%)**
No Treatment	7 (3.3%)	15 (31.9%)	22 (8.5%)
Oral Iron	77 (36.3%)	0	77 (29.7%)
IV Iron[a]	131 (61.8%)	32 (68.1%)	163 (62.9%)
Venofer	112 (52.8%)	15 (31.9%)	127 (49.0%)
Ferrlecit	16 (7.5%)	16 (34.0%)	32 (12.4%)
Iron Dextran	3 (1.4%)	1 (2.1%)	4 (1.5%)

a Subjects could have been assigned to more than 1 treatment.

Summary of Extent of Exposure for Subjects Receiving IV Iron in the Standard Medical Care Group

Total Dose of Iron (mg) Received	NDD	HD	Total
IV Iron Regardless of Individual Dose			
	(N=129)	(N=35)	(N=164)
Mean (SD)	698.7 (341.69)	561.1 (326.97)	669.3 (342.32)
Median	800	500	750
Minimum - Maximum	80, 1200	100, 1200	80, 1200
IV Iron at Individual Doses Not Exceeding 300 mg			
	(N=124)	(N=35)	(N=159)
Mean (SD)	686.5 (343.01)	561.1 (326.97)	658.9 (342.52)
Median	800	500	750
Minimum - Maximum	80, 1200	100, 1200	80, 1200
IV Iron for Subjects Receiving Venofer or Ferrlecit			
	(N=124)	(N=33)	(N=157)
Mean (SD)	686.5 (343.01)	552.7 (331.38)	658.4 (343.93)
Median	800	500	750
Minimum - Maximum	80, 1200	100, 1200	80, 1200
IV Iron for Subjects Receiving Venofer			
	(N=110)	(N=17)	(N=127)
Mean (SD)	697.5 (354.61)	444.1 (319.61)	663.6 (359.52)
Median	875	300	800
Minimum - Maximum	80, 1200	100, 1200	80, 1200

Distribution of IV Iron Total Dose and Maximum Individual Dose for Subjects Receiving Venofer or Ferrlecit in the Standard Medical Care Group

Total Dose (mg)	Maximum Individual Dose (mg)	NDD (N=126[a])	HD (N=33)	Total (N=159)
Venofer		n=112	n=17	n=129
1000	500	2	0	2
900	300	3	0	3
300	300	1	0	1
1200	200	1	0	1
1000	200	51	1	52
800-850	200	8	0	8
600	200	13	0	13
200-400	200	16	1	17
800-1200	100	1	2	3
100-500	100	15	9	24
80-250	25-80	1	4	5
Ferrlecit		n=15	n=16	n=31
500	250	0	1	1
1125	125	0	1	1
1000	125	2	4	6
500-812.5	125	9	7	16
250-375	125	3	0	3
125	125	0	1	1
25-250	25-62.5	1	2	3

- Adverse Events

Among the HD and NDD subjects combined, a statistically significantly greater proportion of subjects in the standard medical care group (11.2%) experienced adverse events associated with General Disorders and Administration Site Conditions compared with the FCM group (5.1%). A statistically significantly greater proportion of subjects in the FCM group (2.4%) experienced muscle spasms compared with subjects in the standard medical care group (0%). The most commonly (≥2%)

experienced treatment-emergent adverse events in the FCM group were nausea (3.9%), vomiting (2.8%), arthralgia, muscle spasms, and hypertension (2.4% each). The most commonly (≥2%) experienced treatment-emergent adverse events in the standard medical care group were hypertension (2.7%), oedema, and oedema peripheral (2.3% each). This is summarised in the table below.

TEAEs Experienced by ≥2% of Subjects in Either the FCM or Standard Medical Care Group - HD and NDD Subjects Combined

MedDRA SOC[a] Preferred Term	Group A: FCM (N=254) n (%)	Group B: SMC (N=259) n (%)	p-value[b]
At Least 1 Treatment-Emergent Adverse Event	**77 (30.3%)**	**85 (32.8%)**	**0.569**
Gastrointestinal Disorders	19 (7.5%)	17 (6.6%)	0.732
Nausea	10 (3.9%)	5 (1.9%)	0.200
Vomiting	7 (2.8%)	3 (1.2%)	0.218
General Disorders and Administration Site Conditions	13 (5.1%)	29 (11.2%)	0.015*
Oedema	3 (1.2%)	6 (2.3%)	0.504
Oedema peripheral	4 (1.6%)	6 (2.3%)	0.752
Musculoskeletal and Connective Tissue Disorders	16 (6.3%)	8 (3.1%)	0.097
Arthralgia	6 (2.4%)	2 (0.8%)	0.173
Muscle spasms	6 (2.4%)	0	0.014*
Vascular Disorders	12 (4.7%)	11 (4.2%)	0.834
Hypertension	6 (2.4%)	7 (2.7%)	1.000

In NDD subjects, at least 1 TEAE was experienced by 27.5% of the subjects in the FCM group, 31.1% of the subjects in the standard medical care group, and 37.9% of the subjects in the standard medical care group receiving Venofer or Ferrlecit (ferrous sulphate). The most commonly (≥2%) experienced TEAEs in the FCM group were nausea (4.4%), vomiting (2.9%), oedema peripheral, arthralgia, dizziness, and hypertension (2.0% each). The most commonly (≥2%) experienced TEAEs in the standard medical care group were oedema (2.8%), oedema peripheral, and hypertension (2.4% each). Three (1.2%) NDD subjects in the FCM group and 1 (0.4%) NDD subject in the standard medical care group were prematurely discontinued from study drug due to the occurrence of AEs.

Drug-related TEAEs experienced by more than 1 subject in the FCM group were nausea (6/254; 2.4%), hypertension (4/254; 1.6%), vomiting, dizziness, flushing (3/254; 1.2%), and dysgeusia (2/254; 0.8%). Drug related TEAEs experienced by more than 1 subject in the SMC group were nausea and dizziness (2/259; 0.8%). In HD subjects, no drug-related TEAEs were experienced by more than 1 subject in the FCM group. In NDD subjects, drug-related TEAEs experienced by more than 1 subject in the FCM group were nausea (5/204; 2.5%), dizziness, hypertension (3/204; 1.5%), vomiting, dysgeusia, and flushing (2/204; 1.0%). Drug-related TEAEs experienced by more than 1 subject in the SMC group were nausea and dizziness (2/212; 0.9%).

Drug-Related Treatment-Emergent Adverse Events Experienced by ≥1 Subject in Either the FCM or Standard Medical Care Group - HD and NDD Subjects Combined

MedDRA SOC[a] Preferred Term	Group A: FCM (N=254) n (%)	Group B: SMC (N=259) n (%)
At Least 1 Treatment-Emergent Adverse Event	**17 (6.7%)**	**8 (3.1%)**
Gastrointestinal Disorders	8 (3.1%)	6 (2.3%)
Abdominal pain	1 (0.4%)	0
Constipation	0	1 (0.4%)
Diarrhoea	0	1 (0.4%)
Faeces discoloured	0	1 (0.4%)
Nausea	6 (2.4%)	2 (0.8%)
Stomach discomfort	0	1 (0.4%)
Vomiting	3 (1.2%)	0
General Disorders and Administration Site Conditions	1 (0.4%)	2 (0.8%)
Chills	0	1 (0.4%)
Fatigue	0	1 (0.4%)
Injection site discolouration	1 (0.4%)	0
Investigations	1 (0.4%)	1 (0.4%)
Blood pressure increased	1 (0.4%)	0
Liver function test abnormal	0	1 (0.4%)
Musculoskeletal and Connective Tissue Disorders	0	1 (0.4%)
Arthralgia	0	1 (0.4%)
Nervous System Disorders	5 (2.0%)	2 (0.8%)
Dizziness	3 (1.2%)	2 (0.8%)
Dysgeusia	2 (0.8%)	0
Skin and Subcutaneous Tissue Disorders	2 (0.8%)	0
Blister	1 (0.4%)	0
Rash pruritic	1 (0.4%)	0
Vascular Disorders	7 (2.8%)	0
Flushing	3 (1.2%)	0
Haematoma	1 (0.4%)	0
Hypertension	4 (1.6%)	0

The majority of the TEAEs experienced during the study were classified by the Investigator as Grade 1 or Grade 2 severity. Grade 3 TEAEs were experienced by 6 subjects (2.4%) in the FCM group (2 HD and 4 NDD subjects) and 16 subjects (6.2%) in the SMC group (1 HD and 15 NDD subjects). Two subjects (0.8%) in the FCM group (1 HD and 1 NDD subject) and 5 subjects (1.9%) in the SMC group (5 NDD subjects) experienced TEAEs classified by the Investigator as Grade 4 severity. In addition, 2 HD subjects (0.8%) in the SMC group experienced TEAEs classified by the Investigator as Grade 5 severity. None of these subjects experienced Grade 3 or higher TEAEs that were considered by the Investigator to be study drug-related.

The applicant states that no subjects experienced a hypersensitivity reaction. However, 7 subjects in the FCM group (1 HD and 6 NDD subjects) and 3 NDD subjects in the standard medical care group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including blister, rash, urticaria, skin ulcer, rash pruritic, pruritus generalised, and swelling face. The majority of these events were considered not related to study drug. The related events included blister and rash pruritic; both in the FCM group and requiring medication.

Three (1.2%) NDD subjects in the FCM group and 1 (0.4%) NDD subject in the SMC group were prematurely discontinued from study drug due to the occurrence of AEs. In 2 of these 3 NDD subjects in the FCM group, the events (nausea (1) and vomiting (1)) were considered to have a probable or possible relationship to study drug by the Investigator. The NDD SMC subject who prematurely

discontinued study drug experienced chills that were considered to have an unlikely relationship to study drug by the Investigator.

The primary safety endpoint of this study was the incidence of treatment-emergent SAEs, overall and related from Day 0 through 30 days after the last dose of study drug. A total of 9 (3.5%) subjects in the FCM group (3 HD and 6 NDD subjects) and 23 (8.9%) subjects in the SMC group (3 HD and 20 NDD subjects), including 2 HD subjects who died, experienced at least 1 SAE during the study. None of these events were considered by the Investigator to be related to study medication. No subject exposed to Ferric Carboxymaltose died during this study. No subjects experienced a hypersensitivity reaction.

- Clinical Laboratory Assessments

No clinically significant findings were observed in the haematology or clinical chemistry analysis between the groups.

Assessor's comment:
Adverse event and clinical laboratory data appear comparable between NDD patients receiving high dose FCM and those receiving standard medical care. However, summary data on adverse events should be provided for subjects in the NDD group who received the maximum dose of 1000 mg of FCM, as compared with those who received lower doses.

Although it is stated that no patients experienced a hypersensitivity reaction, seven subjects in the Ferinject group experienced reactions that would be considered to qualify in this category (eg, urticaria). The applicant should clarify this.

Since no haemodialysis-dependent patients were exposed to the maximum dose of 1000 mg FCM it is unclear how the primary objective of the study can be met for this group of patients. The safety of a single bolus dose of 1000 mg Ferinject has not been demonstrated in HD patients.

IV.3.4 Study 1VIT06011

IV.3.4.1 Methods

This was an open-label, multicentre, randomised study to assess the efficacy, safety and tolerability of intravenous Ferinject in comparison to oral ferrous sulphate in postpartum anaemia.

The duration of the study for each subject was a maximum of 8 weeks. Within 10 days post-delivery, subjects meeting the entrance criteria were randomised into the treatment phase and received their first dose of study drug. Subjects were randomly assigned to either FCM (up to a maximum cumulative iron dose of 2,500 mg administered IV based on iron-deficit calculations; the calculated dose was given in divided doses of up to 1,000 mg weekly) or oral iron (325 mg of ferrous sulphate 3 times daily [TID] x 6 weeks). Assessments for efficacy (hematologic parameters and iron indices) and safety (adverse events and laboratory results) were performed on post-randomisation Days 7, 14, 28, and 42.

- **Study Participants**

Subjects were considered eligible if they met the following inclusion criteria

- Postpartum within 10 days after delivery.
- The average of last 2 consecutive haemoglobin values was ≤10.0 g/dL and the difference between the haemoglobin values must have been ≤1 g/dL.

Exclusion criteria included any history of anaemia (haemolytic, macrocytic, hypoplastic, or sideroblastic) other than anaemia due to iron deficiency or blood loss secondary to delivery, documented history of discontinuing oral iron products due to significant gastrointestinal distress, except discontinuations that occurred during pregnancy, significant vaginal bleeding in the 24-hour period prior to randomisation (estimated blood loss >100 cc), untreated Vitamin B12 or folic acid deficiency, serum transferring saturation (TSAT) >25%, ferritin >100 ng/mL, received erythropoietin within the 3 months prior to screening, myelosuppressive therapy, active severe infection, and receiving treatment for asthma.

Assessor's comment:
The inclusion and exclusion criteria are acceptable.

- **Treatments**

- Group A

  FCM dosage was based on the calculated iron deficit as indicated below. A maximum of 1,000 mg (15 mg per kg for pre-pregnancy weight ≤66 kg) iron as IV FCM was given at weekly intervals until the individual's calculated cumulative dose had been reached or a maximum of 2,500 mg had been administered. For subjects whose pre-pregnancy weight was >66 kg, doses were rounded up to the nearest 100 mg. For weight ≤66 kg, the doses were rounded down to the nearest 100 mg:

  - Screening TSAT ≤20% or Screening Ferritin ≤50 ng/mL
    Dose = Pre-pregnancy weight (kg) x (15-Baseline haemoglobin [g/dL]) x 2.4 + 500 mg
  - Screening TSAT >20% and Screening Ferritin >50 ng/mL
    Dose = Pre-pregnancy weight (kg) x (15-Baseline haemoglobin [g/dL]) x 2.4

The doses were administered as follows:

≤500 mg	Administered undiluted as a slow IV injection at a rate of 100 mg/minute
600-1000 mg	May have been administered either as: • Undiluted as a slow IV injection over 15 minutes *or* • As an IV infusion diluted in 250 cc NSS over 15 minutes

Note: The administration time must not have been shortened.

- Group B

Ferrous sulphate was dispensed as 325 mg tablets (65 mg elemental iron) with instructions to take 1 tablet by mouth TID with 8 ounces of tap water, 1 hour before meals from Day 0 until Day 42.

Assessor's comment:
The treatment regime for Ferinject is not in accordance with the updated proposed regime. However since this study has been submitted to demonstrate the safety of a single IV dose of 1000 mg, the treatments administered are acceptable (subject to a sufficient number of subjects actually receiving this dose).

- **Objectives**

The primary objective of this study was to evaluate the efficacy of intravenous FCM in comparison with oral ferrous sulphate in improving haemoglobin in postpartum anaemia.

The secondary objective of this study was to evaluate the safety and tolerability of IV FCM in comparison with oral ferrous sulphate in postpartum anaemia.

- **Outcomes/endpoints**

The primary measure of efficacy defined "success" as the number of subjects with an increase in haemoglobin of >12 g/dL anytime between Baseline and End of Study or time of intervention.

"Failure" was defined as the number of subjects with ≤12 g/dL increase in haemoglobin at all times between Baseline and End of Study or time of intervention.

Major secondary endpoints included:

- Number and proportion of subjects with an increase in haemoglobin ≥3 g/dL anytime between Baseline and end of study or time of intervention.
- Proportion of subjects who met the criteria for success on or before Day 42, Day 28, and Day 14.
- Proportion of subjects who had an increase in haemoglobin ≥3 g/dL on or before Day 42, Day 28, and Day 14.
- Time to success.

Other secondary endpoints included:

- Proportion of subjects achieving a sustained success when defined as achieving a haemoglobin of >12 g/dL on Day 42/End of Study Visit.
- Number and percent of subjects who had a change from baseline in ferritin ≥160 ng/mL and achieved success.

- Change from baseline to highest haemoglobin during the study.
- Change from baseline to highest ferritin during the study.
- Change from baseline to highest TSAT during the study.
- Time to haemoglobin ≥3 g/dL.
- Improvement based on Rating of Physical Energy.
- Improvement based on Fatigue Severity Scale.

Safety variables included adverse events, and laboratory evaluations (haematology, chemistry, and iron indices).

- **Sample size**

Approximately 320 subjects were to be randomised in a 1:1 ratio to FCM and oral iron. The sample size calculation was acceptable.

- **Randomisation**

Subjects who had met all of the inclusion criteria and none of the exclusion criteria were stratified by haemoglobin levels (9.1-10.0 g/dL, 8.1-9.0 g/dL, ≤8.0 g/dL), requirement for C-section, and screening ferritin (ferritin >25 ng/mL, ≤25 ng/mL) and were randomised in a 1:1 ratio to either of the treatment groups via a central IVRS randomisation system.

- **Statistical methods**

- Analysis populations

The following definitions of analysis populations were used for the data analysis and tabulations.

- **Safety Set**: all subjects who received at least 1 dose of randomised study drug.
- **Modified Intent to Treat population (mITT)**: subjects from the Safety Population who received at least 1 dose of randomised study medication, had at least 1 post-baseline haemoglobin assessment, and had postpartum anaemia characterised by an average of 2 baseline central laboratory haemoglobin values <11.0 g/dL. Treatment assignments were analysed according to the actual treatment received. This was the primary population for evaluating all efficacy endpoints, treatment administration/compliance, as well as subject characteristics.
- **Evaluable Population:** those subjects from the mITT population who received at least 67% of the required study drug, who were followed until the Day 42 evaluation, and who had no major protocol violations. This was a supportive population for efficacy analyses of the primary endpoint and of clinical response.

- Efficacy Evaluation

- **Primary efficacy analysis**: The superiority of the proportion of subjects who achieved success for FCM relative to oral iron was based on a 2-sided Fisher's exact test. The test was performed on the unstratified success rate. The primary endpoint was summarised for each treatment group within a variety of subgroups.

Assessor's comment:
The statistical methods are considered acceptable for the stated objectives of the study.

IV.3.4.2 Results

- **Participant flow**

291 subjects were randomised at 28 centres to receive FCM (143 subjects) or oral iron (148 subjects). Of these 291 subjects, 1 who was randomised to FCM and 1 who was randomised to oral iron were both discontinued from the study due to subject request prior to dosing. Therefore, a total of 142 subjects were treated in the ICM group and 147 subjects were treated in the oral iron group.

138 (97.2%) of the 142 subjects in the FCM group and 144 (98.0%) of the 147 subjects in the oral iron group completed the study. Of the 4 subjects in the FCM group who did not complete the study, 3 were lost to follow-up and 1 had an intervention and received a blood transfusion. Of the 3 subjects in the oral iron group who did not complete the study, 1 was lost to follow-up, 1 discontinued due to subject request, and 1 had an intervention and received a blood transfusion.

A summary of subject disposition and study termination is presented in the table below.

	ICM	Oral Iron	Total
All Randomized Subjects	143	148	291
Treated Subjects	142 (100%)	147 (100%)	289 (100%)
Subjects Discontinued From Study	4 (2.8%)	3 (2.0%)	7 (2.4%)
Subject had intervention			
Received blood transfusion	1 (0.7%)	1 (0.7%)	
Did not complete study per protocol			
Lost to follow-up	3 (2.1%)	1 (0.7%)	
Subject request	0	1 (0.7%)	
Subjects Who Completed Study	138 (97.2%)	144 (98.0%)	282 (97.6%)

Assessor's comment:
Subject discontinuation data is acceptable.

- **Conduct of the study**

One amendment was made to the protocol. Six subjects in the FCM group and 14 subjects in the oral iron group had violations of inclusion/exclusion criteria.

Assessor's comment:
Protocol amendments and deviations are not considered to have impacted significantly on the study results.

- **Baseline data**

Subject demographic data and baseline characteristics are shown in the tables below.

Demographic Characteristic	ICM (N=142)	Oral Iron (N=147)
Age (years)		
Mean (SD)	26.43 (6.02)	26.49 (5.55)
Median	25.40	26.32
Minimum – Maximum	16.79 – 43.16	15.76 – 43.41
<19	14 (9.9%)	7 (4.8%)
≥19	128 (90.1%)	140 (95.2%)
Race		
Caucasian	104 (73.2%)	96 (65.3%)
Hispanic	15 (10.6%)	20 (13.6%)
African American	22 (15.5%)	27 (18.4%)
Asian	0	3 (2.0%)
Other	1 (0.7%)	1 (0.7%)
Weight (kg) at Screening	(N=142)	(N=143)
Mean (SD)	81.51 (18.17)	79.93 (19.55)
Median	77.11	77.57
Minimum – Maximum	46.63 – 136.08	46.27 – 154.22
Height (cm)	(N=142)	(N=146)
Mean (SD)	163.16 (6.72)	163.40 (6.61)
Median	162.56	163.45
Minimum – Maximum	142.24 – 180.34	147.32 – 179.07
Current Neonate Feeding Method		
Not Applicable	2 (1.4%)	1 (0.7%)
Breastfeed Exclusively	55 (38.7%)	70 (47.6%)
Breastfeed and Formula	43 (30.3%)	37 (25.2%)
Formula Exclusively	42 (29.6%)	39 (26.5%)
Blood Loss From Delivery (cc)	(N=58)	(N=53)
Mean (SD)	756.03 (126.38)	791.51 (193.09)
Median	750.00	750.00
Minimum – Maximum	600.00 – 1000.00	550.00 – 1500.00
≤500 cc	80 (56.7%)	91 (62.8%)
>500 cc	61 (43.3%)	54 (37.2%)
Missing/Unknown	1	2
Drug Allergy		
No	112 (78.9%)	116 (78.9%)
Yes	30 (21.1%)	31 (21.1%)

Baseline Characteristic	ICM (N=142)	Oral Iron (N=147)
Baseline Hemoglobin (g/dL)		
Mean (SD)	8.89 (0.90)	8.88 (0.89)
Median	9.13	9.10
Minimum – Maximum	5.65 – 10.35	6.10 – 10.50
Hemoglobin Category (Central Lab)		
>10 g/dL	6 (4.2%)	9 (6.1%)
9.1 – 10.0 g/dL	72 (50.7%)	66 (44.9%)
8.1 – 9.0 g/dL	44 (31.0%)	49 (33.3%)
≤8.0 g/dL	20 (14.1%)	23 (15.6%)
Hemoglobin Category (at Randomization)		
9.1 – 10.0 g/dL	81 (57.0%)	78 (53.1%)
8.1 – 9.0 g/dL	41 (28.9%)	48 (32.7%)
≤8.0 g/dL	20 (14.1%)	21 (14.3%)
Baseline TSAT (%)		
Mean (SD)	9.44 (4.65)	9.35 (4.71)
Median	8.00	8.00
Minimum – Maximum	2.00 – 26.00	2.00 – 28.00
Baseline Ferritin (ng/mL)		
Mean (SD)	24.05 (18.52)	23.91 (16.34)
Median	19.80	19.20
Minimum – Maximum	4.40 – 123.90	3.70 – 91.60
Prior Iron Intolerance		
No	136 (95.8%)	139 (94.6%)
Yes	6 (4.2%)	8 (5.4%)
Previous Iron Therapy		
No	28 (19.7%)	31 (21.1%)
Yes	114 (80.3%)	116 (78.9%)

In both the mITT population and safety populations, mean study drug usage and the proportion of subjects who used 67% of study drug were comparable between the FCM treatment group and the oral iron treatment group.

Assessor's comment:
Baseline data is comparable for the two groups.

The mean weight for postpartum women seems high. The applicant is requested to comment on this.

- **Outcomes and estimation**
  - Efficacy Endpoints
    - **Primary Efficacy Endpoint**:
      Proportion of subjects who achieved success (haemoglobin >12.0 g/dL) anytime during the study

Hemoglobin >12 g/dL Anytime During Study	Number (%) Subjects ICM n/N (%)	Number (%) Subjects Oral Iron n/N (%)	Fisher's Exact p-value	95% CI
Modified Intent-to-Treat Population	127/139 (91.4%)	98/147 (66.7%)	<0.0001	15.20, 34.20
Evaluable Population	126/138 (91.3%)	96/143 (67.1%)	<0.0001	14.65, 33.70
Intent-to-Treat Population	127/143 (88.8%)	98/148 (66.2%)	<0.0001	12.97, 32.22

n = number of subjects who achieved success, N = number of subjects in group, % = n divided by N

Subgroup analyses support the superiority of FCM over oral iron.

    - **Selected Secondary Efficacy Endpoints**:

- Proportion of subjects who had an increase from baseline in haemoglobin ≥3.0 g/dL anytime during the study

≥3 g/dL Increase From Baseline in Hemoglobin Anytime During Study	Number (%) Subjects		Fisher's Exact p-value	95% CI
	ICM n/N (%)	Oral Iron n/N (%)		
Modified Intent-to-Treat Population	127/139 (91.4%)	95/147 (64.6%)	<0.0001	17.08, 36.41
Evaluable Population	126/138 (91.3%)	92/143 (64.3%)	<0.0001	17.21, 36.72

n = number of subjects who achieved an increase in hemoglobin ≥3 g/dL, N = number of subjects in group, % = n divided by N

- Mean changes from baseline in haemoglobin, TSAT, and ferritin at each visit

  - Hb (g/dL)

	ICM				Oral Iron				Overall
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]	p-value[b]
Day 7	138	8.9 (0.89)	2.1 (0.80)	<0.0001	147	8.9 (0.89)	2.0 (0.75)	<0.0001	0.1658
Day 14	138	8.9 (0.84)	3.0 (0.83)	<0.0001	144	8.9 (0.89)	2.7 (0.88)	<0.0001	0.0003
Day 28	138	8.9 (0.89)	3.8 (0.95)	<0.0001	145	8.9 (0.89)	3.1 (0.94)	<0.0001	<0.0001
Day 42	137	8.9 (0.89)	4.0 (1.06)	<0.0001	143	8.9 (0.89)	3.4 (1.09)	<0.0001	<0.0001
Highest	139	8.9 (0.89)	4.1 (1.01)	<0.0001	147	8.9 (0.89)	3.5 (1.09)	<0.0001	<0.0001

  - TSAT (%)

	ICM				Oral Iron				Overall
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]	p-value[b]
Day 7	138	9.5 (4.70)	17.4 (10.72)	<0.0001	144	9.2 (4.66)	10.7 (12.57)	<0.0001	<0.0001
Day 14	138	9.5 (4.68)	29.2 (13.21)	<0.0001	144	9.4 (4.73)	13.7 (16.96)	<0.0001	<0.0001
Day 28	138	9.4 (4.69)	27.6 (13.44)	<0.0001	144	9.4 (4.72)	15.1 (14.86)	<0.0001	<0.0001
Day 42	137	9.5 (4.71)	28.8 (11.60)	<0.0001	143	9.4 (4.73)	17.2 (17.57)	<0.0001	<0.0001
Highest	139	9.5 (4.69)	36.5 (12.57)	<0.0001	147	9.3 (4.71)	28.2 (18.17)	<0.0001	<0.0001

  - Ferritin (ng/mL)

	ICM				Oral Iron				Overall
	N	BL (SD)	Change from BL (SD)	p-value[a]	N	BL (SD)	Change from BL (SD)	p-value[a]	p-value[b]
Day 7	139	24.1 (18.67)	575.0 (202.90)	<0.0001	147	23.9 (16.34)	2.4 (21.33)	0.1815	<0.0001
Day 14	139	24.1 (18.67)	580.6 (213.33)	<0.0001	145	23.8 (16.36)	1.2 (16.62)	0.4053	<0.0001
Day 28	138	24.2 (18.71)	308.7 (140.50)	<0.0001	145	23.9 (16.34)	1.6 (16.82)	0.2551	<0.0001
Day 42	138	24.2 (18.72)	225.9 (117.96)	<0.0001	143	24.1 (16.36)	2.7 (20.36)	0.1144	<0.0001
Highest	139	24.1 (18.67)	646.7 (214.32)	<0.0001	147	23.9 (16.34)	12.2 (23.26)	<0.0001	<0.0001

Assessor's comment:
The superiority of IV Ferinject (according to the regime used in this study) over oral iron in the treatment of postpartum anaemia has been demonstrated.

- **Safety Evaluation**

  - Extent of Exposure

Mean exposures to IV and oral iron are shown in the table below.

Total Dose of Iron (mg) Received	ICM	Oral Iron
Safety Population	(N=142)	(N=147)
Mean (SD)	1503.5 (384.53)	7906.1 (981.42)
95% Confidence Interval of Mean	1439.73, 1567.31	7746.14, 8066.10
Median	1500	8190
Minimum – Maximum	400 - 2500	1170 – 9620
Modified Intent-to-Treat Population	(N=139)	(N=147)
Mean (SD)	1522.3 (365.16)	7906.1 (981.42)
95% Confidence Interval of Mean	1461.06, 1583.54	7746.14, 8066.10
Median	1500	8190
Minimum – Maximum	600 - 2500	1170 – 9620

A total of 31 subjects received at least one 500 mg dose of undiluted FCM over 5 minutes and 16 subjects received at least one 1000 mg dose of undiluted FCM over 15 minutes.

- Adverse Events

No statistically significant difference was observed between the treatment groups for the overall incidence of TEAEs (FCM: 45.8%; oral iron: 56.5%). The most commonly (≥5% of subjects) experienced TEAEs by preferred term were headache (4.9%) in the FCM group and constipation (12.2%) and headache (7.5%) in the oral iron group.

TEAEs experienced by ≥5% subjects in either treatment group

MedDRA SOC Preferred Term	ICM (N=142)	Oral Iron (N=147)	p-value
At Least One Treatment-Emergent Adverse Event	**65 (45.8%)**	**83 (56.5%)**	**0.0779**
Gastrointestinal Disorders	12 (8.5%)	39 (26.5%)	<0.0001
Constipation	2 (1.4%)	18 (12.2%)	0.0003
General Disorders and Administration Site Conditions	13 (9.2%)	10 (6.8%)	0.5185
Infections and Infestations	29 (20.4%)	22 (15.0%)	0.2800
Investigations	2 (1.4%)	9 (6.1%)	0.0609
Nervous System Disorders	11 (7.7%)	14 (9.5%)	0.6776
Headache	7 (4.9%)	11 (7.5%)	0.4676

Among the drug-related TEAEs reported by ≥2% of subjects in either treatment group, those that were higher in the oral iron group than in the FCM group included constipation (10.9% versus 0.0%), nausea (2.0% versus 1.4%), alanine aminotransferase increased (4.1% versus 0.7%), and aspartate aminotransferase increased (2.0% versus 0.7%). The only drug-related TEAE reported by ≥2% of subjects in either treatment group that was higher in the FCM group compared with the oral iron group was urticaria (2.1% versus 0.7%).

Drug-related TEAEs experienced by ≥2% subjects in either treatment group

MedDRA SOC Preferred Term	ICM (N=142)	Oral Iron (N=147)
At Least One Treatment-Emergent Adverse Event	**15 (10.6%)**	**32 (21.8%)**
Gastrointestinal Disorders	3 (2.1%)	25 (17.0%)
Constipation	0 (0.0%)	16 (10.9%)
Nausea	2 (1.4%)	3 (2.0%)
General Disorders and Administration Site Conditions	3 (2.1%)	0
Investigations	1 (0.7%)	6 (4.1%)
Alanine Aminotransferase Increased	1 (0.7%)	6 (4.1%)
Aspartate Aminotransferase Increased	1 (0.7%)	3 (2.0%)
Nervous System Disorders	4 (2.8%)	1 (0.7%)
Skin and Subcutaneous Tissue Disorders	4 (2.8%)	1 (0.7%)
Urticaria	3 (2.1%)	1 (0.7%)

The majority of the TEAEs experienced during the study were classified by the Investigator as Grade 1 or Grade 2. Grade 3 TEAEs were experienced by 5 subjects (3.5%) in the FCM group and 7 subjects (4.8%) in the oral iron group and Grade 4 TEAEs were experienced by no subjects in the FCM group and 3 (2.0%) subjects in the oral iron group. None of the subjects in either treatment group experienced a Grade 5 TEAE. Only 2 of the Grade 3 TEAEs (abdominal pain and gastrointestinal pain), which were reported by oral iron subjects, were considered by the Investigator to be study drug-related. None of the Grade 3 TEAEs in FCM subjects and none of the Grade 4 TEAEs in oral iron subjects were considered by the Investigator to be study drug-related.

The applicant states that no subjects experienced a hypersensitivity reaction. However, 7 subjects in the FCM group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including urticaria (3 subjects), generalised urticaria (1 subject), erythema (2 subjects), rash (1 subject), and rash macular (1 subject). 2 of the 4 urticaria events experienced in the FCM group led to premature discontinuation of study drug. Comparatively, 5 subjects in the oral iron group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including urticaria (2 subjects), rash (2 subjects), and pruritus (2 subjects). Only 1 of the events (an episode of urticaria) was considered related to study drug.

No subject died during the conduct of the study. Four (2.8%) subjects in the FCM group and 4 (2.7%) subjects in the oral iron group experienced at least 1 SAE during the study, none of which were considered by the Investigator to be related to study medication or led to premature discontinuation of study medication.

- Clinical Laboratory Assessments

Evaluations of vital signs and physical examinations showed no clinically important differences between subjects treated with Ferric Carboxymaltose or oral iron. Analysis of clinical chemistry and urinalysis variables were unremarkable, apart from a greater mean change to the lowest phosphate value in Ferric Carboxymaltose-treated patients. The mean change to the lowest phosphate value was statistically significantly greater in the FCM group (-1.3 mg/dL) compared to the oral iron group (-0.3 mg/dL). The mean decreases from baseline noted in phosphate among FCM subjects reached a nadir approximately 2 weeks after initiating therapy and spontaneously resolved thereafter. 12 (8.5%) subjects in the FCM group had low phosphate values during the study that met the CTCAE Grade 3 toxicity criteria, while none of the subjects in the oral iron group met these criteria. The low values were transient and none resulted in a TEAE.

Assessor's comment:
This study has been submitted to support an increase in the dose of IV Ferinject that may be given in a single IV injection from 200 mg to 1000 mg. However, since only 16 patients in this study received the maximum dose of 1000 mg (undiluted) the results are of limited use.

Although it is stated that no patients experienced a hypersensitivity reaction, seven subjects in the Ferinject group experienced reactions that would be considered to qualify in this category (eg, urticaria). The applicant should clarify this.

Safety and demographic data (to include weight) for the 16 subjects who received the maximum dose of 1000 mg (undiluted) IV FCM should be presented in comparison to subjects who received lower doses of FCM or oral iron. The applicant should specify how many of the 12 subjects with a CTCAE grade 3 decrease in phosphate received the maximum dose of FCM.

IV.3.4.3 Conclusions

Three clinical studies have been presented in patients with iron deficiency anaemia due to heavy uterine bleeding, childbirth, and chronic kidney disease, aimed at supporting the safety of increasing the dose of ferric carboxymaltose that may be given as an undiluted IV bolus from 200 to 1000 mg (up to a dose of 15 mg/kg).

This proposed change to the posology of Ferinject could be approvable based on the data provided; however further clarification is required. Specifically, detailed safety data should be provided for subjects in the studies who actually received the highest doses of Ferinject, to ensure that safety signals have not been missed in the background noise generated from lower doses.

No data have been presented to support the safety of doses higher than 200 mg in haemodialysis-dependent chronic kidney disease patients. This would need to be reflected in the SPC.

Higher bolus doses of parenteral iron may increase the risk of events such as anaphylactic reactions and injection site complications. Anaphylactic reactions are an uncommon occurrence and so a small increase in frequency would be difficult to detect in the clinical trial setting with small patient numbers. Several subjects experienced hypersensitivity reactions (eg, urticaria) during the studies. Injection site reactions were observed as a common occurrence in Study 1VIT07017, and 6 patients discontinued the study due to such an event. The potential for an increase in the frequency of these reactions needs further discussion, and comparisons should be presented with frequencies observed in other trials with Ferinject.

IV.4 UK/H/0894/001/II/013

IV.4.1.1 Introduction

Currently, Ferinject may be administered at doses of 15 mg iron/kg body weight. Hence, in patients requiring 1000 mg iron (which would be the minimum in the majority of patients who are iron deficient) and weighing 50-66 kg, two individual doses are required to achieve a cumulative dose of 1000 mg iron. The applicant estimates that the number of patients with a body weight ≤66 kg is at least 50% (50-66 kg is at least 45%).

This application proposes to increase the allowable dose of iron from 15 to 20 mg/kg body weight per day, therefore allowing patients who weigh at least 50 kg to receive a single dose of 1000 mg IV Ferinject. As such, the applicant has re-examined the data used in the initial MAA to investigate the impact of body weight on the pharmacokinetics (PK) and safety (adverse event) profile of Ferinject in those patients that received a single IV dose of 1000 mg.

Assessor's comment:
The applicant estimates that the number of patients with a body weight ≤66 kg requiring intravenous iron therapy is at least 50%; however, in the 3 studies submitted in support of variation UK/H/0894/001/II/012 the mean body weight of patients was significantly higher. The applicant should comment on this.

IV.4.1.2 Clinical Study Data

In two Phase 1 studies (VIT-IV-CL-02 and VIT-IV-CL-03) submitted in the initial MAA, PK and safety data is available for 32 patients who received 1000 mg doses of Ferinject, 6 from VIT-IV-CL-02 and 26 from VIT-IV-CL-03 (19 with a body weight >66 kg and 13 ≤ 66 kg (50-66 kg). The clinical study reports for these PK studies have not been provided, but reference has been made to the clinical assessment report from the initial MAA for Ferinject. A summary of these studies is presented in the table below.

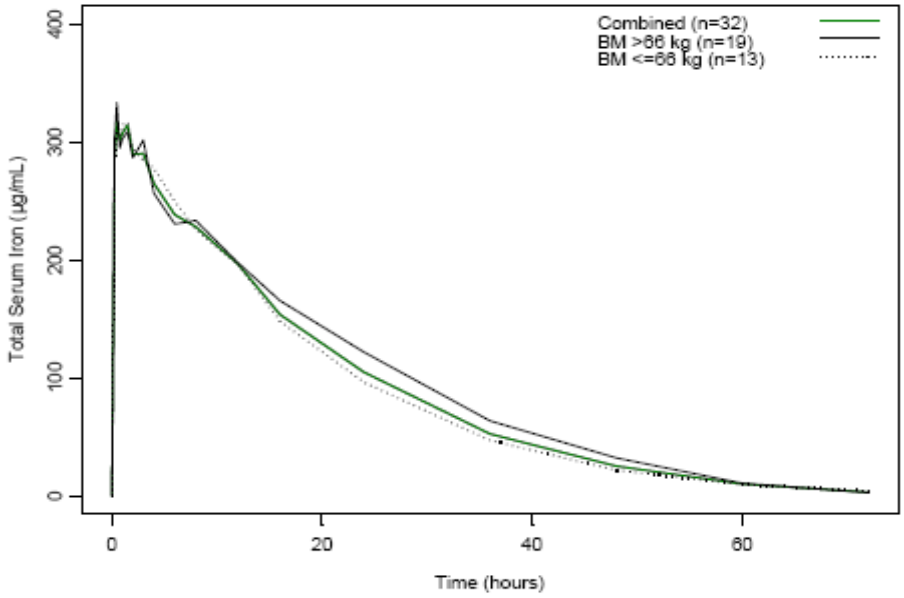
Phase	Study Number	Objectives	Dosage
I/II	VIT-IV-CL-02	Assess the Safety and PK/PD of ascending single doses of Ferinject in patients with mild IDA. Total number of patients: 32 Ferric Carboxymaltose: 24 Placebo: 8 Patients receiving a single IV dose of 1,000 mg: 6	Single IV bolus injection over 1 minute (100 mg) or single IV infusion over 15 minutes (500 mg, 800 mg and 1,000 mg). Patients followed for 1 week.
I/II	VIT-IV-CL-03	Assess the Safety and PK/PD after multiple doses of Ferinject in patients with moderate IDA. Total number of patients: 46 Ferric Carboxymaltose: 46 Patients receiving a single IV dose of 1,000 mg: 26	Ferinject IV infusion at a dose of 500 mg iron (Cohort 1) or 1,000 mg iron (Cohort 2) at weekly intervals for up to 4 weeks (Cohort 1) or 2 weeks (Cohort 2). The last dose could be less, depending on the calculated total iron requirement

In VIT-IV-CL-02 32 subjects (30 female, 2 male) with mild IDA of unspecified aetiology received single doses of IV iron in 4 groups of 6 subjects each. The mean body weight of the subjects was 64 kg. The

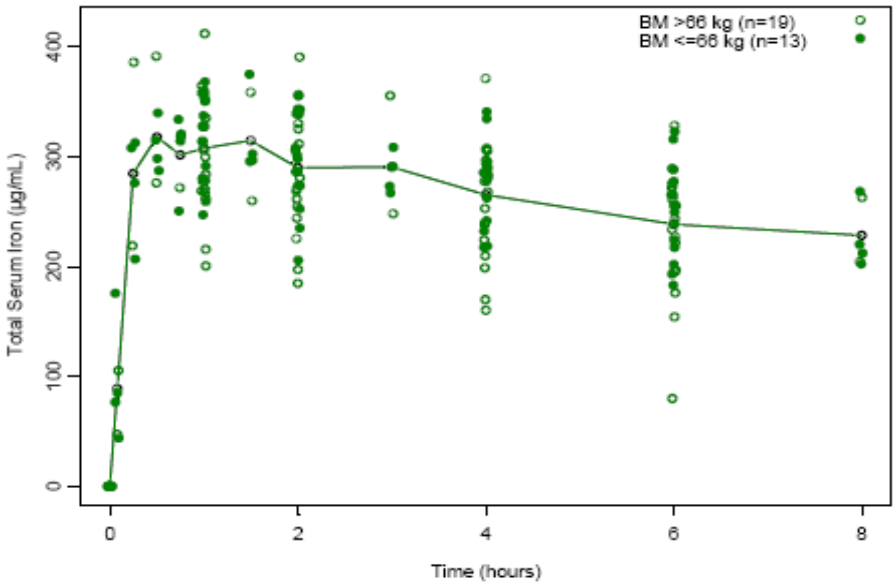
higher doses of IV iron (500, 800, or 1000 mg) were diluted in saline to achieve a volume of 250 mL, which was infused over a 15 minute period.

In VIT-IV-CL-03 46 subjects with moderate IDA secondary to gastrointestinal disorders were split into 2 cohorts (1 and 2) and given 500 or 1000 mg IV iron once weekly for up to 4 weeks (Cohort 1) or 2 weeks (Cohort 2). In Cohort 2, 26 subjects (21 female, and 5 male) received at least one dose of 1000 mg IV iron diluted in saline to achieve a volume of 250 mL and infused over a 15 minute period. The mean weight of the study patients was 72 kg.

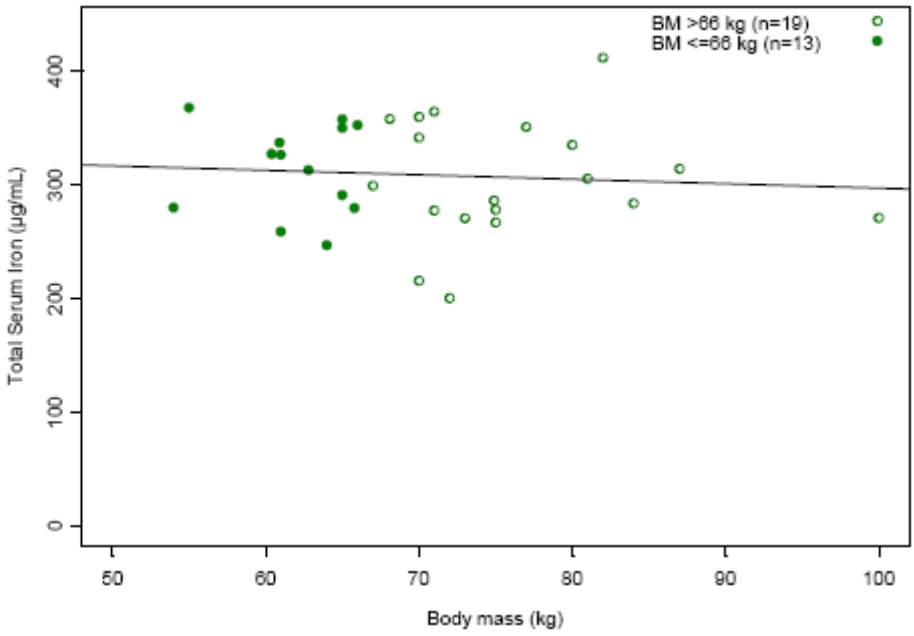
The figure below shows the mean PK profile of total serum iron for patients in both studies after an IV infusion dose of 1000 mg split by body weight (≤66 kg and >66 kg). The PK profiles for low and higher body weight patients was very similar.



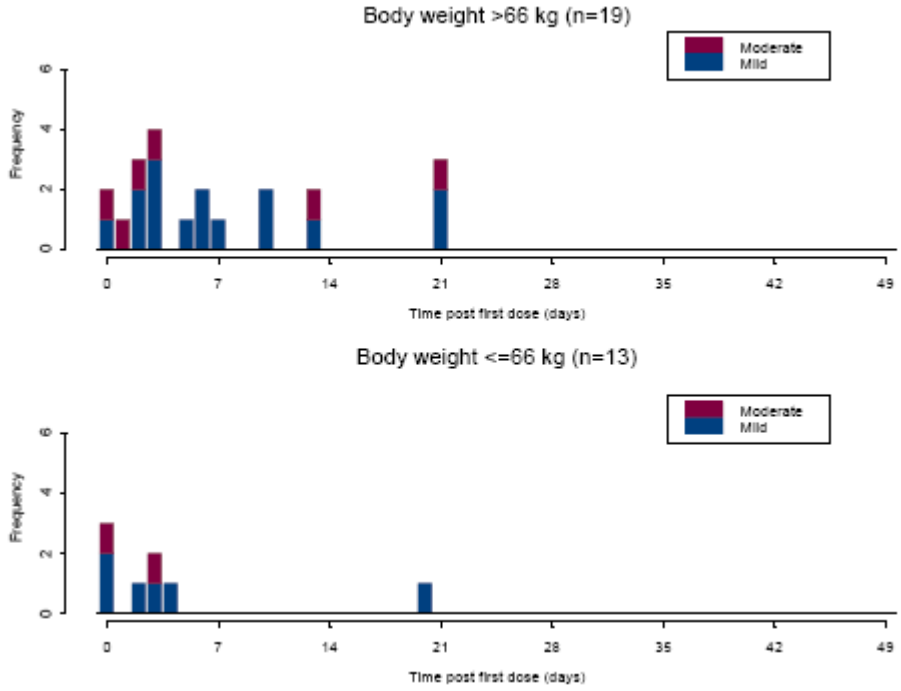
The figure below shows the same mean PK profile overlaid with the actual observations.



The figure below shows the maximum observable total serum iron concentration, by body weight, in patients who received an IV infusion dose of 1000 mg iron. There appears to be little correlation between body weight and measured total serum iron concentration.



The figure below shows the time course, incidence and severity of all TEAEs in patients that received an IV infusion dose of 1000 mg iron. There were no serious or severe AEs reported. Since the patient numbers are so small, limited conclusions can be made from the influence of body weight on adverse events.



Assessor's comment:
Whilst this reanalysis of PK studies provides reasonable evidence that body weight has little influence on the PK profile of high dose IV iron, it is difficult to draw conclusions on the safety of such dose levels in low body weight patients. Few (8) mild to moderate adverse events were reported, but there were only 13 subjects in the desired weight range. Details of the nature of the adverse events reported for these patients should be provided.

The applicant should provide detailed clinical laboratory data for the subjects with body weight ≤66kg, and should specifically discuss whether such subjects might be at increased risk of derangements of liver function tests or hypophosphataemia.

All of the patients in these PK studies received FCM as a diluted IV infusion; no patients with a body weight of 66 kg or less have received an undiluted bolus dose of 1000 mg IV FCM. Therefore, the safety of doses up to 20 mg/kg as an undiluted IV bolus has not been demonstrated.

IV.4.1.3 Conclusion

A reanalysis has been conducted of two original PK studies with Ferinject to investigate the effects of body weight on the pharmacokinetic and adverse event profiles. Only 13 patients in the two studies analysed had body weights of 66 kg or less. It appears that the PK profiles for Ferinject are very similar for patients weighing above and below 66 kg.

However, safety data to support an increase of the maximum daily dose from 15 to 20 mg/kg is very limited. Further information is required on the nature of the adverse events reported in lower body weight patients, and clinical laboratory data should be provided. In addition, no low body weight patients have received undiluted bolus injections, and the implications of this should be discussed by the applicant.

V ASSESSMENT OF APPLICANT'S RESPONSE TO PRELIMINARY REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Potential serious risks to public health

V.1.2 Non clinical aspects

- *The argumentation to remove the contraindication is not conclusive and there is sufficient evidence to suggest treatment related delayed ossification in rabbits in the absence of maternal toxicity. In addition the applicant is proposing to increase the maximum tolerated single dose to 1000 mg of iron (20 ml) per day or 20 mg of iron (0.4 ml) per kg body weight (previously was 15 mg of iron per kg body weight). At present there is insufficient experience in human exposure to warrant removal of the pregnancy contraindication, and the findings of the non-clinical studies further support continued caution to be applied for the use of this product during pregnancy.*

Summary of Applicant's Response

Iron deficiency anaemia (IDA) is the most prevalent deficiency disorder and the most frequent form of anaemia in pregnant women. It is well known that, depending on its severity, anaemia constitutes an important risk factor in both maternal and foetal morbidity. If the mother suffers from IDA, the risks to the foetus include a higher rate of premature birth, intrauterine growth retardation, unfavourable impact on placental development, and reduced neonatal iron stores. Maternal risks are also manifold. For these reasons, the efficient treatment of anaemia has a positive impact on maternal as well as foetal outcomes.

During pregnancy, oral iron therapy is given as first-line treatment. With lack of efficacy, unwarranted side effects or very low haemoglobin (Hb) values, intravenous (IV) iron treatment, although safety data in humans are limited, is a preferable alternative to oral iron therapy. Therefore the decision to use IV iron therapy during pregnancy must be based on the careful assessment of both the demonstrated benefits as well as the potential risks. Based on the current body of evidence the applicant does not feel that prohibiting Ferinject® use during the second and third trimester of pregnancy is supported by the data and thus not justified.

Preclinical Data for Ferinject
Five reproductive and developmental toxicity studies have been conducted with Ferinject (VIT-45 or ferric carboxymaltose (FCM)) in 2 different species (rats and rabbits; see Table 1). The 3 rat studies examined Ferinject's effects on embryo-foetal development; fertility and early embryonic development; and pre- and postnatal development. The additional 2 embryo-foetal studies were conducted in rabbits. One of the embryo-foetal studies in rabbits (UBW00001: Developmental toxicity study on the effects of IV infusion of VIT-45 on embryo-foetal toxicity in rabbits) has not previously been submitted and has been included in this submission.

Table 1 Overview of Reproductive and Developmental Toxicity Studies

Report Number	Species/Route	Study Type	Doses (mg Fe/kg)	NOAEL-Maternal/Foetal (mg Fe/kg)
VFR048/002163 (Table 2.6.7.9B)	CD rat/ intravenous	Embryo-foetal toxicity	3, 9, 30 – daily from Days 6-17 gestation	3/9
VFR049/004349 (Table 2.6.7.9D)	NZW rabbit/ intravenous	Embryo-foetal toxicity	4.5, 9, 13.5, 18 – daily from Days 6-19 gestation	9/4.5
UBW00001 (Table 2.6.7.9E)	NZW rabbit/ intravenous	Embryo-foetal toxicity	1, 2.25, 4.5, 9 – daily from Days 6-19 gestation	4.5/9
VFR050/004685 (Table 2.6.7.8)	CD rat/ intravenous	Fertility and early embryonic development	3, 9, 30 – 3 times/week ♂ – 4 weeks PM ♀ - 2 weeks PM, then Days 0, 3, 7 of gestation	9/30
VFR052/013368 (Table 2.6.7.10)	CD rat/ intravenous	Pre- and post-natal development	3, 9, 18 – daily from Days 6-19 gestation, then on Days 1,4,7, 10 and 14 postpartum	9/18

Notes: ♀ = Female; ♂ = Male; NOAEL = No observable adverse effect level; PM = Pre-mating.

Taken in its entirety, the data gathered in reproductive and developmental toxicity studies does not suggest that Ferinject causes reproductive toxicity in doses below the maternal toxicity dose. In all 3 rat toxicity studies the foetal no observable adverse effect level (NOAEL) is about 2 to 3-fold higher than the maternal NOAEL. For example, in the embryo-foetal study (VFR048/002163) the foetal NOAEL is 9 mg Fe/kg/day and the maternal NOAEL is 3 mg Fe/kg/day.

This finding is further supported by the lack of postnatal development toxicity effects in doses up to 18 mg Fe/kg/day and no early embryonic developmental effects at doses up to 30 mg Fe/kg/day that coincide with maternal NOAELs of 9 mg Fe/kg/day in each of the other rodent studies (VFR050/004685 and VFR052/013368).

In the VFR048/002163 rodent study, signs of maternal toxicity (dose-related reductions in weight gain with food intake discontinuation observed at 30 mg Fe/kg/day dose, and orange/brown discoloration of internal organs at necropsy on Day 20 of gestation) were observed at dosages of 9 and 30 mg Fe/kg/day, while embryo-foetal survival and growth was unaffected at all treatment levels. The only potential treatment-related change seen was an increased frequency of foetuses with thickened or kinked ribs at 30 mg Fe/kg/day. However, these rib abnormalities are a common and reversible finding in rodent embryo-foetal toxicity studies at maternally toxic dose levels.

Therefore, these findings should not be considered a specific Ferinject embryo-foetal toxic effect. In addition, one of the embryo-foetal studies conducted in rabbits (UBW00001) appears to validate the rodent findings that the foetal NOAEL is at least 2-fold higher than the maternal NOAEL, while the other study (VFR049/004349) found the opposite. The initially conducted rabbit study (VFR049/004349) found a 4.5 mg Fe/kg/day foetal NOAEL and a 9 mg Fe/kg/day maternal NOAEL. As the initial rabbit study did not corroborate the body of evidence collected in rats, a second rabbit study (UBW00001), which included the same potential effect dosages (4.5 and 9 mg Fe/kg/day) plus 2 lower dosages (1.0 and 2.25 mg Fe/kg/day), was conducted to investigate the reproducibility of the skeletal changes observed in Study VFR049/004349 and to establish a NOAEL dosage for any such changes.

In this second study, maternal toxicity (deaths, reduced weight gain and food intake) was observed at 9 mg Fe/kg/day, but there was no evidence of embryo-foetal toxicity at any dosage in the study. There was a marginally lower degree of ossification in the forelimb phalanges of foetuses at 9 mg Fe/kg/day, but no changes in the hind limb phalanges, or evidence of defective ossification at other sites in the foetal skeleton.

The reported foetal NOAEL was 9 mg Fe/kg/day and the maternal NOAEL was 4.5 mg Fe/kg/day. The total cumulative study exposure of 126 mg Fe/kg for a 14-day treatment period corresponds to an administration of 8.8 g of iron in a 70 kg human.

The study authors concluded, 'there were no adverse effects on embryo-foetal development as evaluated in this study and based on these data, VIT 45 should not be identified as a developmental toxicant'. Thus, the findings of the second rabbit study appear to corroborate the rodent findings.

To better understand the discrepancy in the finding of the 2 rabbit studies, the initial rabbit study (VFR049/004349) was evaluated in a historical context. The frequency of unossified phalanges in the control groups reported in the 5 preceding and 5 succeeding embryo-foetal toxicity studies in rabbits, conducted in the same laboratory and using the same source of rabbits were compared to the results of the VFR049/004349 test dose results. As can be seen in Table 2 (see below) the frequency of affected control foetuses increased over time in the 10 studies reported.

While the studies conducted before the VFR049/004349 Ferinject study (before June 2000) identified only minimal findings in the controls, the studies conducted after June 2000 indentified a higher frequency of unossified phalanges (up to 16%) in the controls.

Table 2 Historical Control Data for Frequency of Unossified Phalanges in Control Rabbit Litters from Embryo-foetal Toxicity Studies Performed at CRO Between November 1997 and August 2001

Study No.	Date of Study Conduct	Frequency of Unossified Phalanges in Control Litters					
		Litters Affected			Foetuses Affected		
		No.	N	(%)	No.	N	(%)
1	Nov-1997	0	4	0.0	0	38	0.0
2	Nov-1997	0	5	0.0	0	46	0.0
3	Dec-1997	0	4	0.0	0	31	0.0
4	Jul-1998	0	20	0.0	0	123	0.0
5	Feb-2000	1	6	16.7	1	31	3.2
6	Aug-2000	4	20	20.0	5	126	4.0
7	Feb-2001	2	18	11.1	2	113	1.8
8	Jun-2001	3	19	21.1	8	96	8.3
9	Jul-2001	5	25	20.0	13	136	9.6
10	Aug-2001	5	18	27.8	14	88	15.9

Notes: Refer to [3].
No. = Frequency; N = Total number examined.

As these studies were conducted externally to Vifor, the applicant cannot assess if the increase in findings in the control group over the approximately 4 year time span was due to changes in the animals themselves, changes in the study or housing conditions, a lack of consistency of the assessment over time or simply biological variation.

Table 3 provides the results of the VFR049/004349 study for the controls as well as for the 3 tested doses for comparison.

Table 3 Frequency of Unossified Phalanges in Control and Test Dose Rabbit Litters from the Embryo-foetal Study VFR049/004339

Dosage mg Fe/kg/day	Date of Study Conduct	Frequency of Unossified Phalanges in Litters					
		Litters Affected			Foetuses Affected		
		No.	N	(%)	No.	N	(%)
Control	Jun-2000	2	22	9.1	2	118	1.7
4.5		5	16	31.3	10	102	9.8
9.0		6	19	31.6	24	105	22.9
13.5		6	16	37.5	22	94	23.4

Notes: No. = Frequency; N = Total number examined.

While the difference in the frequency of unossified phalanges in the controls and all 3 test doses in the VFR049/004349 study is statistically significantly different, the frequency of unossified phalanges in the 4.5 mg Fe/kg/day group is not appreciably different to the findings in the control group of approximately one-third of the historical control groups studies (see Table 2).

It is also important to note that unossified phalanges, such as those reported at 4.5 mg Fe/kg/day, represent a slight delay in the development of foetal skeleton (possibly as a consequence of maternal toxicity induced by iron overload) that is readily repairable via postnatal skeletal remodelling.

Therefore, taking the entire body of evidence into account, the applicant feels that sufficient evidence exists that suggest that Ferinject does not causes reproductive toxicity in doses below the maternal toxicity dose. In all 3 rat toxicity studies the foetal NOAEL is approx 2 to 3-fold higher than the maternal NOAEL. One of the 2 rabbit toxicity studies conducted substantiated the finding that Ferinject is associated with a higher incidence of minor skeletal abnormalities only at maternal toxic doses, most likely due indirectly to maternal toxicity caused by iron overload and not a direct foetotoxic effect. Also, while the maternal NOAEL was lower than the foetal NOAEL in the first rabbit study, similar to the other studies, maternal iron overload should be assumed and no overt signs of toxicity were seen. In addition, the frequency in the 4.5 mg group was in the range of historical control data of studies performed in this lab at that time.

In addition, the applicant feels that the following points should also be taken into consideration:
• The general pattern of changes (namely, minor skeletal anomalies and variations at maternally toxic dosages) seen in some of the embryo-foetal toxicity studies with Ferinject is similar to that seen in reproductive studies performed with the iron-carbohydrate complex, iron-poly (sorbitol-gluconic acid) complex, and are considered to be secondary to iron overload in pregnant animals. Similar changes were seen in embryo-foetal toxicity studies performed with iron sucrose (Venofer®). These preparations are not contraindicated during the second and third trimester of pregnancy due to reproductive toxicity.

• Data from literature as well as from studies with Ferinject show that the supply of iron is closely regulated by the placenta confirming that the observed effects are a consequence of maternal toxicity induced by iron overload and are not likely to be expected at therapeutic doses.

• This has been confirmed by 2 placenta transfer studies which demonstrated that there is no direct transfer of Ferinject to the foetus, but iron is only delivered after metabolism of Ferinject in the reticuloendothelial system and subsequent release to transferrin.

Therefore, the animal data do not preclude administration of Ferinject during the second and third trimester of pregnancy. We feel that sufficient evidence is available to state that Ferinject does not cause foetotoxicity at doses under the maternal toxicity level. Although the entire body of evidence do not provide strong evidence that Ferinject should be contraindicated in the first trimester, given the results of the initial rabbit study the applicant proposes not to remove the current contraindication during the first trimester of pregnancy and to leave Section 4.2 as currently labelled.

Assessment of Applicant's Response

The applicant has provided the supportive historical data for control rabbits and further detailed discussion of the merits and arguments for use in pregnancy for second and third trimester administration. This is in line with what is currently approved.

The applicant has retained the contraindication in pregnancy during the first trimester due to the findings in the embryo-fetal toxicity study in rabbits. This is agreed.

Assessor's conclusion *Point resolved*

V.1.3 Clinical efficacy

- *The efficacy of the proposed standardised dosage regime for Ferinject has not been adequately demonstrated in study FER-IBD-COR.*

  a. There is a serious concern about the active comparator used in this study. Iron sucrose has been compared to ferric carboxymaltose, therefore the significance of the efficacy and safety findings are difficult to interpret. A justification for this is required.

Summary of Applicant's Response

Iron sucrose (Venofer) was selected as the active comparator due to this product being the "gold standard" in iron management at time of designing this study (early 2008) and the use of FCM was unapproved in many countries. The applicant acknowledges that the study did not compare 2 different dose regimes of FCM. Therefore, to aid this assessment, the applicant proposes to utilise the VIT-IV-CL-008 study (A multi-centre, randomised, controlled, phase III study to investigate the safety and efficacy of IV infusions of VIT-45 in patients with IDA secondary to chronic inflammatory bowel disease as published by Kulnigg et al), a pivotal registration study, which has a similar population to FER-IBD-07-COR and in which FCM was dosed per Ganzoni formula. This arm will be analysed in combination with the FCM arm of the FER-IBD-07-COR to permit a direct comparison of FCM response. The study design, key inclusion criteria and baseline demographics for the individual studies are shown below to permit confirmation of the similar study designs.

FER-IBD-07-COR and VIT-IV-CL-008 Study Comparison

	FER-IBD-07-COR	VIT-IV-CL-008
Design	Multicentre, open-label, randomised, controlled, Phase 3b study. FCM versus Venofer®.	Multicentre, open-label, randomised, controlled, Phase 3 study. FCM versus oral iron.
Planned patients	420	252
Key inclusion criteria	Male and female subjects ≥18 years of age; suffering from mild IBD (Crohn's disease or ulcerative colitis) or in remission; IDA defined as Hb 7-12 g/dL (women) or 7-13 g/dL (men) and serum ferritin <100 mcg/L.	Male and female subjects 18 to 80 years of age (inclusive); suffering from chronic IBD (Crohn's disease or ulcerative colitis); IDA defined as Hb ≤11.0 g/dL and at least one of the following: TSAT<20%, serum ferritin <100 mcg/L
Number subjects treated with FCM	244	111
Dosing regimen for FCM	Standardised regimen. Individual maximum dose of 1,000 mg.	Ganzoni formula. Individual maximum dose of 1,000 mg
Mean total iron as FCM administered (mg)[1]	1,377.0	1,489. 8

1 Total iron administered for patients randomised and treated in the FCM arm. Doses of comparator drug not listed in this table.
Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin; IBD = Inflammatory bowel disease; IDA = Iron deficiency anaemia; TSAT = Transferrin saturation.

The total iron administered between studies differs due to baseline Hb which drives the calculations in both formulas. The response defined as "Hb increase ≥2 g/dL or Hb ≥12 g/dL (female) or Hb ≥13 g/dL (male)" has been used to permit direct comparison of FCM per standardised dosing regimen (FER-IBD-07-COR study) to FCM per Ganzoni formula (VIT-IV-CL-008 study). When the data is analysed in this manner, the standardised regimen is equivalent to Ganzoni for response to treatment.

FER-IBD-07-COR and VIT-IV-CL-008 FCM Responder Rates

Responder Rates[1]	FER-IBD-07-COR FCM (Standardised)	VIT-IV-CL-008 FCM (Ganzoni)
Number of observations	218	111
Number of responders	184	94
Percentage of responders	84.4%	84.7%

1 Response defined as Hb increase ≥2 g/dL or Hb ≥12 g/dL (female) or Hb ≥13 g/dL (male).
Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin.

However in the above, no adjustment has been made for differences in baseline Hb, which is recognised as a key driver of response. As such, a logistic regression model, adjusted for baseline Hb, was fitted to the data from FER-IBD-07-COR and VIT-IV-CL-008. The results suggest equivalent efficacy for FCM dosed in a standardised manner when compared to FCM dosed per Ganzoni formula (odds ratio (OR)=1.42, in favour of standardised dosing regimen for response to treatment which did not reach significance (95% confidence interval (CI): 0.72-2.81)).

Additionally, the safety profile between studies was assessed for the patients receiving FCM. Comparable compliance to FCM treatment was seen between the studies (94% in FER-IBD-07-COR and 95% in VIT-IV-CL-008) for FCM administered per planned dose. Events are similar for both studies.

Assessment of Applicant's Response

The justification provided by the applicant for the comparison of FCM with iron sucrose is accepted. A comparison between FER-IBD-07-COR and another study involving FCM administered according to the Ganzoni formula has been provided. Although the mean baseline Hb of the subjects in the two studies is different, the responder rate is comparable, with similar safety profiles. The applicant's response therefore provides supportive evidence for the efficacy of administration of FCM using the standardised dosing regime.

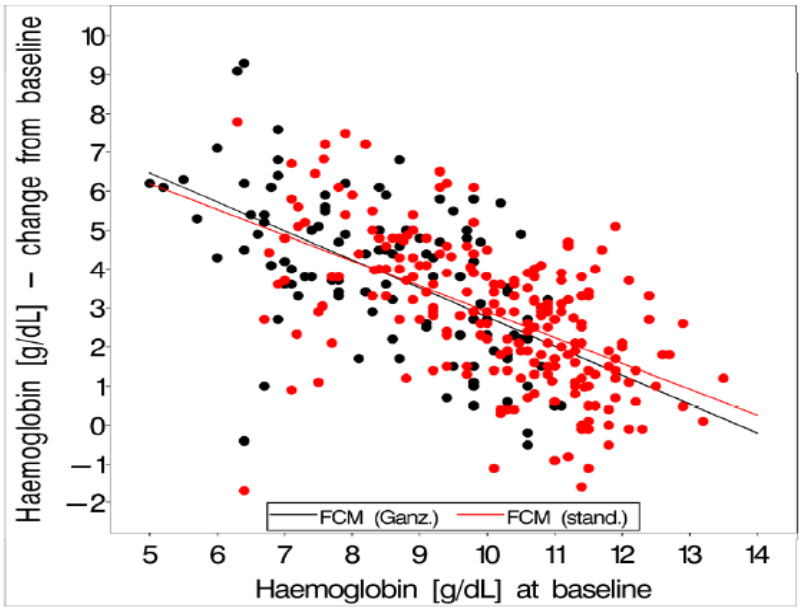
b. Results for the primary efficacy endpoint (increase in haemoglobin of at least 2 g/dL) and one of the secondary endpoints (change in mean haemoglobin from baseline) were lower than expected from previous studies with ferric carboxymaltose – this raises a concern over the external validity of the study, and an explanation should be provided.

Summary of Applicant's Response

The difference in results when compared to the similar population from the VIT-IV-CL-008 study may be attributed to baseline Hb which is known to be an independent predictor of response. The differences in baseline Hb were 10.1 g/dL versus 8.6 g/dL (FER-IBD-07-COR versus VIT-IV-CL-008 respectively).

Hence, the applicant has performed multiple analyses to demonstrate that results for the primary efficacy endpoint (increase in Hb ≥2g/dl) and key secondary endpoint (change in mean Hb from baseline) do not differ significantly between studies, with a focus on the prior study in the IBD population (VIT-IV-CL-008).

FER-IBD-07-COR and VIT-IV-CL-008: Change in Hb (from Baseline) Plotted by Baseline Hb



In the figure above, the fitted regression lines are nearly superimposed suggesting similar responses between the studies, illustrating the similarity of Hb response based on baseline Hb. When the primary endpoint is assessed with adjustment for baseline Hb the responses per standardised formula versus Ganzoni are equivalent in patients treated with FCM (OR=1.41) – see table below.

FER-IBD-07-COR and VIT-IV-CL-008: OR Estimates Adjusted for Baseline Hb Comparing Response to FCM Standardised versus FCM Ganzoni Dosing

	Point Estimate[1]	95% Wald Confidence Limits	
FCM (standardised dosing[2] versus Ganzoni[3]	1.414	0.743	2.694
FCM (Ganzoni[3]) versus Venofer (Ganzoni[2])	1.160	0.607	2.217
FCM (standardised dosing[2]) versus Venofer (Ganzoni[2])	1.641	1.032	2.610

1 Response defined as Hb increase ≥2 g/dL.
2 Patients per FER-IBD-07-COR.
3 Patients per VIT-IV-CL-008.
Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin; OR = Odds ratio.

Finally, sub-analyses using the 2 response definitions per the question assessed by baseline Hb sub-groups were performed for the FER-IBD-07-COR, VIT-IV-CL-008 and 1VIT03001 studies. Similar responses are seen in each sub-group although it should be noted that the 1VIT03001 study was conducted in postpartum (PP) women where there was no underlying limitation (e.g., inflammation) or subsequent iron loss which may explain the slightly higher overall responses. Additionally, the response data for 1VIT03001 was measured at Week 6 whilst in the IBD studies, assessment was at Week 12.

FER-IBD-07-COR, VIT-IV-CL-008 and 1VIT03011 Response Rate by Hb Cut-off Value of 10 g/dL

	FER-IBD-07-COR		VIT-IV-CL-008		1VIT3001	
	Baseline Hb <10 (n=86)	Baseline Hb ≥10 (n=132)	Baseline Hb <10 (n=88)	Baseline Hb ≥10 (n=23)	Baseline Hb <10 (n=144)	Baseline Hb ≥10 (n=16)
Primary response rate[1]	78 (90.7%)	66 (50.0%)	78 (88.6%)	12 (52.2%)	138 (95.8%)	14 (87.5%)
Secondary response rate[2]	78 (90.7%)	106 (80.3%)	78 (88.6%)	16 (69.6%)	138 (95.8%)	16 (100%)

1 Primary response = Hb increase ≥2 g/dL.
2 Secondary response = Hb increase ≥2 g/dL or Hb ≥12 g/dL (female) or Hb ≥13 g/dL (male).
Note: Hb = Haemoglobin.

Assessment of Applicant's Response

The difference in response rates in study FER-IBD-07-COR and previous studies with FCM can be attributed to baseline Hb values. The data provided by the applicant demonstrate that when adjustments are made for baseline Hb, the response to FCM treatment is comparable using the standardised dosing regime and the Ganzoni formula.

c. The study presented has been conducted in a population with IDA secondary to inflammatory bowel disease, and the applicant has failed to discuss how the results may be representative of the wider population of IDA due to other causes.

Summary of Applicant's Response

Ferinject is indicated for the treatment of iron deficiency (ID) when oral iron preparations are ineffective or cannot be used. Multiple conditions may lead to ID, poor nutrition, blood loss and/or diseases that restrict iron absorption (such as CKD, IBD or CHF). Independent of cause, this ID leads to adverse effects on patients including anaemia and other known and well documented complications. Inflammatory bowel disease leads to ID due to blood loss and restriction of iron absorption. Additionally, also iron metabolism is independent of underlying disease status. For repletion of the iron deficit, the currently marketed iron preparations (including Ferinject) use the Ganzoni formula to determine the requirements for repletion, independent of the underlying pathology of ID. Therefore, the applicant selected the indication of IBD (due to the high number of iron deficient patients) for investigating the new standardised dosing regimen (compared to Ganzoni). However, whilst IBD may be the underlying cause for the ID in these patients, the indication examined was ID and not IBD. The setting of IBD was also used in the early pharmacokinetic (PK)/pharmacodynamic (PD) research as well as the key registrational study (VIT-IV-CL-008) which further justified the use of IBD patients with ID in the FERGI-COR study. In summary, IBD is a representative disease indicative of restricted iron absorption and thus was a key disease indication as used in the initial submission package. Therefore, research in IBD patients seems appropriate to demonstrate that a standardised regimen is equivalent to the more complicated Ganzoni formula approach.

Assessment of Applicant's Response

The applicant's justification for the use of IBD patients in the study package is accepted, and the results from this study can be considered as representative for the general population with iron deficiency anaemia.

d. In addition, there are concerns regarding one of the inclusion criteria (serum ferritin level), which may affect the validity of the study.

Summary of Applicant's Response

The applicant feels that the included population was appropriate to address the endpoints of the FER-IBD-07-COR study. In relation to the serum ferritin level, the value selected (ferritin <100 mcg/L) was agreed after consultation with an external steering committee. The values are also in line with the current European Guidelines for the treatment of IDA in patients with IBD which state that a serum ferritin of 30 to <100 mcg/L is indicative of depleted iron stores and must be interpreted taking account of the degree of inflammation due to the IDA and anaemia of chronic disease overlapping features. A serum ferritin of <30 mcg/L can be considered a suitable threshold indicative of empty iron stores in patients with no biochemical (C-reactive protein, leukocyte count) or clinical sign/symptoms of inflammation, whereas a level of <100 mcg/L is viewed as a more appropriate cut-off for serum ferritin indicative of ID associated with inflammatory states.

However, independent of the permitted population, the baseline serum ferritin values (see Table below) were considerably lower than the inclusion criteria and, in most cases, indicative of absolute ID.

FER-IBD-07-COR: Baseline Serum Ferritin (mcg/L) (FAS)

Baseline Serum Ferritin (mcg/L)	Ferinject® n=232	Venofer® n=225
Mean	14.94	17.91
SD	24.83	27.81
Median	7.00	8.00
Range	2.0-299.0	2.0-255
95% CI of the mean	11.73, 18.16	14.26, 21.56

Notes: CI = Confidence interval; FAS = Full analysis set; SD = Standard deviation.

Assessment of Applicant's Response

Whilst there may be differences in opinion within Europe on the cut-off value for serum ferritin for the diagnosis of IDA, the mean and median baseline ferritin values of subjects in the FER-IBD-07-COR study are below 30 µ/L, and therefore this objection may be considered resolved.

Assessor's conclusion
The responses provided by the applicant provide adequate justification of the efficacy of FCM administered according to the proposed standardised regime. Although a different active comparator was used in the main study, comparisons with a previous study that utilised FCM administered according to the Ganzoni formula show comparable efficacy. Regarding the response rates observed in study FER-IBD-07-COR, differences can be attributed to a higher average baseline Hb of participants as compared to previous studies with FCM. When baseline Hb is taken into account, the response to treatment in study FER-IBD-07-COR is comparable to that observed in previous studies.

Given that the purpose of these variations is to improve the safety and ease of administration of intravenous iron rather than to enhance efficacy, this objection can be considered resolved.

Point resolved

V.1.4 Clinical safety

- *The safety of the proposed standardised dosage regime for Ferinject has not been adequately demonstrated.*

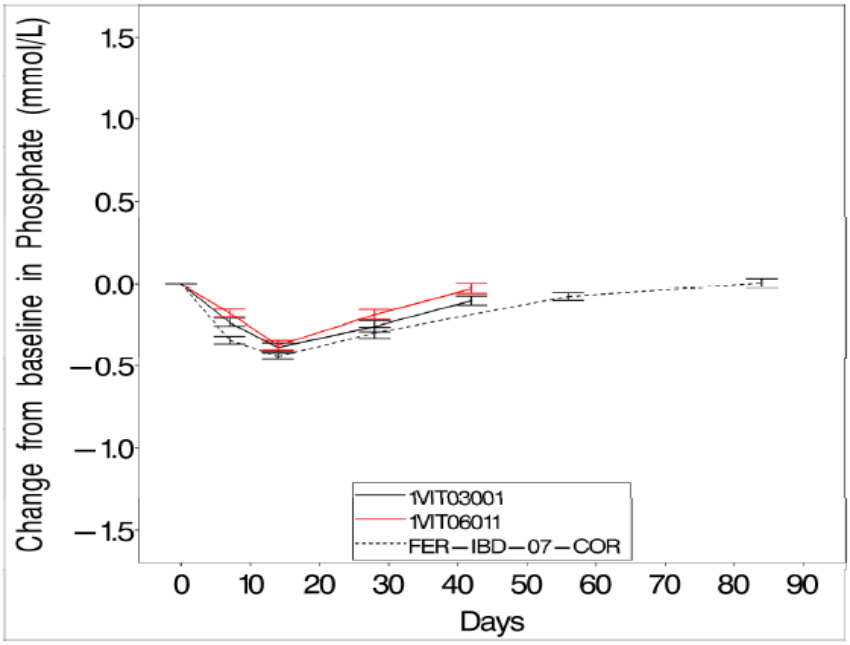
  a. As a different product was used as an active comparator in study FER-IBD-COR it is difficult to assess the significance of the decrease in serum phosphate. The applicant should present comparative data from other trials with Ferinject (which used the standard dosing regime) and discuss the potential clinical relevance of this issue.

Summary of Applicant's Response

The FER-IBD-07-COR is the only study completed to date using the standardised dosing regimen. However, the total individual dose given at any single time in the FER-IBD-07-COR was 1,000 mg (and no change is proposed to this as part of the submitted variation) and the total average dose given to patients matches that from other studies performed. When multiple doses are required, the time period between doses is recommended as at least 1 week (per SPC).

Therefore, the applicant has performed an analysis of serum phosphate changes (from baseline). Studies analysed were limited to those where patients received an initial 1,000 mg dose (or maximum dose permitted per 15 mg iron/kg body weight limit) and multiple measurements. Only the studies FER-IBD-07-COR, 1VIT03001 and 1VIT06011 were included in the analysis of serum phosphate changes, as all other studies did either not plan for phosphate measurements or did not have planned visits between Day 0 and Week 4. This is important as the phosphate drop is only observed between these time points and hence studies without regular visits do not provide additional information (other than confirming that if a drop was observed, this is indeed transient). In the 3 studies presented below, the second dose of Ferinject (where applicable) was given at least 1 week after the first dose and does not seem to impact the phosphate decrease or pattern seen.

Degree of Hypophosphataemia for All Studies with FCM Dosed at 1,000 mg iron (by Change from Baseline Phosphate Value)



Assessment of Applicant's Response

A comparison of studies with FCM dosed at similar levels to those administered in FER-IBD-07-COR shows a comparable degree of hypophosphataemia, with a nadir at around week 2 and a subsequent return to baseline. This does not raise a significant concern for the safety of FCM.

b. The applicant is requested to discuss the potential for iron overload with the proposed Ferinject regime, given that serum ferritin levels were twice as high as those in the Venofer group until Week 4.

Summary of Applicant's Response

The higher levels of serum ferritin initially seen correspond with the more rapid repletion of iron stores with the standardised dosing using Ferinject. Specifically, the formulation and Ferinject complex permitted repletion dosing at individual doses of 500 or 1,000 mg iron on Days 1, 8 and 15 compared with Venofer, where doses (per protocol) were specified as 200 mg iron up to twice per week. An average of 2 doses of FCM was administered versus 6 doses for Venofer. As such, the repletion of iron for patients in the FCM group was completed in 2 weeks (based on average of 2 doses administered) whilst patients receiving Venofer had on average 3 weeks of dosing (based on receipt of 200 mg 2 times). Additionally, the total dose administered for FCM was approximately 20% higher resulting in the higher percentage of response seen and more appropriate overall repletion of serum ferritin. By Week 8, no significant differences were observed in total serum ferritin values between groups.

Iron overload or haemochromatosis may result in haemosiderosis. However no iron overload or associated AEs were observed in FER-IBD-07-COR. It is important to note that iron overload is usually the result of long term chronic use and in all patients treated with FCM the use was acute (less than 2,000 mg) with the aim to replete iron stores. In a recently published article, Kalantar-Zadeh et al underpins that the "fear" of iron overload based on elevated iron parameters is not confirmed with data in the haemodialysis-dependent chronic kidney disease (HD-CKD) population. The authors concluded, after multivariate adjustment for the confounding effect of surrogates of inflammation and malnutrition, there was no increased death rate for ferritin levels as high as 1,200 mcg/L. In summary, the observed difference at Week 4 may be explained by the fact that the FCM patients mostly had all their total iron requirements administered in 2 weeks versus taking 3 weeks in the Venofer arm (along with a 20% higher total dose of iron in the FCM group). No AEs of iron overload were observed.

Assessment of Applicant's Response

The disproportionate serum ferritin levels in the first few weeks after transfusion seen between the FCM and the iron sucrose groups appears to be related to the higher doses of FCM administered and the consequent earlier repletion of iron stores. Differences in serum ferritin were minimal from week 8 onwards. Furthermore the paper by Kalantar-Zadeh et al provides reassurance that transient ferritin levels in the region of 300 µg/L are unlikely to pose a significant risk of iron overload to patients.

Assessor's conclusion
The concerns regarding the post-treatment decreases in serum phosphate and the increases in ferritin with potential for iron overload have been adequately addressed by the applicant.

Point resolved.

- *Insufficient data have been presented to support the safety of increasing the maximum daily dose of Ferinject from 15 to 20 mg/kg.*

a. *Data for only 13 subjects who have received doses between 15 and 20 mg/kg have been presented to support this variation. Few mild to moderate adverse events were reported, but details of the nature of these adverse events have not been provided, and are required.*

Summary of Applicant's Response

The details and nature of the AEs reported for patients who have received doses between 15 and 20 mg/kg are presented below in the table below. For comparison, the AEs for patients who have received doses lower that 15 mg/kg are also presented.

Summary Details of Respective AEs Split by Body Weight Group (15-20 mg/kg)

PID	Gender	Weight (kg)	PTerm	Day	Severity	SAE	Relationship	Action	Outcome	study
32	F	62.8	HEADACHE	0	MODERATE	N	POSSIBLE	NONE	RESOLVED	CL-002
32	F	62.8	ABDOMINAL PAIN NOS	4	MILD	N	UNLIKELY	NONE	RESOLVED	CL-002
5012	F	61.0	ARTHRITIS	20	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5027	F	61.0	URTICARIA	0	MILD	N	POSSIBLE	REMEDIAL	RESOLVED	CL-003
6012	M	65.0	BLOOD PRESSURE INCREASED	0	MILD	N	UNRELATED	REMEDIAL	RESOLVED	CL-003
6020	F	65.0	LYMPHOPENIA	3	MODERATE	N	UNRELATED	NONE	RESOLVED	CL-003
6021	M	64.0	NASOPHARYNGITIS	2	MILD	N	UNRELATED	NONE	RESOLVED	CL-003
6021	M	64.0	C-REACTIVE PROTEIN INCREASED	3	MILD	N	UNRELATED	NONE	RESOLVED	CL-003

Notes: AE = Adverse event; PID = Patient identification;; PTerm = Preferred Term; SAE = Serious adverse event.

Summary Details of Respective AEs Split by Body Weight Group (<15 mg/kg)

PID	Gender	Weight (kg)	PTerm	Day	Severity	SAE	Relationship	Action	Outcome	study
27	F	68.1	HEADACHE	0	MODERATE	N	UNLIKELY	REMEDIAL	RESOLVED	CL-002
30	F	74.9	HEADACHE	2	MODERATE	N	UNLIKELY	REMEDIAL	RESOLVED	CL-002
30	F	74.9	DISCOMFORT NOS	2	MILD	N	UNLIKELY	NONE	RESOLVED	CL-002
30	F	74.9	DIZZINESS	2	MILD	N	UNLIKELY	NONE	RESOLVED	CL-002
30	F	74.9	SYNCOPE	3	MILD	N	UNLIKELY	NONE	RESOLVED	CL-002
30	F	74.9	NAUSEA	3	MILD	N	UNLIKELY	NONE	RESOLVED	CL-002
2005	F	87.0	HAEMATURIA	3	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
2005	F	87.0	C-REACTIVE PROTEIN INCREASED	6	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
2005	F	87.0	HAEMATURIA	10	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
2005	F	87.0	C-REACTIVE PROTEIN INCREASED	13	MODERATE	N	UNLIKELY	NONE	RESOLVED	CL-003
2005	F	87.0	HAEMATURIA	21	MODERATE	N	UNLIKELY	NONE	RESOLVED	CL-003
2005	F	87.0	PROTEIN URINE	21	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5009	F	67.0	ATRIAL FIBRILLATION	5	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5016	F	73.0	HAEMATURIA	13	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5017	F	100.0	HAEMATURIA	21	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5022	M	72.0	HYPERTHERMIA	0	MILD	N	POSSIBLE	NONE	RESOLVED	CL-003
5024	F	71.0	SUPRAVENTRICULAR EXTRASYSTOLES	7	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
5024	F	71.0	HAEMATURIA	10	MILD	N	UNLIKELY	NONE	RESOLVED	CL-003
6015	F	82.0	DERMATITIS ALLERGIC	1	MODERATE	N	POSSIBLE	DISCONTINUED PERMANENTLY	RESOLVED	CL-003
6015	F	82.0	C-REACTIVE PROTEIN INCREASED	3	MODERATE	N	UNRELATED	NONE	RESOLVED	CL-003
6019	F	77.0	RETICULOCYTE COUNT INCREASED	6	MILD	N	POSSIBLE	NONE	RESOLVED	CL-003

Notes: AE = Adverse event; PID = Patient identification; PTerm = Preferred Term; SAE = Serious adverse event.

Assessment of Applicant's Response

Details of the adverse events reported by subjects who received doses between 15 and 20 mg/kg have been provided. These do not raise any additional concerns regarding the safety of higher doses of FCM.

b. In addition the applicant should provide detailed clinical laboratory data for the subjects with body weight ≤66 kg, and should specifically discuss whether such subjects might be at increased risk of derangements of liver function tests or hypophosphataemia.

Summary of Applicant's Response

Per request, the applicant has provided additional requested data for patients with a weight of ≤66 kg (or having received 15-20 mg/kg). Detailed clinical laboratory summaries have been provided for 1,000 mg patients from VIT-IV-CL-002 and VIT-IV-CL-003 further split by body weight group. These are consistent with the laboratory summaries in the respective CSRs with no medically relevant issues. In relation to the liver function tests, ALT, AST, ALP, GGT and bilirubin are presented. The table below summarises the number of patients who developed liver function-related measurements 1, 2 and 3 times above the ULN. In the majority of cases, elevations were at isolated time points and were less than 20% above the normal range and therefore considered not clinically significant. In the group that received between 15 and 20 mg/kg, Patient 6012 from VIT-IV-CL-003 had an ALT measurement of >2 times ULN (ULN=28 U/L). This measured value of 65 U/L was taken at the first follow-up visit (Day 23) and returned to below the ULN (19 U/L) at the next follow-up visit (Day 37).

Patients with Selected Liver Function-related Clinical Chemistry Parameters 1, 2 and 3 Times Above the ULN (Studies VIT-IV-CL-002 (Module 5.3.4.2.1) and VIT-IV-CL-003 (Module 5.3.4.2.2), Split by Body Weight Group (15-20 mg/kg)

Parameter	>1xULN (N=13)	>2xULN (N=13)	>3xULN (N=13)
	n (%)	n (%)	n (%)
ALT (U/L)	2 (15.4)	1 (7.7) [1]	0
AST (U/L)	1 (7.7)	0	0
ALP (U/L)	1 (7.7)	0	0
GGT (U/L)	0	0	0
TB (umol/L)	0	0	0

1 Patient 6012 (CL-003) follow-up visit, value returned below ULN at subsequent visit 2 weeks later.
Notes: ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma-glutamyltransferase; TB = Total bilirubin; ULN = Upper limit of normal.

Patients with Selected Liver Function-related Clinical Chemistry Parameters 1, 2 and 3 Times Above the ULN (VIT-IV-CL-002 and VIT-IV-CL-003), Split by Body Weight Group (<15 mg/kg)

Parameter	>1xULN (N=19)	>2xULN (N=19)	>3xULN (N=19)
	n (%)	n (%)	n (%)
ALT (U/L)	5 (26.3)	0	0
AST (U/L)	7 (36.8)	0	0
ALP (U/L)	1 (5.3)	0	0
GGT (U/L)	4 (21.1)	0	0
TB (umol/L)	3 (15.8)	1 (5.3)	0

Notes: ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma-glutamyltransferase; TB = Total bilirubin; ULN = Upper limit of normal.

In relation to hypophosphataemia, phosphate was not measured in the VIT-IV-02 or VIT-IV-03 studies. As such, no data can be presented from these studies based on weight. However, the applicant has analysed the patients from FER-IBD-07-COR, plotting the change from baseline value for each study week to permit assessment of the influence of dose (in mg/kg) on degree of hypophosphataemia as well as the maximum

decrease from baseline in phosphate. When change in serum phosphate is analysed as above, the impact of dose by total milligram of iron per kilogram body weight appears to be minimal.

To permit further assessments of the influence of body weight on degree of hypophosphataemia, the change in serum phosphate was analysed by body weight. This was completed for all patients in the FER-IBD-07-COR dataset as well as restricted for patients receiving 1,000 mg at baseline (although only 2 patients received 1,000 mg as a first dose that had a weight less than 66 kg). Body weight, above or below 66 kg, appears to have minimal influence of change in serum phosphate levels. In sub-analyses, the evolution of serum phosphate appears to follow the same trend with nadir at approximately 2-6 weeks with return to normal (or baseline) figures by Week 8-12.

Assessment of Applicant's Response

Data provided by the applicant show no safety signals with regard to risk to liver function in low body weight patients in study FER-IBD-07-COR. There also appears to be no significant correlation between body weight and degree of post-infusion hypophosphataemia.

c. *All of the patients in these PK studies received FCM as a diluted IV infusion; no patients with a body weight of 66 kg or less have received an undiluted bolus dose of 1000 mg IV FCM. Therefore the safety of doses up to 20 mg/kg as an undiluted IV bolus has not been demonstrated, and this should be discussed by the applicant.*

Summary of Applicant's Response

Post submission of the variation package to the MHRA and all CMS, the applicant has completed the Bolinj08 study (CSR). This study is titled "Ascending Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Ferric Carboxymaltose (FCM) with 10% Iron Following Single I.V. Doses Administered as Bolus Injection in Patients with Iron Deficiency or Iron Deficiency Anaemia". This Phase 1/2 study was a single-centre, randomised, double-blind, placebo-controlled, single dose-escalating study to assess the safety, tolerability, PK and PD data of 5 ascending doses of FCM formulation with 10% iron administered as bolus injection; 2 mL (200 mg iron) in 10 seconds, 2 mL (200 mg iron) in 2 seconds, 5 mL (500 mg iron) in 5 seconds, 8 mL (800 mg iron) in 8 seconds, and 10 mL (1,000 mg iron) in 10 seconds. In each dose group 8 male and female patients with ID or IDA participated, 6 of whom received the active drug and 2 received placebo. Each patient received one single IV dose of FCM formulation with 10% iron or one IV placebo dose, in fasting condition.

The primary objective was to evaluate the safety and tolerability of escalating single doses of FCM with 10% iron administered as IV bolus injection in patients with ID or IDA. Overall, the key study conclusion, per CSR was that the overall administration of FCM formulation with 10% iron can be considered as safe and generally well tolerated. Of key importance, an additional 6 patients received an undiluted IV dose of 1,000 mg, 3 of which received doses >15 mg/kg. As can be seen in the updated plots presented in Appendix 4.4, the PK and AE data can be considered similar to the data based on studies VIT-IV-CL-02 and VIT-IV-CL-03 presented in the initial variation submission. The details and nature of the AEs reported for these 6 patients are presented below.

Summary Details of AEs with Body Weight Group (15-20 mg/kg) in Patients Receiving an 1,000 mg IV Dose of FCM in the BOLINJ08 Study

PID	Gender	Weight	PTerm	Day	Severity	SAE	Relationship	Action	Outcome
0036	F	53.4	INFLUENZA LIKE ILLNESS	1	MILD	N	POSSIBLE	NONE	RESOLVED
0036	F	53.4	ABDOMINAL PAIN	2	MILD	N	POSSIBLE	NONE	RESOLVED
0040	F	60.6	SOMNOLENCE	0	MILD	N	UNLIKELY	NONE	RESOLVED

Notes: AE = Adverse event; F = Female; FCM = Ferric carboxymaltose; IV = Intravenous; PID = Patient identification; PTerm = Preferred term; SAE = Serious adverse event.

Summary Details of AEs with Body Weight Group (<15 mg/kg) in Patients Receiving an 1,000 mg IV Dose of FCM in the BOLINJ08 Study

PID	Gender	Weight	PTerm	Day	Severity	SAE	Relationship	Action	Outcome
0033	F	67.7	WOUND	6	MODERATE	N	NOT RELATED	NON-DRUG TREATMENT	RESOLVED

Notes: AE = Adverse event; F = Female; FCM = Ferric carboxymaltose; IV = Intravenous; PID = Patient identification; PTerm = Preferred term; SAE = Serious adverse event.

In the group that received between 15 and 20 mg iron/kg body weight (body weight <66 kg), there were no liver function-related measurements above the ULN. In the group that received <15 mg iron/kg body weight (body weight >66 kg) there was 1 patient with increased ALT and AST measurements during screening and follow-up. These were all <2 times ULN and without clinical sequelae.

Based on the data presented in variation UK/H/0894/001/II/013, the applicant concludes that the safety profile for administering undiluted bolus injections is equivalent to infusions. Whilst limited data exists for patients up to 20 mg/kg, similar PK/PD, safety and tolerability results have been observed as described above. Therefore we do not anticipate any potential for increased safety risk due to undiluted injection versus infusion.

Assessment of Applicant's Response

The applicant has presented new data from a Phase I trial with a new strength of FCM, a 10% w/v solution of iron in water for injection. Bolus doses were administered to patients with IDA at a rate of 100 mg iron per second in a placebo-controlled 6:2 ratio. Doses of 200, 400, 600, 800 and 1000 mg iron were administered, in accordance with individual iron deficit as calculated by the Ganzoni formula. A total of 16 (51.6%) patients reported 38 AEs following any dose of FCM formulation (10 AEs were reported following 200 mg FCM, 4 AEs with 200 mg FCM, 2 AEs with 500 mg FCM, 18 AEs with 800 mg FCM and 4 AEs with 1000 mg iron as FCM). The system organ classes mostly affected in this clinical study were general disorders and administration site conditions (12 AEs) with chills, fatigue and feeling hot reported twice, respectively, and nervous system disorders with headache as the leading AE (5 AEs). Three patients experienced skin and subcutaneous tissue disorders and further investigations for allergy testing were performed in these patients, which proved negative for an immunological mechanism. Three of the patients in the 1000 mg group had a body weight below 66 kg, and received FCM at doses above 15 mg/kg.

The results of this study provide only preliminary information on the tolerability of undiluted bolus injections of 10% w/v FCM. The present variations propose to allow administration of a (weaker) 5% w/v solution as an intravenous injection at a slower rate, of 67 mg per minute over 15 minutes for higher dose levels. However, there are still insufficient data to support the safety of high dose, undiluted bolus injections of FCM (≥15 mg/kg), and an increased risk of hypersensitivity reactions at high dose levels has not been adequately excluded. Such doses should therefore be administered as a diluted infusion over a minimum of 15 minutes.

Assessor's conclusion
No specific safety signals have been observed from the database of patients receiving FCM at a maximum daily dose level of at least 20 mg/kg, and therefore variations UK/H/0894/001/II/012 and 13 are approvable subject to the condition that doses between 15 and 20 mg/kg be administered as a diluted intravenous infusion.

Point resolved with appropriate changes to SPC

V.2 Other concerns

V.2.2 Non clinical aspects

- *The applicant should provide historical data for the incidence of unossified phalanges in control animals in studies conducted at the time of study no. VFR049/004349 to fully support their argument.*

Answered in response to Question 1.

- *The applicant should provide any human exposure data during pregnancy to further support their claim to remove the contraindication during first trimester of pregnancy.*

Summary of Applicant's Response

There is no human exposure data during pregnancy to justify the inclusion of the contraindication during the first trimester in pregnancy. As per guideline 'Guideline On Risk Assessment Of Medicinal Product On Human Reproduction And Lactation: From Data To Labelling' (EMEA/CHMP/203927/2005) this would not warrant a contraindication during pregnancy in the first trimester, as expressed by the Afssaps. However, the applicant accepts the recommendation of the MHRA to retain this contraindication of pregnancy in the first trimester.

Assessment of Applicant's Response

Discussed in response to Question 1.

Assessor's conclusion
Point resolved

V.2.3 Clinical efficacy

- *Justification is required for the inclusion criterion of serum ferritin <100 µg/L in study FER-IBD-COR. The British Society of Gastroenterology cites a level of <12-15 µg/L in a normal population, and < 50 µg/L in those with co-existent disease. Given that the study population comprised only patients with either mild IBD or those in remission, a level of <100 µg/L may be considered inappropriately high and may have resulted in the inclusion of patients who were not iron deficient.*

Summary of Applicant's Response

The British Society of Gastroenterology has updated its guidelines for the management of IDA. The previous version (June 2000) suggested that a level of ferritin >100 mcg/L was considered synonymous with adequate iron stores; the updated document (May 2005) suggests that a serum ferritin level of ≤50 mcg/L is consistent with ID in the context of co-existing disease, implying that the levels above this exclude ID. This cut-off level was challenged by Koulaouzidis et al in 2009, who concluded from a series of 198 patients, using soluble transferrin receptor/log 10 ferritin ratio (sTfR-F Index), that the negative predictive value for ID using a ferritin cut-off of ≤50 mcg/L was only 22%, which rose to 34.8% if the level was raised to 100 mcg/L. Therefore, even normocytic patients with a serum ferritin of >50 mcg/L can be iron deficient and therefore need additional iron infusions to fill the iron stores. This paper concludes that "ferritin cut-off level used to confidently exclude ID should be higher than 50 mcg/L."

Additionally, in 2007, Gasché et al published guidelines on the treatment of ID in patients with IBD, including experts across Europe, including the UK. Gasché states that a ferritin level <30 mcg/L is equivalent to absent iron stores, and during active IBD, iron stores are depleted if serum ferritin is <100 mcg/L, and that adequate iron stores are those >100 mcg/L, with an upper limit of 800 mcg/L. In an analysis of 3 randomised prospective trials, Kulnigg et al could show that patients with a serum ferritin >100 mcg/L had a longer time to recurrence of ID as compared to those with serum ferritin <100 mcg/L. This paper concludes that patients should have a serum ferritin level of 400 mcg/L after IV iron therapy. It has been shown that 1 mcg/L serum ferritin corresponds to approximately 8 mg of storage iron. Having said that, the application of a mean 1,413 mg (range 1,000-2,000 mg) of iron as FCM would increase serum ferritin by 141-176 mcg/L (range 100-250 mcg/L) and therefore there is no risk of iron overload for the patient.

Even if the upper limit of serum ferritin was not chosen as stringently, the patient's baseline characteristics in FER-IBD-07-COR showed that the patients randomised had serum ferritin values which were considerably lower than 100 mcg/L, and in most cases were indicative for absolute ID (see earlier table detailed baseline serum ferritin).

The highest increase in the FCM group was seen at Week 2 (increase to mean 330 mcg/L; range 9.0-600 mcg/L), with a very high variability in the change from baseline (-74.0 to 594.1 mcg/L). The changes in the Venofer group were not as pronounced (increase to 185.71 mcg/L by Week 2, range 3.0-560.0 mcg/L), but with a similar variability in change from baseline (-143.8-537.0 mcg/L). No patient exceeded the upper limit of serum ferritin of 800 mcg/L, a level which could be indicative of iron overload in this patient population using current guidelines.

Assessment of Applicant's Response

As discussed above there are varying opinions on the level of ferritin required for a diagnosis of IDA. Nevertheless, the mean baseline ferritin level for patients in study FER-IBD-COR was low and would therefore not have been affected by a different value for the inclusion criterion.

Assessor's conclusion
Point resolved

- *Under the proposed standardised dosage regime for Ferinject it appears that heavier patients (≥85 kg) with more severe anaemia would receive lower doses of iron than under the previous regime. The applicant should comment on the relevance of this and should present a subgroup analysis for the primary and secondary endpoints in study FER-IBD-COR stratified by patient weight.*

Summary of Applicant's Response

The applicant agrees that patients of heavy body weight (>85 kg) and very low Hb (<7 g/dL) would require >2,000 mg according to the Ganzoni formula, but would only receive 2,000 mg of FCM according to the currently utilised standardised dosing regimen. When performing the requested additional sub-analyses for primary and key secondary endpoints, no differences are observed between the populations when stratified by weight (and severe anaemia) although the small numbers in the "heavier" population make interpretation of data limited. In FER-IBD-07-COR, the overall response in patients with baseline Hb <10 g/dL is 90%. When stratified by patient weight (85 kg) with baseline Hb <10 g/dL, a response of 91% (<85 kg) versus 83% (>85 kg) is seen for the primary endpoint. However, only 17 subjects had weight >85 kg and severe anaemia (Hb <10 g/dL) therefore comparisons between groups is limited. Specifically, in the below analysis 5 patients versus 1 patient responded in the standardised regimen compared with 8 versus 1 in the Ganzoni regimen (2 patients had response missing).

FER-IBD-07-COR: Responder Rates in Patients with Severe Anaemia (Hb <10 g/dL) by Body Weight

All Patients with Hb <10 g/dL	FCM Per Standardised Regimen			Venofer® Per Ganzoni Formula		
Sub-groups per body weight	Overall	<85 kg	>85 kg	Overall	<85 kg	>85 kg
Responder[1]						
n (%)	83 (90)	78 (91)	5 (83)	67 (78)	59 (77)	8 (89)

1 Responder defined as increase in Hb of at least 2 g/dl at Week 12 as compared to baseline.
Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin.

The heaviest patient involved in the study had a baseline weight of 137 kg. At baseline, this patient had an Hb of 11.1 g/dL and after receiving FCM per the standardised formula, the Hb evolved to a maximum of 15.5 g/dL at Week 8 and was stable at 15.0 g/dL at study end (Week 12). The patient with the greatest iron deficit at baseline weighed 105 kg with an Hb of 7.2 g/dL. This patient received 2,000 mg (2 x 1,000 mg) of FCM and the Hb evolved from 7.2 g/dL to 12.1 g/dL at Week 4 thereafter, remaining stable until end of study (with final value of 12.3 g/dL).

However, the applicant agrees with the assessment that in very few cases a lower dosing may result compared to the calculation per Ganzoni formula. Although the applicant is confident that correction of ID will be achieved with this slightly lower dose (than when calculated with Ganzoni formula) as shown in the above analyses, we would propose to amend the following sentence in the SPC: "*Post repletion, regular assessments should be completed to ensure that iron levels are corrected and maintained ~~in case continuous loss of iron is suspected~~.*"

Assessment of Applicant's Response

The subgroup analysis of the results of FER-IBD-COR stratified by patient weight has obvious limitations with regard to the small group sizes. Whilst use of the standardised regime will result in the administration of lower doses to patients with more severe anaemia weighing more than 85 kg the RMS is satisfied with the addition of the proposed statement in Section 4.2 of the SPC.

Assessor's conclusion
Point resolved

- *A clinical justification for the non-inferiority margin used in study FER-IBD-COR has not been provided and is required.*

Summary of Applicant's Response

According to the International Conference on Harmonisation E9, the non-inferiority margin should be smaller than differences observed in superiority trials of the active comparator. Seven studies with Venofer and 1 study with Ferinject, conducted in IBD patients, were analysed for the calculation of the non-inferiority margin in the FER-IBD-07-COR Study. The response rate as defined for the primary endpoint (i.e., proportion of patients with an increase of Hb ≥2 g/dL) was used for calculation of non-inferiority margin. Under the 7 studies conducted with Venofer, the study of Gasché et al, 1997 was considered the most appropriate to use for the calculation of the non-inferiority margin, as the same endpoint, a similar follow-up and a similar patient population was chosen. The response rate in the study mentioned above showed a response with Venofer of 85%.

As there is no superiority study available in the IBD indication with a similar treatment schedule as used in the FER-IBD-07-COR study, the treatment superiority of Venofer versus an appropriate comparator has to be estimated. The most appropriate comparator drug would be ferrous sulphate. To make this comparison, data from Kulnigg can be used. In this study, patients receiving ferrous sulphate achieved a response rate of 68% after 12 weeks. Therefore, in order for FCM to be non-inferior compared to Venofer, the non-inferiority margin was set to be the difference between ferrous sulphate (68%) and Venofer (75%), i.e., 7% (=0.07).

Assessment of Applicant's Response

An adequate justification for the non-inferiority margin used in study FER-IBD-COR has been provided.

Assessor's conclusion
Point resolved

- *Baseline data for haemoglobin and ferritin status for subjects in study FER-IBD-COR should be provided.*

Summary of Applicant's Response

Values for Hb and serum ferritin at baseline for patients in the FER-IBD-07-COR study have been provided.

Assessment of Applicant's Response

Baseline Hb and ferritin values are comparable for subjects in each arm of the study.

Assessor's conclusion
Point resolved

- *In study FER-IBD-COR the group using TNF alpha blockers as a concomitant medication is the only group in which Ferinject was not superior to Venofer. The significance of this should be discussed by the applicant.*

Summary of Applicant's Response

In the full analysis set (FAS), the response rates in TNF alpha blocker users were 52% with FCM and 60% with Venofer and in the per protocol set (PPS), 57% with FCM and 63% with Venofer. However, there were only approximately 20 patients in each group that received a TNF alpha blocker. Due to this small number of subjects and differences in baseline characteristics, specifically serum ferritin and Hb (see Tables in response document), interpretations of this sub-analysis cannot be used to draw conclusions.

When fitting a logistic regression for the TNF alpha blocker user population using treatment group and baseline Hb as covariates, the odds of response are slightly in favour of FCM over Venofer (OR 1.05 with 95% CI 0.24-4.55 in the PPS), although the number of observations is, as previously stated, too small to make strong conclusions. In summary, the applicant does not feel that any significance of the non-inferiority of FCM to Venofer in the sub-group of patients receiving concomitant TNF alpha blockers should be drawn due to small non baseline equivalent populations.

Assessment of Applicant's Response

The subset of patients who were using TNF alpha blockers as a concomitant medication is small, and the response adjusted for baseline Hb and ferritin levels is comparable for the Ferinject and Venofer groups, suggesting that no significance should be drawn from this observation.

Assessor's conclusion
Point resolved

V.2.4 Clinical safety

- *The applicant should discuss why gamma-glutamyltransferase was not included in the battery of clinical chemistry tests in study FER-IBD-COR, since an increase in this enzyme is a known (though rare) risk of IV iron carboxymaltose therapy.*

Summary of Applicant's Response

The main reason for inclusion of the gamma-glutamyltransferase (GGT) measurements as part of the routine safety biochemistry in some of the previous studies was to help detect and/or observe potential liver toxicity. Although the clinical chemistry data collected during the clinical trials performed with FCM as part of the original MAA submission package showed no consistent evidence of a detrimental drug effect on liver function, the decision to insert the PTs of "GGT increased"/"Investigations" system organ class (SOC) in Section 4.8 of the SPC was driven by a conservatively selected cut-off threshold.

It is the applicant's assertion that in a heterogeneous population of IDA patients with other disorders such as renal impairment (including HD) or chronic IBD as were those included in the performed clinical trials it is not at all surprising that such mild, asymptomatic elevations of GGT occurred without necessarily being a reliable indicator of hepatic dysfunction. Notwithstanding the above and as discussed below, the applicant considers that the monitoring of the liver enzymes in the FER-IBD-07-COR was adequately covered by the inclusion of the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) tests which are considered diagnostically more useful than GGT in assessing possible liver injury.

Owing to limitations the importance of GGT as a routine test in the diagnostic repertoire remains controversial and guidelines published by the National Academy of Clinical Biochemistry (NACB) and the American Association for the Study of Liver Diseases (AASLD) no longer recommend its use. In conclusion, the applicant considers that the lack of GGT measurements in the FER-IBD-COR trial was of no untoward safety consequence in relation to the assessment of hepatic function and the ongoing monitoring and reporting of the product's adverse effects as part of the post marketing safety surveillance activities should provide sufficient means of detecting potential signals of liver toxicity.

Assessment of Applicant's Response

It is accepted that gamma-glutamyltransferase is a non-specific marker of liver injury and that assessment of other liver enzymes is appropriate for the detection of liver toxicity. However, given that elevation of gamma-glutamyltransferase is a listed adverse reaction with FCM, it should have been included in the test-battery in study FER-IBD-COR. This does not however raise a serious safety concern.

Assessor's conclusion
Point resolved

- *The applicant should clarify whether iron deficiency was confirmed by measurement of serum ferritin or assessment of red cell parameters in study 1VIT07017.*

Summary of Applicant's Response

Subjects enrolled into the 1VIT07017 study were required to have IDA per protocol based on Hb (i.e., all patients were anaemic at time of randomisation). Further, subjects with anaemia due to any other causes (i.e., haemolytic, macrocytic, hypoplastic and sideroblastic) were specifically excluded. The Hb values for inclusion had been set with a limit of ≤11 g/dL for both cohorts (postpartum and heavy uterine bleeding). Separately, for heavy uterine bleeding (HUB), an Hb limit of≤11.5 g/dL was allowed as a point of care testing. No specific ferritin values were specified for inclusion. Note: the baseline Hb and ferritin values are provided in tables below.

1VIT07017: Baseline Hb and Serum Ferritin for PP Population (Safety Set)

	FCM (N=606)	SMC (N=623)
Haemoglobin (g/dL)		
Baseline		
N	606	623
Mean (SD)	10.20 (1.161)	10.11 (1.191)
Median	10.35	10.30
Minimum, Maximum	6.7, 12.9	6.1, 13.2
Ferritin (ng/mL)		
Baseline		
N	606	623
Mean (SD)	25.99 (22.730)	26.55 (24.973)
Median	19.75	20.10
Minimum, Maximum	3.2, 163.3	1.7, 260.7

Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin; PP = postpartum; SD = Standard deviation; SMC = Standard medical care.

1VIT07017: Baseline Hb and Serum Ferritin for HUB Population

	FCM (N=390)	SMC (N=399)
Haemoglobin (g/dL)		
Baseline		
N	390	399
Mean (SD)	9.34 (1.387)	9.40 (1.310)
Median	9.60	9.60
Minimum, Maximum	5.0, 11.9	4.5, 12.1
Ferritin (ng/mL)		
Baseline		
N	390	399
Mean (SD)	8.89 (15.529)	7.95 (15.072)
Median	4.90	4.50
Minimum, Maximum	1.2, 248.8	1.1, 189.5

Notes: FCM = Ferric carboxymaltose; Hb = Haemoglobin; SD = Standard deviation; SMC = Standard medical care.

Assessment of Applicant's Response

Baseline Hb and ferritin values for subjects in study 1VIT07017 have been provided and raise no concerns.

Assessor's conclusion
Point resolved

- *Summary safety (adverse events and clinical laboratory data) and demographic data (to include weight) for the subjects who received the maximum dose of 1000 mg FCM should be provided for studies 1VIT07017, 1VIT07018, and 1VIT06011, and this should be compared with those for subjects receiving lower doses. Also, the mg/kg dose of FCM administered should be provided for these subjects.*

Summary of Applicant's Response

In response to the above question, the applicant has completed an analysis of the demographic and safety data for patients that received the maximum dose of 1,000 mg compared with those receiving a lower dose. Due to variance in total amount of iron in second and subsequent doses, patients with a first dose of 1,000 mg (irrespective of subsequent doses), are grouped in the 1,000 mg populations. Additionally, for Study 1VIT07018 only the non-dialysis-dependent chronic kidney disease (NDD-CKD) patients are included as

the HD-CKD patients all received lower and more frequent dosing and hence no comparison can be made within this population. The demographics and dose (mg/kg) is summarised using the mean values in the table below. As expected, the patients that received the 1,000 mg doses were heavier with increased BMI. In relation to laboratory values, all patients may be considered to have IDA although higher baseline ferritin values were observed in patients entering the 1VIT07018 study and receiving less than 1,000 mg bolus injections of iron.

1VIT06011, 1VIT07017 and 1VIT07018: Key Demographic Information

Demographic (mean values, unless stated otherwise)	1VIT06011 PP		1VIT07017 HUB and PP		1VIT07018[1] NDD-CKD	
	<1,000 mg	1,000 mg	<1,000 mg	1,000 mg	<1,000 mg	1,000 mg
Number of Subjects	70	72	371	625	34	170
Age (years)	25.2	27.6	28.1	33.0	65.4	64.2
Sex (female)	100%	100%	100%	100%	82.35	64.12
Height (cm)	161.3	164.9	161.5	164.5	160.9	166.4
Weight (kg)	67.6	95.0	64.1	92.6	63.0	97.5
BMI (kg/m2)	26.0	35.0	24.6	34.3	24.4	35.2
Dose (mg/kg)						
Mean (SD)	12.0 (1.5)	10.8 (1.7)	13.4 (1.8)	11.2 (2.1)	14.0 (2.6)	10.8 (2.3)
Median	12.1	10.5	13.6	11.3	15.0	10.8
Min	4.7	7.3	2.8	5.5	5.4	5.5
Max	15.0	15.7	18.1	16.6	14.1	15.0
Baseline Laboratory						
Hb (mg/dL)	8.91	8.87	10.11	9.71	10.24	10.43
TSAT (%)	9.94	8.94	10.97	8.75	22.33	19.26
Ferritin (ng/mL)	24.52	23.59	23.8	16.6	102.55	87.84

1 The study population included HD-CKD patients however these have been excluded from this analysis as all HD-CKD patients only received 200 mg iron.

Notes: BMI = Body mass index; Hb = Haemoglobin; HD-CKD = Haemodialysis-dependent chronic kidney disease; HUB = Heavy uterine bleeding; NDD-CKD = Non-dialysis-dependant chronic kidney disease; PP = postpartum; TSAT = Transferrin saturation.

When analysed by study and dose (<1,000 mg versus 1,000 mg) the differences in adverse events was not clinically meaningful with a similar number of events per PT in both groups.

1VIT06011, 1VIT07017 and 1VIT07018: Key Safety Data According to Dose of Iron as FCM (<1,000 mg or 1,000 mg)

Demographic	1VIT06011 PP		1VIT07017 PP and HUB		1VIT07018[1] NDD-CKD	
	1,000 mg	<1,000 mg	1,000 mg	<1,000 mg	1,000 mg	<1,000 mg
Number of Subjects	72	70	625	371	170	34
All TEAE	38 (52.8%)	27 (38.6%)	169 (27.0%)	103 (27.8%)	45 (26.5%)	12 (35.3%)
Related TEAE	7 (9.7%)	8 (11.4%)	81 (13.0%)	46 (12.4%)	8 (4.7%)	6 (17.6%)
TEAE leading to D/C	1 (1.4%)	1 (1.4%)	0	7 (1.9%)	0	3 (8.8%)
SAE	1 (1.4%)	3 (4.3%)	6 (1.0%)	0	4 (2.4%)	2 (5.9%)
SADR	0	0	0	0	0	0
Death	0	0	0	0	0	0

1 Only includes patients with NDD-CKD.
Notes: FCM = Ferric carboxymaltose; HUB = Heavy uterine bleeding; NDD-CKD = Non-dialysis-dependent chronic kidney disease; PP = postpartum; SADR = Serious adverse drug reaction; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

Assessment of Applicant's Response

A large number of patients received the maximum dose of 1000 mg FCM in studies 1VIT07017, 1VIT07018, and 1VIT06011, and baseline demographic data and adverse event data are comparable for those subjects versus those receiving lower doses of iron.

Assessor's conclusion
Point resolved

- *In study 1VIT07017 a figure of 95% is quoted for mean compliance (number of pills taken/number of pills prescribed) in the standard medical care treatment group, but is difficult to determine from the clinical study report exactly how much oral iron was prescribed for these subjects during the study. Summary data should be provided for doses of oral iron prescribed in the standard medical care group.*

Assessment of Applicant's Response

The full compliance data for the oral iron used in study 1VIT07017 has been provided by the applicant, and raises no new concerns.

Assessor's conclusion
Point resolved

- *The applicant should comment on the frequency of injection site reactions observed in study 1VIT07017 compared to that observed with lower bolus doses of IV FCM.*

Summary of Applicant's Response

No statistically significant or clinically meaningful differences, either at SOC or PT level, were observed in the frequency of injection site reactions when a sub-analysis was performed by dose received (1,000 mg versus <1,000 mg see table below).

1VIT07017: Injection Site Reactions by Bolus Dose of Iron as FCM (<1,000 mg or 1,000 mg)

System Organ Class Preferred Term	1,000 mg (N=625)		<1,000 mg (N=371)	
	N	%	N	%
General disorders and administration site conditions	33	5.3	26	7.0
Injection site extravasation	10	1.6	14	3.8
Injection site pain	7	1.1	5	1.3
Injection site bruising	7	1.1	4	1.1
Injection site irritation	6	1.0	2	0.5
Injection site paraesthesia	4	0.6	2	0.5
Injection site coldness	3	0.5	2	0.5
Injection site reaction	2	0.3	1	0.3
Injection site anaesthesia	0	0.0	1	0.3
Injection site erythema	1	0.2	0	0.0
Injection site haematoma	1	0.2	0	0.0
Injection site haemorrhage	0	0.0	1	0.3
Injection site rash	0	0.0	1	0.3
Injection site swelling	0	0.0	1	0.3

Of the above events, all were Grade 1 (mild) in patients receiving 1,000 mg whereas 5 patients in the <1,000 mg had a least 1 Grade 2 events (and all others being Grade 1 severity).

For other studies with bolus injection administration (1VIT06011 and 1VIT07018) data for injection site reactions is presented below and continues to support the above conclusion, namely that no difference is observed in relation to the frequency of injection site reactions when comparing 1,000 mg doses to <1,000 mg doses.

1VIT07018: Injection Site Reactions by Bolus Dose of Iron as FCM (<1,000 mg or 1,000 mg)

		1,000 mg N=170		<1,000 mg N=34		
SOC	PT	N	%	N	%	p-value <0.05
Total	Total	1	0.6	0	0.0	
General disorders and administration site conditions	Total	1	0.6	0	0.0	
	Injection site discolouration	1	0.6	0	0.0	

1VIT06011: Injection Site Reactions by Bolus Dose of Iron as FCM (<1,000 mg or 1,000 mg)

		1,000 mg N=72		<1,000 mg N=70		
SOC	PT	N	%	N	%	p-value <0.05
Total	Total	1	1.4	2	2.9	
General disorders and administration site conditions	Total	1	1.4	2	2.9	
	Injection site erythema	0	0.0	2	2.9	
	Injection site extravasation	1	1.4	0	0.0	

Notes: FCM = Ferric carboxymaltose; PT = Preferred term; SOC = System organ class.

Assessment of Applicant's Response

Data presented by the applicant shows no increased risk of injection site reactions with larger bolus doses of intravenous FCM.

Assessor's conclusion
Point resolved

- *In study 1VIT07017, 1.2% of subjects in the Ferinject group experienced an AE of increased aspartate aminostransferase (categorised as 'uncommon' in the SPC). This appears to be attributable to the postpartum group, in whom increases in AST and ALT were more pronounced. An explanation should be provided for this.*

Summary of Applicant's Response

Liver enzyme increases in the postpartum subjects were significantly higher in the FCM group (17 (2.8%) for ALT and 14 (2.3%), for AST) than in the comparator group (6 (1.0%) for ALT and 8 (1.3%) for AST). However, not all were considered drug related as assessed by the study Investigators with 13 (2.1%) for ALT and 12 (2.0%), for AST in the FCM group and 4 (0.6%) for ALT and 5 (0.8%), for AST in the standard medical care group.

The values for all patients with increases in ALT and/or AST (causally drug related or not) were individually reviewed and most of the changes in the FCM group were severity Grade 1 (>upper limit of normal (ULN) to 2.5 x ULN) with only 4 ALT elevations of severity Grade 2 (>2.5 x ULN to 5.0 x ULN) and 1 ALT elevation of severity Grade 3 (>5.0 x ULN to 20 x ULN). There were no liver changes associated with these observations, nor were there any discontinuations or severe serious adverse events (SAE) for elevated liver enzymes. These findings are in contrast with observations gathered from 2 other studies conducted with the same population (i.e., postpartum subjects) using similar intended FCM doses, enrolment timeframe post-delivery, and AEs grading criteria (National Cancer Institute common toxicity criteria (NCI-CTC) or common terminology criteria for adverse events (CTCAE)) but with longer treatment periods. In Study 1VIT03001 with respect to treatment-emergent clinical chemistry values, the most notable difference between the treatment groups was for the proportion of subjects with clinically significant ALT and AST values, which was greater in the oral iron group (3.4% each) compared with the FCM group (1.1% and 0%, respectively). Whereas in the FCM group there were no subjects (0/174) with treatment-emergent clinically significant liver enzymes (AST/ALT) values that met Grade 3 or 4 NCI-CTC, on the oral iron group 2/178 (1.1%) and 1/178 (0.6%) patients met such criteria for the ALT and AST values, respectively. In Study 1VIT06011 ALT increased (4.1% versus 0.7%), and AST increased (2.0% versus 0.7%) more so in the oral iron group than in the FCM group, respectively. For both the above studies, when the ALT and AST values were compared between baseline and end of treatment, there was a slight tendency for the ALT to increase. However, the AST decreased with changes of similar magnitude (table below). The applicant feels that these changes are not clinically relevant and in addition there was no statistical significance between the two treatment arms.

Mean Changes From Baseline to Day 42 in Clinical Chemistry Parameters (Safety Population) for study 1VIT03001

Biochemistry Parameter (Units)	VIT-45		Oral Iron		
	N	Change to Day 42 (SD)	N	Change to Day 42 (SD)	P-value
Albumin(g/dL)	161	1.3 (0.39)	162	1.3 (0.38)	0.3309
Alkaline phosphatase (U/L)	164	-25.9 (27.26)	162	-31.0 (39.47)	0.1784
ALT (SGPT) (U/L)	161	4.8 (29.41)	162	3.7 (25.52)	0.7264
AST (SGOT) (U/L)	161	-3.4 (20.72)	162	-1.2 (17.32)	0.3206
GGT (U/L)	164	5.3 (38.10)	162	-0.4 (20.62)	0.0963
LDH (U/L)	163	-102.8 (77.61)	162	-98.7 (85.54)	0.6556
Total bilirubin (mg/dL)	161	0.1 (0.17)	162	0.1 (0.30)	0.2369

Mean Changes From Baseline to Day 42 in Clinical Chemistry Parameters (Safety Population) for study 1VIT06011

Biochemistry Parameter (Units)	ICM			Oral Iron			
	N	Baseline Mean (SD)	Change to Day 42 (SD)	N	Baseline Mean (SD)	Change to Day 42 (SD)	p-value
ALT (SGPT) (U/L)	137	24.2 (16.52)	2.1 (21.80)	143	25.5 (17.86)	5.1 (49.58)	0.5056
AST (SGOT) (U/L)	137	26.9 (14.29)	-5.3 (13.88)	143	28.4 (18.92)	2.7 (83.18)	0.2669
Albumin (g/dL)	137	2.8 (0.34)	1.3 (0.38)	143	2.8 (0.34)	1.3 (0.37)	0.1327
Alkaline phosphatase (U/L)	137	127.4 (32.13)	-28.5 (30.10)	143	127.3 (39.02)	-31.8 (36.37)	0.4140
GGT (U/L)	137	16.3 (15.33)	1.5 (17.08)	143	15.7 (11.80)	1.2 (26.10)	0.9037
LDH (U/L)	137	232.7 (68.06)	-84.6 (64.90)	141	237.4 (51.91)	-81.1 (81.62)	0.6961
Total bilirubin (mg/dL)	137	0.3 (0.13)	0.1 (0.17)	143	0.3 (0.12)	0.1 (0.17)	0.8345

Notes: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma-glutamyltransferase; LDH = Lactate dehydrogenase; SD = Standard deviation;.

The applicant acknowledges that in Study 1VIT07017 there is a higher occurrence of ALT and AST increases particular to the postpartum cohort of the FCM group although at a lower incidence, ALT and AST increases are also noted in the postpartum subjects of the medical standard care group.

Liver transaminase elevations may be expected in pregnancy and up to 6 weeks post-delivery. Significant physiological changes occur during pregnancy with the hepatic function being subtly affected, especially bile transport. Gall bladder motility is reduced and bile lithogenicity increased due to increased hepatic cholesterol synthesis and excretion into bile. Relatively minor, but nevertheless important changes in blood tests occur due to haemodilution or alterations in hepatic synthesis. Routine liver function tests are often elevated with the ALP rising progressively during the third trimester and maybe up to 2 to 3 times the normal levels at term although the increase is more attributable to the placental production of this enzyme as opposed to hepatic dysfunction.

Conditions such as hyperemesis gravidarum, intrahepatic cholestasis, acute fatty liver, or hypertension associated liver diseases which are specific to pregnancy, occur with different frequencies and often play a significant influence on the hepatic activity.

Other confounding factors such as concomitant medication received by the subjects in the FCM postpartum group were also considered in some cases identifying therapeutic agents (local anaesthetics, anti-inflammatory, antibacterials, antiemetics/antinauseants) that might have additionally contributed to the AST and ALT abnormalities. Why the same level of out-of-range values were not observed in the other 2 presented postpartum studies remains unclear, although the applicant accepts that the numbers of

observations (although well balanced between groups) were smaller in Studies 1VIT03001 and 1VIT06011 as compared to Study 1VIT07017 which could have played a part.

In light of the above the applicant would suggest that the occurrence of ALT and AST elevations in Study 1VIT07017 are more likely to be related to specific characteristics of the population under study and the imbalance in events frequencies between the FCM group and the standard medical care may in part be attributed to chance. As the post-marketing experience with FCM provides greater exposure numbers, the applicant continues to monitor these events since they have already been recognised in the SPC and any perceived signal in the change of their frequency of occurrence would be duly notified in the submitted Periodic Safety Update Reports.

Assessment of Applicant's Response

Data from two other studies in similar populations of women with postpartum anaemia provide reassurance that the increases in aminotransferases observed in study 1VIT07017 are unlikely to be of significance. It is accepted that late-stage pregnancy is commonly associated with changes in liver function and liver enzyme levels. The applicant has committed to continue surveillance for any potential safety signals.

Assessor's conclusion
Point resolved

- *For study 1VIT07017 summary data on adverse events and clinical laboratory assessments should be provided for subjects who received the maximum dose of 1000 mg of FCM, as compared with those who received lower doses. In addition, similar summary data should be provided for subjects according to baseline stratification categories (baseline haemoglobin (≤8, 8.1 to 9.5, ≥9.6 g/dL), cardiac risk (category 1, category 2), and past response to oral iron).*

Summary of Applicant's Response

Please refer to Question 14 in relation to summary data on AEs by maximum dose received for the 1VIT07017 study. Additionally, Question 16 summarises Injection Site Reactions for patients receiving 1,000 mg or <1,000 mg. Overall 5.3% and 7.0% of patients experienced an event in the 1,000 mg and <1,000 mg dose groups respectively. Key clinical laboratory data for patients receiving 1,000 mg or <1,000 mg is provided below.

1VIT07017: Key Clinical Laboratory Assessments for Patients Receiving 1,000 mg or <1,000 mg Iron as FCM

Clinical Laboratory Value	<1,000 mg		1,000 mg	
	N	Mean (SD)	N	Mean (SD)
Baseline Hb (g/dL)	371	10.2 (1.2)	625	9.7 (1.3)
Highest Hb post baseline (g/dL)	362	12.5 (0.9)	610	12.0 (1.1)
Hb at Day 30 (g/dL)	362	12.5 (0.9)	609	12.1 (1.1)
Baseline serum ferritin (ng/mL)	371	23.8 (25.0)	625	16.6 (19.3)
Highest serum ferritin post baseline (ng/mL)	367	165.9 (101.9)	616	140.3 (100.3)
Serum ferritin value at Day 30 (ng/mL)	367	164.7 (101.5)	615	138.5 (98.4)

Sub-analyses have been provided by the baseline stratification categories (baseline Hb (=8, 8.1 to 9.5, =9.6 g/dL), cardiac risk (category 1, category 2), and past response to oral iron). In summary, there were no key differences between the groups when compared for dose by 1,000 mg and <1,000 mg iron for safety, efficacy or other laboratory values or baseline stratification factors.

Assessment of Applicant's Response

A higher proportion of TEAEs was reported by subjects with the lowest baseline Hb who received both the maximum and lower doses of FCM. This is however more likely to represent the effect of the degree of anaemia rather than an effect of the treatment. No trend is seen in the analysis of TEAEs for the subgroups of past response to oral iron. Patients in the higher cardiac risk group 2 experienced slightly more TEAEs than those in the lower risk group, however the numbers are relatively small, and no obvious trends can be found. Regarding laboratory assessments, no significant trends can be found.

Assessor's conclusion
Point resolved

- *In study 1VIT07018 justification is required for the serum ferritin inclusion criteria. Guidelines issued by the UK Renal Association in 2010 (available from www.renal.org/guidelines) and NICE in 2006 on the management of anaemia in CKD refer to lower ferritin levels in the diagnosis of IDA in both non-dialysis and haemodialysis dependent patients with CKD. Furthermore, in the original Ferinject studies in patients with CKD (Study 53214 and Study VIT-IV-CL-015) a serum ferritin of less than 200 µg/L was used as an inclusion criterion.*

Summary of Applicant's Response

There is a spectrum of ID occurring in CKD particularly in those patients treated with ESA stimulating the bone marrow to supra-physiological levels of red blood cell production and for whom the rate of iron delivery to the bone marrow (limited by the transferrin bound circulating iron) becomes insufficient to meet demands of the ESA over-stimulated marrow. Therefore, there has to be a distinction between the absolute ID characterised by absent bone marrow staining and underlined by causes such as inadequate dietary iron intake, impaired intestinal absorption, blood loss (from the gastrointestinal tract or HD sessions), inhibition of iron release from macrophages, role of hepcidin and that of the functional ID defined by the response to IV iron in order to obtain an increase in Hb levels or a reduction in the dose of ESA to maintain previously achieved Hb levels. In the latter the issue is one of supply and demand and not necessarily a total body ID and can occur at very variable serum ferritin levels substantially higher (up to 800 ng/mL) than those characterising the absolute ID.

To further complicate the clinical picture, in the setting of chronic inflammation there is the possibility of an extreme reticuloendothelial blockade when the iron contained within the reticuloendothelial system is not released to transferrin leading to low transferrin bound iron (TSAT) despite normal or even elevated serum ferritin levels. There is a clinical dilemma of how to interpret the body iron stores in this group of patients further compounded by the level of accuracy with which the serum ferritin and TSAT values could be used in order to help the decision of whether patients may or may not benefit from further iron administration. Both serum ferritin and TSAT have their limitations in determining ID as they exhibit some acute-phase reactivity in the setting of inflammation. By using both values for assessment of ID rather than either threshold in isolation the prevalence is being increased. In spite of the currently defined cut-off values for

both serum ferritin and TSAT values, the KDOQI and European Best Practice Guidelines repeatedly caution that there is no reliable signal threshold value to distinguish between ID and iron sufficiency.

In addition there is mounting evidence that CKD patients with higher serum ferritin and TSAT values are responding to iron repletion treatment. For example patients with high baseline ferritin levels (mean, 930 ng/mL) were administered IV iron if TSAT was less than 50% and ferritin level was less than 1,000 ng/mL. After receiving an average IV iron dose of 38 mg per week for 12 months, patients showed an increase in ferritin (mean, 1,383 ng/mL) and TSAT (from 27% to 36%) values and a 25% ESA dose decrease.

The FDA has recently reviewed and approved the application for Ferumoxytol® based on 3 pivotal studies conducted in patients with ID and CKD Stage 1-5 or 5D undergoing HD accepting IDA as defined by Hb of ≤11 g/dl or ≤11.5 g/dl (non-dialysis or dialysis, respectively), TSAT ≤30% and serum ferritin ≤600 ng/mL. Even this serum ferritin level is 25% below the 800 ng/mL proposed by KDOQI for IV iron therapy which is an opinion-based and not an evidence-based cut-off. Literature citations predating the use of ESA show that patients receiving multiple blood transfusions to maintain reasonable functional Hb levels had serum ferritin levels in the range of 100-2,000 ng/ml but on autopsy revealed little evidence of iron tissue overload. KDOQI have also determined that a realistic risk for iron overload is when the TSAT values exceed >50%.

The other quoted studies, 53214 and VIT-IV-CL-015, were completed prior to 1VIT07018 and were hence more conservative in inclusion criteria and provided the early data of which further hypotheses can be developed – ultimately permitting advances in the understanding of appropriate ferritin targets and iron replacement therapy. It is worth noting that in the last few years, especially in the field of CKD, higher ferritin targets have been indicative of better response and reduced ESA requirements (DRIVE study – ClinicalTrials.gov Identifier: NCT00224081). Additionally, the largest randomised clinical trial in NDD-CKD assessing impact of ferritin targeting is currently being performed to further elucidate the appropriate ferritin value in this disease setting.

In conclusion the serum ferritin values in the 1VIT07018 study were agreed taking into consideration the current concept of functional IDA as well as the guidelines recommendations of overall iron therapy targets. These values were lower than the non-response threshold and applied together with the TSAT values were expected to enhance the prevalence and thus boost the post-test probability that a low TSAT would be associated with ID in both non-dialysis as well as dialysis CKD patients. The applicant presents below the baseline characteristic of the study enrolled patients by both groups combined 1VIT07018 (non-dialysis/HD) as well as separately (see tables below):

Baseline Characteristics – HD Subjects (Safety Population) from Study 1VIT07018

Baseline Characteristic	Group A: FCM (N=50)	Group B: SMC (N=47)
Screening Haemoglobin (g/dL)		
Mean (SD)	11.24 (0.729)	11.29 (0.673)
Median	11.3	11.3
Minimum – Maximum	9.0, 12.4	9.3, 12.5
Haemoglobin Category		
≤9.0 g/dL	1 (2.0%)	0
9.1-11.0 g/dL	13 (26.0%)	15 (31.9%)
≥11.1 g/dL	36 (72.0%)	32 (68.1%)
Screening TSAT (%)		
Mean (SD)	22.60 (4.891)	24.62 (4.839)
Median	23	25
Minimum – Maximum	10, 31	9, 36
<20%	12 (24.0%)	7 (14.9%)
Screening Ferritin (ng/mL)		
Mean (SD)	273.22 (112.339)	247.87 (135.612)
Median	273.0	224.6
Minimum – Maximum	50.8, 499.4	15.5, 496.5
<100 ng/mL	4 (8.0%)	8 (17.0%)

Baseline Characteristics – NDD Subjects (Safety Population) from Study 1VIT07018

Baseline Characteristic	Group A: FCM (N=204)	Group B: SMC (N=212)
Screening Haemoglobin (g/dL)		
Mean (SD)	10.37 (0.801)	10.24 (0.857)
Median	10.6	10.3
Minimum – Maximum	6.9, 11.6	7.7, 11.7
Haemoglobin Category		
≤9.0 g/dL	14 (6.9%)	18 (8.5%)
9.1-11.0 g/dL	148 (72.5%)	151 (71.2%)
≥11.1 g/dL	42 (20.6%)	43 (20.3%)
Screening TSAT (%)		
Mean (SD)	19.07 (5.813)	18.49 (6.289)
Median	19	19
Minimum – Maximum	4, 30	4, 39
<20%	108 (52.9%)	118 (55.7%)
Screening Ferritin (ng/mL)		
Mean (SD)	89.34 (71.775)	91.75 (86.968)
Median	66.9	61.2
Minimum – Maximum	4.1, 298.1	3.6, 796.5
<100 ng/mL	135 (66.2%)	134 (63.2%)

Notes: Percentages based on subjects who were treated in Group A and subjects who were randomised in Group B.
FCM = Ferric carboxymaltose; NDD = Non-dialysis dependent; SD = Standard deviation; SMC = Standard medical care; TSAT = Transferrin saturation.

Assessment of Applicant's Response

The applicant's response is acknowledged, however the criteria for baseline ferritin and TSAT are still considered too high for both NDD and HD dependent CKD patients. This would be of greater concern if the purpose of the study was to demonstrate efficacy; no new safety concerns have been highlighted by the study. The baseline data for HD subjects shown in the table above is of particular concern, with only 8% in the FCM group having a baseline ferritin of <100 ng/mL and 24% having a TSAT of <20%. However, these patients did not receive the maximum dose of FCM, and a statement has been added to the SPC highlighting that no safety data are available for use of higher doses in this subset. This point of concern is therefore not considered a major obstacle to the granting of this variation.

Assessor's conclusion
Point resolved

- *Although it is stated that no patients experienced a hypersensitivity reaction in studies 1VIT07018 and 1VIT06011, several subjects in the Ferinject group experienced reactions that would be considered to qualify in this category (eg, urticaria). The applicant should clarify this.*

Summary of Applicant's Response

The results of a comprehensive 'broad' MedDRA based search of the 1VIT07018 and 1VIT06011 Clinical Trial database for events which could be considered as 'potentially' hypersensitivity related are provided below.

1VIT07018
Seven subjects in the FCM group and 3 subjects in the standard medical care group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including blister, rash, urticaria, skin ulcer, rash pruritic, pruritus generalised, and swelling face. Each of these events was classified by the Investigator as either mild or moderate in severity. The majority of these events were considered as not related to study drug.

1VIT06011
Seven subjects in the FCM group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including urticaria, erythema, and rash. Each of these events was classified by the Investigator as either mild or moderate in severity. The events of urticaria, and rash were considered related to the study drug. Comparatively, 5 subjects in the oral iron group experienced TEAEs associated with Skin and Subcutaneous Tissue Disorders including urticaria, rash and pruritus. Each of these events was also classified by the Investigator as either mild or moderate in severity. The event of urticaria was considered related to the oral iron.

In conclusion, these skin and subcutaneous events were comparable in both the FCM/control arms and it is difficult to define these events as 'true' hypersensitivity reactions based on many factors including severity and latency to drug exposure.

Assessment of Applicant's Response

The applicant has provided details of subjects who experienced potential hypersensitivity reactions in studies 1VIT07018 and 1VIT06011. The risk of this adverse reaction is adequately detailed in the SPC.

Assessor's conclusion
Point resolved

- *Since no haemodialysis-dependent patients were exposed to the maximum dose of 1000 mg FCM it is unclear how the primary objective of the study can be met for this group of patients. The safety of doses higher than 200 mg in haemodialysis-dependent chronic kidney disease patients has not been demonstrated, and this should be reflected in the SPC.*

Summary of Applicant's Response

The applicant agrees with the above response and would therefore propose the following additional sentence for the SPC:

4.4 Special warnings and precautions for use
"*No safety data on haemodialysis-dependant chronic kidney disease patients receiving single doses of more than 200 mg iron are available.*"

Assessment of Applicant's Response

The statement proposed by the applicant is acceptable for Section 4.4. However Section 4.2 requires the addition of a special populations sub-section containing dosing advice for renal impairment. It should be stated here that a single maximum daily dose of 200 mg iron should not be exceeded in HD-dependent CKD patients.

Assessor's conclusion
Point partially resolved

- *For study 1VIT06011 the applicant should specify how many of the 12 subjects with a CTCAE grade 3 decrease in phosphate received the maximum dose of FCM.*

Summary of Applicant's Response

Six of the 12 subjects with CTCAE Grade 3 decrease in phosphate received the maximum dose of FCM. The dose of FCM administered per patient is listed in the table below.

1VIT06011: Subject Listing for CTCAE Grade 3 Decrease in Phosphate

Subject	Dose on Day 0 (mg iron)	Dose on Day 7 (mg iron)	Dose on Day 14 (mg iron)	Day of Grade 3 Event	Phosphate (mg/dL)	Phosphate (mmol/L)
1101114	1,000	1,000	200	Day 14	1.7	0.55
1102327	1,000	700	.	Day 7	1.8	0.58
1104161	800	500	.	Day 14	1.8	0.58
1105176	700	300	.	Day 28	1.9	0.61
1106160	900	400	.	Day 14	1.7	0.55
1107125	1,000	700	.	Day 14	1.6	0.52
1107316	900	600	.	Day 14	1.4	0.45
1109242	800	500	.	Day 7	1.6	0.52
				Day 14	1.7	0.55
1109276	1,000	500	.	Day 28	1.8	0.58
1109386	500	1,000	100	Day 14	1.8	0.58
1116370	800	400	.	Day 14	1.5	0.48
1120199	1,000	1,000	100	Day 28	1.9	0.61

Note: CTCAE = Common terminology criteria for adverse events.

Assessment of Applicant's Response

As discussed above, it does not appear that there is a correlation between dose of FCM and the degree of post-dose hypophosphataemia.

Assessor's conclusion
Point resolved

- *Higher bolus doses of parenteral iron may increase the risk of events such as anaphylactic reactions and injection site complications. Anaphylactic reactions are an uncommon occurrence and so a small increase in frequency would be difficult to detect in the clinical trial setting with small patient numbers. Several subjects experienced hypersensitivity reactions (eg, urticaria) during the studies. Injection site reactions were observed as a common occurrence in Study 1VIT07017, and 6 patients discontinued the study due to such an event. The potential for an increase in the frequency of these reactions needs further discussion, and comparisons should be presented with frequencies observed in other trials with Ferinject.*

Summary of Applicant's Response

In the 1VIT07017 study, 6 patients withdrew due to injection site reactions resulting in extravasation. In all cases, the AE was independent of planned dose which varied from 250 mg to 800 mg. Therefore, no dose dependency or relationship to higher bolus dose has been observed in these patients. To further address the concern raised, the applicant has compared the PTs considered to be indicative of potential hypersensitivity/allergic reactions (as defined in the 1VIT07017 CSR) with other PP and HUB studies (1VIT03001, 1VIT06011 and VIT-IV-CL-009) as well as all studies submitted as part of the MAA.

Summary of Potential Hypersensitivity and Allergic Reactions

Preferred Term	1VIT07017 (n=996)		PP and HUB Studies (Excluding 1VIT07017) (n=543)		All Studies (Including PP and HUB but Excluding 1VIT07017) (n=1417)	
	N	%	N	%	N	%
Angioedema	1	0.1	0	0.0	0	0.0
Bronchospasm	0	0.0	0	0.0	0	0.0
Erythema	1	0.1	2	0.4	5	0.4
Erythema multiforme	1	0.1	0	0.0	0	0.0
Eye pruritus	0	0.0	0	0.0	1	0.1
Eye swelling	0	0.0	0	0.0	0	0.0
Eyelid oedema	0	0.0	0	0.0	1	0.1
Eyelids pruritus	0	0.0	0	0.0	0	0.0
Face oedema	0	0.0	0	0.0	0	0.0
Flushing	1	0.1	2	0.4	5	0.4
Genital pruritus female	0	0.0	0	0.0	0	0.0
Idiopathic urticaria	0	0.0	1	0.2	1	0.1
Infusion site pruritus	0	0.0	1	0.2	1	0.1
Infusion site rash	0	0.0	0	0.0	0	0.0
Injection site rash	1	0.1	0	0.0	0	0.0
Injection site urticaria	0	0.0	0	0.0	0	0.0
Pruritus	6	0.6	4	0.7	11	0.8
Pruritus ani	0	0.0	0	0.0	0	0.0
Pruritus generalised	1	0.1	0	0.0	1	0.1
Pruritus genital	0	0.0	0	0.0	0	0.0
Rash	7	0.7	11	2.0	22	1.6
Rash erythematous	0	0.0	0	0.0	2	0.1
Rash generalised	0	0.0	0	0.0	1	0.1
Rash macular	0	0.0	3	0.6	3	0.2
Rash maculo-papular	0	0.0	1	0.2	1	0.1
Rash papular	1	0.1	0	0.0	0	0.0
Rash pruritic	0	0.0	0	0.0	1	0.1
Skin reaction	0	0.0	0	0.0	0	0.0
Swelling face	1	0.1	0	0.0	0	0.0
Swollen tongue	1	0.1	0	0.0	0	0.0
Urticaria	6	0.6	4	0.7	12	0.8
Urticaria generalised	0	0.0	1	0.2	1	0.1
Vulvovaginal pruritus	0	0.0	0	0.0	0	0.0
Wheezing	0	0.0	0	0.0	0	0.0

Notes: HUB = Heavy uterine bleeding; PP = postpartum.

In summary, an increase in the frequency of above reactions was not observed when compared with other clinical studies previously completed.

Assessment of Applicant's Response

As discussed in the responses to questions 16 and 20, there does not appear to be an excess risk of injection site reaction or hypersensitivity-type reaction with higher bolus doses of FCM. The data above confirm that no increased risk was detected in study 1VIT07017 as compared with previous studies involving FCM.

Assessor's conclusion
Point resolved

- *The applicant estimates that the number of patients with a body weight ≤66 kg requiring intravenous iron therapy is at least 50%; however, in the 3 studies submitted in support of variation UK/H/0894/001/II/012 the mean body weight of patients was significantly higher. The applicant should comment on this, and on the potential impact of the high mean body weight and BMI of patients included in Studies 1VIT06011, 1VIT07017, and 1VIT07018 on the interpretation of the safety data.*

Summary of Applicant's Response

Studies 1VIT06011, 1VIT07017, and 1VIT07018 were completed in the US. This might be an explanation to why the mean body weight was somewhat higher than seen in previous studies performed mostly outside of the US. To enable a comparison of the relevant safety data, AEs have been analysed compared to previously submitted MAA studies and for the 3 individual studies submitted with this variation package (1VIT06011, 1VIT07017 and 1VIT07018), by body weight of greater than or less than 66 kg.

1VIT06011, 1VIT07017 and 1VIT07018: Comparison of AEs with Previously Submitted MAA Studies

Safety	1VIT06011 N=142	1VIT07017 N=996	1VIT07018[1] N=204	Combined N=1392	MAA studies[1] N=896
ADR	15 (10.6%)	127 (12.8%)	17 (6.7%)	159 (11.4%)	139 (15.5%)
D/C ADR	2 (1.4%)	6 (0.6%)	2 (0.8%)	10 (0.7%)	6 (0.7%)
SAE	4 (2.8%)	6 (0.6%)	9 (3.5%)	19 (1.4%)	33 (3.7%)
SADR	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

1 Studies included: VIT-IV-CL-001; VIT-IV-CL-015; 53214; VIT-IV-CL-02, 1VIT03001; VIT-IV-CL-009, VIT-IV-CL-03; VIT-IV-CL-008.
Study VIRD-VIT-45-IM excluded as route of administration was IM (and only 4 patients assessed).
Notes: ADR = Adverse drug reaction; AE = Adverse event; MAA = Marketing Authorisation Application; SADR = Serious adverse drug reaction; SAE = Serious adverse event.

1VIT06011, 1VIT07017 and 1VIT07018: Comparison of AEs by Body Weight

Demographic	1VIT06011			1VIT07017			1VIT07018[1] NDD-CKD		
	≤66 kg	66-75 kg	>75 kg	≤66 kg	66-75 kg	>75 kg	≤66 kg	66-75 kg	>75 kg
No. of subjects	29	33	80	236	202	554	29	34	141
All TEAE	11 (37.9%)	15 (45.5%)	39 (48.8%)	61 (25.8%)	59 (29.2%)	152 (27.4%)	7 (24.1%)	10 (29.4%)	40 (28.4%)
Related TEAE	2 (6.9%)	6 (18.2%)	7 (8.8%)	27 (11.3%)	30 (14.9%)	70 (12.6%)	5 (17.2%)	2 (5.9%)	7 (5.0%)
TEAE leading to D/C	0	2 (6.1%)	0	0	1 (0.5%)	6 (1.1%)	1 (3.4%)	2 (5.9%)	0
SAE	0	3 (9.1%)	1 (1.3%)	0	1 (0.5%)	5 (0.9%)	2 (6.9%)	0	4 (2.8%)
SADR	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0

Notes: AE = Adverse event; NDD=CKD = Non-dialysis-dependent chronic kidney disease; SADR = Serious adverse drug reaction; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event.

In summary, the 3 studies have an overall safety profile which is comparative to that from previously submitted studies. Additionally, when reviewing the AEs by body stratification (≤66 kg versus 66 kg to 75 kg versus >75 kg), the AE profile is similar between groups. As such, the applicant concludes that the high mean body weight and BMI of patients included in Studies 1VIT06011, 1VIT07017, and 1VIT07018 does not distort the interpretation of the safety data when compared with previously submitted studies.

Assessment of Applicant's Response

The numbers of reported TEAEs per patient in the studies submitted for these variations is similar to those from the original studies submitted for the initial MAA of FCM. It can also be seen that the proportion of TEAEs does not appear to vary greatly with patient weight. The conduct of trials in an entirely US-based population with a mean bodyweight significantly higher than that in Europe limits the generalisability of the results, however in this situation the benefit-risk profile is not unduly influenced.

Assessor's conclusion
Point resolved

VI ASSESSMENT OF APPLICANT'S RESPONSE TO SUBSEQUENT REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

In response to the issues raised in the FVAR dated 10 June 2011, the applicant has proposed the following amendments to the SPC.

Section 4.2
The sub-sections "Intravenous injection" and "Intravenous drip infusion" have been updated to reflect that dose levels above 15mg/kg are to be administered as a diluted intravenous infusion, as requested.

A new sub-section "Haemodialysis-dependent chronic kidney disease" added to reflect dosing advice for this special population, as requested by MHRA.

The sub-section heading entitled "Paediatric population" inserted, as requested.

Section 4.5
The sub-section "Pregnancy" amended as stated in the FVAR.

Section 4.8
We would like to suggest an editorial change for "undesirable effects" as the wording in the proposed SmPC lacks context to some extend.

Section 5.3
Section amended as stated in the FVAR.

These amendments are acceptable to RMS, and the variations are therefore considered approvable.

VII OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

At present there is insufficient experience in human exposure to warrant removal of the pregnancy contraindication, and the findings of the non-clinical studies further support continued caution to be applied for the use of this product during pregnancy. The applicant agreed to maintain the contraindication in the first trimester of pregnancy, making variation **UK/H/0894/001/II/010** approvable. A PSRPH was raised by France concerning the maintenance of the contraindication in the first trimester of pregnancy. This variation was referred to CMDh. During the arbitration process it was agreed by the RMS and CMSs to remove the contraindication for use in the first trimester of pregnancy, but to clarify the use of the product in pregnancy with additional warnings in Section 4.6 of the SPC and additional information in Section 5.3 of the SPC. The matter was therefore resolved.

The current method for calculating the required cumulative dose of iron using the Ganzoni formula is complicated and may lead to dosing errors. Furthermore, the current licence allows administration of up to only 200 mg FCM per day, increasing the burden on patients who would need to attend clinic on frequent occasions for iron repletion. Variation **UK/H/0894/001/II/011** proposes to introduce a new standardised dosing regime, aimed at reducing dosing errors. Variation **UK/H/0894/001/II/012** proposes to increase the maximum single daily dose of FCM to 1000 mg, and is aimed at reducing the dosing frequency required for iron repletion, and therefore potentially improving patient compliance. The final variation, **UK/H/0894/001/II/013**, proposes to increase the maximum dose of iron per kg of bodyweight, allowing the standardised regime with the increased maximum daily of dose of 1000 mg iron to be used in patients weighing between 50 and 66 kg, a significant proportion of the target population according to the applicant.

There were initially serious concerns about the failure to demonstrate the efficacy and safety of the new dosing regime in comparison to dosing as per the Ganzoni formula. The efficacy concerns were based on the use of a different comparator in the pivotal study, differences in the degree of efficacy observed in the present study when compared to previous studies, and the generalisability of the results of the study. The safety concerns included the relative risk of post-dose hypophosphataemia, and the potential for iron overload. These concerns have been adequately addressed by the applicant in the response document, and the benefit-risk profile of the standardised dosing regime is considered positive; variation **UK/H/0894/001/II/011** is therefore considered approvable.

The variation to increase the maximum single daily dose of FCM to 1000 mg (**UK/H/0894/001/II/012)** is considered approvable, following clarification of some safety data which has been provided by the applicant and a restriction of the maximum dose to 200 mg in haemodialysis-dependent chronic kidney disease patients.

There were initially concerns regarding the safety data provided to support the proposal to increase the maximum dose of iron per kg of bodyweight (**UK/H/0894/001/II/013)**. Detailed adverse event and clinical laboratory data were provided by the applicant for subjects with low body weight receiving the higher dose levels, and no safety signals can be observed to suggest an increased risk of increasing the maximum daily dose of FCM from 15 to 20 mg/kg. However, despite additional data from the applicant from a Phase I/II study with a new strength of FCM in which 3 subjects were administered undiluted, bolus doses of >15 mg/kg, it is still considered that the benefit-risk ratio for undiluted, bolus doses >15 mg/kg is negative, since an increased risk of hypersensitivity reactions at high dose levels has not been adequately excluded. This variation is only approvable on the basis that doses of FCM between 15 and 20 mg/kg are administered as a diluted infusion over a minimum of 15 minutes. This amendment was accepted by the applicant, making variation **UK/H/0894/001/II/013** approvable. A PSRPH was raised by Germany concerning this variation.

The variation was referred to CMDh and the matter was resolved, with all parties in agreement that the benefit-risk profile of the higher dose level was positive.

Annex 1.7

Our Reference:	PL 14017/0140, Application 0036
Product:	Ferinject 50mg iron/ml solution for injection/infusion
Marketing Authorisation Holder:	Vifor France SA
Active Ingredient(s):	Ferric carboxymaltose
Type of Procedure:	Mutual Recognition
Submission Type:	Variation
Submission Category:	Type II
Submission Complexity:	Complex
EU Procedure Number (if applicable):	UK/H/0894/II/035/G

Reason:

To update Section 4.6 (Fertility, Lactation and Pregnancy) and Section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SmPC), to include additional information from studies investigating the use of Ferinject in the treatment of iron deficiency/iron deficiency anaemia in the therapeutic areas of cardiology and women's health. To also update Section 4.8 (Undesirable effects) of the SmPC, and consequentially the leaflet, in line with recent Company Core Data Sheet (CCDS) and Quality Review of Documents (QRD) template.

Supporting Evidence and Evaluation:

- Cardiology: treatment of iron deficiency (ID) in subjects with chronic heart failure (CHF)
  - Summary of the efficacy results of Study FER-CARS-05 (CONFIRM-HF): a pivotal, Phase 4, confirmatory, randomised controlled trial (RCT)
- Women's health (pregnancy): treatment of IDA in the second and third trimester of pregnancy
  - Summary of efficacy results of the RCT, FER-ASAP-2009-01
- Company Core Data Sheet (CCDS) for Ferinject (Version 6.0, dated 23 July 2015).
- Updated SmPC fragments and leaflet

Data Supporting Revision to Section 5.1 of the EU SmPC:

Treatment of ID in Subjects with CHF

The efficacy and safety of Ferinject for the treatment of ID in CHF has been evaluated in 4 double-blind RCTs, including a total of 507 subjects treated with ferric carboxymaltose (FCM), 27 subjects treated with iron sucrose, and 335 subjects treated with placebo. In the first 3 RCTs (FER-CARS-01, FER-CARS-02, FER-CARS-03), conducted by the Marketing Authorisation Holder (MAH), the dosage of ferric carboxymaltose (FCM) for iron repletion was based on each subject's calculated iron deficit, whereas in the most recently completed RCT (FER-CARS-05), the iron repletion dose was determined using the currently approved simplified dosing regimen based on subject body weight (BW) and haemoglobin (Hb) level.

Overview of the Efficacy and Safety Results of Study FER-CARS-05

Study FER-CARS-05 was a randomised, double-blind, multicentre, controlled, Phase 4 study to compare the efficacy (i.e., functional capacity) and safety of intravenous (IV) FCM with placebo in 304 subjects with CHF and ID, with and without anaemia, over a 1-year period.

For inclusion in the study, subjects were required to have New York Heart Association (NYHA) II or III functional class (due to stable symptomatic CHF); left ventricular ejection fraction ≤45%; brain natriuretic peptide >100 pg/mL and/or N-terminal-pro-brain natriuretic peptide >400 pg/mL; Hb <15 g/dL; and ID defined as serum ferritin <100 mcg/L (or 100 to 300 mcg/L with transferrin saturation (TSAT) <20%).

Subjects were randomised 1:1 to receive either FCM or placebo. A total of 152 subjects were treated with FCM. FCM was administered using the currently approved standardised dosing regimen for iron replenishment (based on screening weight and Hb levels) followed by maintenance dosing (based on serum ferritin and TSAT levels) (see Table 2).

Table 2 Study Drug Dosing per Visit (mL) in Study FER-CARS-05

	Total mL FCM (mg Iron) or Saline (mL)					
	Screening Weight <70 kg			Screening Weight ≥70 kg		
	Screening Hb			Screening Hb		
	Hb <10 g/dL	Hb 10-14 g/dL	Hb >14, <15 g/dL	Hb <10 g/dL	Hb 10-14 g/dL	Hb >14, <15 g/dL
Correction doses						
Day 1	20 mL (2 vials FCM (1,000 mg) or 4 vials saline)	20 mL (2 vials FCM (1,000 mg) or 4 vials saline)	10 mL (1 vial FCM (500 mg) or 2 vials saline)	20 mL (2 vials FCM (1,000 mg) or 4 vials saline)	20 mL (2 vials FCM (1,000 mg) or 4 vials saline)	10 mL (1 vial FCM (500 mg) or 2 vials saline)
Week 6	10 mL (1 vial FCM (500 mg) or 2 vials saline)	No dose	No dose	20 mL (2 vials FCM (1,000 mg) or 4 vials saline)	10 mL (1 vial FCM (500 mg) or 2 vials saline)	No dose
Maintenance doses						
Weeks 12, 24 and 36	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)	If required 10 mL (1 vial FCM (500 mg) or 2 vials saline)(1)

1 Dose to be administered where serum ferritin <100 ng/mL or serum ferritin 100-300 ng/mL with transferrin saturation <20%.

The primary efficacy analysis demonstrated the benefit of FCM relative to placebo in improving functional capacity as measured by the change in 6-minute walk test (6MWT) distance from baseline (BL) to Week 24, with a difference between treatment groups (least squares (LS) mean (±SE)) of 33.2 ± 10.52 metres (95% CI: 12.51, 53.94; p=0.002) (full analysis set). This confirmed the results of Study FER-CARS-02 in which the mean (SD) change in 6MWT distance from BL to Week 24 (a key secondary endpoint) was 38.6 (75.38) metres in the FCM group compared to 10.2 (66.67) metres in the placebo group (p<0.001).

The treatment benefit of FCM in improvement of 6MWT distance was sustained throughout the study to Week 52 (p≤0.001), demonstrating the long-term benefit of iron repletion over a period of 1 year. This sustained improvement was consistent across subgroups, including subjects with and without anaemia at screening (i.e., Hb <12 g/dL, ≥12 g/dL).

Table 3 Results for ANCOVA Analysis of Primary Efficacy Endpoint in FER-CARS-05 (FAS, N=301)

Statistic	LS Mean	SE	95% CI	p-value
Change in 6MWT distance (metres) from BL to Week 24				
FCM (n=130)	17.5	8.16	1.43, 33.58	–
Placebo (n=131)	-15.7	8.00	-31.49, 0.04	–
FCM-placebo	33.2	10.52	12.51, 53.94	0.002*

The magnitude of the treatment effect of FCM on 6MWT distance in this study, which exceeded 30 metres (relative to placebo) from Week 24 onwards, is clinically meaningful.

Results of the other secondary efficacy parameters demonstrated additional benefits of FCM with respect to improvements in subjects' functional status and QoL throughout the study ; Improvements in Patient Global Assessment (PGA), NYHA functional class, fatigue score, and overall Kansas City Cardiomyopathy Questionnaire (KCCQ) score were seen in FCM-treated subjects, with statistical significance for the difference between treatment groups achieved from Week 12 (PGA, fatigue score, KCCQ) or Week 24 (NYHA) onwards. Improvements in KCCQ symptom frequency score were also seen in FCM-treated subjects, although the difference between treatment groups was statistically significant at Week 52 only. Improvements in European quality of life - 5 dimensions (EQ-5D) health score and index score were also seen in the FCM group, but statistical significance between treatment groups was observed at Week 36 only.

Treatment with FCM versus placebo was also associated with a clinically relevant and statistically significant reduction in the risk of hospitalisation due to worsening CHF (HR: 0.4; 95% CI: 0.2, 0.8; p=0.009). The positive treatment effect of FCM versus placebo on reducing the number of recurrent hospitalisations due to worsening CHF was demonstrated in a post-hoc sensitivity analysis (incidence ratio of FCM versus placebo of 0.30 (95% CI: 0.14, 0.64; p=0.0019). There were no significant differences between treatment groups in the risk of death.

Treatment with FCM was also shown to result in statistically significant increases in haematocrit, Hb, mean corpuscular volume, mean corpuscular Hb, and mean corpuscular Hb concentration. Increases were visible at Week 6 and sustained throughout the study. For FCM-treated subjects, clinically meaningful and statistically significant increases from BL were seen at all time points for serum ferritin and TSAT, as well as statistically significant decreases in transferrin.

The overall incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to treatment withdrawal were similar between the FCM and placebo treatment groups, 79.6% and 75.7% respectively, and the majority of events in both groups were mild. There were no unexpected TEAEs or clinical laboratory findings related to FCM and/or for the population studied.

As in the previous 3 cardiology studies (i.e., FER-CARS-01, FER-CARS-02 and FER-CARS-03), the patient population was identified on the basis of laboratory biomarkers of ID – serum ferritin and TSAT. However, in contrast to the previous studies which used the Ganzoni formula, Study FER-CARS-05 used the currently approved standardised dosing regimen for correction of ID (1 or 2 administrations of FCM for a cumulative dose of 500 mg to 2,000 mg iron), with up to 3 additional maintenance doses of 500 mg iron administered as applicable, according to serum ferritin and TSAT levels (see Table 2). The treatment benefit observed with FCM was achieved with 66.4% of subjects receiving correction dosing only (1 or 2 doses) to replete and maintain their iron parameters during the 52-week study period. In comparison, >93% of

subjects in the placebo group required additional maintenance doses of 500 mg iron equivalents each during the study.

Conclusions
Treatment of stable, symptomatic, iron deficient CHF patients with a simplified dosing regimen of FCM over a 1-year period resulted in sustained improvement in functional capacity, symptoms, and QoL, and reduced the risk of hospitalisations due to worsening of CHF. FCM was well-tolerated in this patient population with no new safety findings or unexpected risks identified.

Treatment of IDA During the Second and Third Trimester of Pregnancy
Study FER-ASAP-2009-01 was a multicentre, randomised, open-label, active-controlled study to evaluate the efficacy and safety of FCM compared to oral iron in the treatment of IDA in 247 pregnant women during the second and third trimester.

For inclusion in the study, a subject's gestational week was required to be between ≥16 and ≤33 at BL. Subjects were also required to have serum ferritin ≤20 mcg/L at screening and IDA defined as Hb between ≥8.0 g/dL and ≤10.4 g/dL (during gestational weeks 16 to 26) or ≤11.0 g/dL (during gestational weeks 27 to 33). Eligible subjects were randomised 1:1 to receive FCM or oral iron.

A total of 123 subjects were treated with FCM. Treatment with FCM utilised a simplified dosing regimen for correction of ID as shown below:

Table 4 Determination of FCM Dosing in Study FER-ASAP-2009-01

Hb at Screening	Total FCM Cumulative Dose	
	BW <66 kg	BW ≥66 kg
8-9 g/dL	3 x 500 mg	1 x 1,000 mg, 1 x 500 mg
9.1-11.0 g/dL	2 x 500 mg	1 x 1,000 mg

The primary efficacy endpoint in this study (superiority of FCM versus oral iron for the change in Hb from BL to Week 3) was not met. Although increases in mean Hb were numerically higher in the FCM group compared to the oral iron group at each time point, the difference between groups was statistically significant at Week 6 only (LS mean difference: 0.28 g/dL; 95% CI: 0.02, 0.55; p=0.032). There was a higher proportion of subjects with anaemia correction (Hb level of ≥11.0 g/dL) before delivery in the FCM group (83.5%) than the oral iron group (70.2%), and subjects in the FCM group were twice as likely to achieve anaemia correction (OR: 2.06; 95% CI: 1.07, 3.97; p=0.031). Increases from BL in mean serum ferritin, reticulocyte cell Hb content, and TSAT were observed in both treatment groups, with a statistically significant difference in favour of FCM for serum ferritin at Weeks 3, 6, and 9 (p<0.001).

At the last visit prior to delivery, statistically significant improvements in favour of the FCM group were seen for vitality score (LS mean difference 5.90; 95% CI: 0.75, 11.04; p=0.025) and social functioning score (LS mean difference 5.76; 95% CI: 0.01, 11.51; p=0.049.

The majority of TEAEs reported in this study were previously described events with IV or oral iron treatment. Overall, the proportion of subjects with at least 1 TEAE was slightly higher in the FCM group (48.8%) compared to the oral iron group (40.3%). The majority of events in both treatment groups were mild (FCM: 71.7%; oral iron: 56.0%). No subjects in the FCM group experienced a severe TEAE compared

to 2 (1.6%) subjects in the oral group. The most frequent TEAEs by PT (≥5% in either group) were as follows: nausea (FCM: 6.5%; oral iron: 4.8%), headache (FCM: 8.1%; oral iron: 0.8%), and dyspepsia (FCM: 0.8%; oral iron: 6.5%).

Treatment-related TEAEs and TEAEs leading to discontinuation were more frequent in the oral iron group. With the exception of the efficacy laboratory parameters (e.g., iron status parameters), there were no notable changes in clinical laboratory findings. No trends or clinically relevant changes were observed in vital signs or physical examination findings.

Treatment of mothers with FCM was not associated with safety concerns for newborns (N=221) in this study. There were few adverse events (AEs) reported for the newborns and none of these AEs were assessed as related to study treatment. AEs were reported in 9.8% of newborns from the FCM group and in 6.4% of newborns from the oral iron group. Few of these AEs were experienced by more than 1 newborn in this study. AEs reported for >2 subjects overall were as follows: premature baby (FCM: 2.7%; oral iron: 1.8%), meconium stain (FCM: 2.7%; oral iron: 0.0%), and use of accessory respiratory muscles (FCM: 0.9%; oral iron: 0.9%).

One congenital abnormality (congenital foot malformation) was reported in an FCM newborn in this study. This was not considered related to study treatment and no action was taken.

The mean newborn parameters were similar between the groups for all parameters with the exception of the mean and median cord serum ferritin which was slightly higher in the FCM group.

Conclusions of the study

Although the primary efficacy endpoint of this study was not met, treatment of IDA during the second and/or third trimester of pregnancy with IV FCM, using a simplified dosing regimen for iron replenishment based on BW and screening Hb, resulted in higher mean Hb levels at each time point compared to oral iron treatment, with subjects in the FCM group twice as likely to achieve anaemia correction by delivery (p=0.031). Clinically relevant and statistically significant increases in serum ferritin were also observed. QoL assessments, including vitality and social function scores, were also more favourable in the FCM group. Despite a higher frequency of serious TEAEs in the FCM group, the overall tolerability of FCM was similar to oral iron in this study, and the majority of TEAEs were mild in both treatment groups. There were no new or unexpected safety findings in mothers or newborns.

Data Supporting Revisions to Section 4.6 of the EU SmPC

With completion of Study FER-ASAP-2009-01, new data are available for 123 women treated with FCM during the second and/or third trimester of pregnancy.

Based on this new data, the MAH proposes revision of Section 4.6 of the SmPC by deleting the statement, “There are no adequate and well-controlled trials of Ferinject in pregnant women” and inserting the following new statement: “There are limited data from the use of Ferinject in pregnant women.”

Data Supporting the Revisions to Section 4.8 of the EU SmPC

The MAH proposes updates to Section 4.8 of the EU SmPC to amend the information on adverse drug reactions (ADRs) reported post-marketing and in clinical trials for consistency with the most recent Company Core Data Sheet (CCDS) for Ferinject (Version 6.0, dated 23 July 2015).

The CCDS, which serves as the Reference Safety Information (RSI) for assessing listedness of events, was recently fully reviewed and updated based on availability of new clinical trial data (total number of subjects treated with FCM updated to from 6,755 to 7,391) and harmonisation of all treatment-emergent ADRs to Version 15.1 of the Medical Dictionary for Regulatory Activities (MedDRA), and review of ADRs to subsume medically similar preferred terms (PTs) allowing for final frequency classification.

Post-marketing data were also reviewed as supportive data.

The proposed changes to the SmPC and PIL are considered satisfactory.

Conclusion

The efficacy and safety of FCM for the treatment of ID in subjects with systolic CHF has been investigated in 4 randomised, double-blind RCTs. No clinically significant new or unexpected safety concerns were found.

The efficacy and safety of FCM for the treatment of IDA during the second and third trimester of pregnancy was also evaluated in a single multicentre, randomised, open-label, active-controlled study. Based on the data from this single study, although the primary objective was not met, FCM is considered well-tolerated for the treatment of IDA in pregnant women in their second or third trimester. There were also no new or unexpected safety findings in mothers or newborns.

Therefore the benefit/risk ratio for FCM in the treatment of ID/IDA is considered unchanged and favourable.

The proposed changes are considered acceptable, and there are no objections to approval.

In accordance with Directive 2010/84/EU, the SmPC and PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision

Approved on 29 March 2017