Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ferric Carboxymaltose

Proprietary Product Name: Ferinject

Sponsor: Vifor Pharma Pty Ltd

May 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	5 April 2011
Active ingredient(s):	Ferric carboxymaltose
Product Name(s):	Ferinject
Sponsor's Name and Address:	Vifor Pharma Pty Ltd Level 8, 80 Dorcas Street South Bank Melbourne Vic 3006
Dose form(s):	Injection solution (colloidal)
Strength(s):	100 mg iron/2 mL and 500 mg iron/10 mL
Container(s):	Glass vial
Pack size(s):	1 or 5 vials
Approved Therapeutic use:	Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.
Route(s) of administration:	Intravenous
Dosage:	The adequate cumulative dose of Ferinject must be calculated for each patient individually and must not be exceeded (See Dosage and Administration in Product Information)
ARTG Number (s):	162636, 162641

Product Background

This AusPAR describes the evaluation of an application for registration submitted by Commercial Eyes Pty Ltd as an agent to the sponsor (Vifor Pharma Pty Ltd) for Ferinject.

A number of iron preparations have been used in the treatment of iron deficiency for many years. Therapy consists in the replacement of the iron deficit via the oral or parenteral route and treatment of the underlying disease. An optimal parenteral iron preparation needs to be able to effectively deliver iron in a controlled way. The iron should be incorporated into the iron transport and storage proteins (transferrin and ferritin, respectively), without formation of large amounts of "free" unbound iron and, thus, with a reduced risk of toxic reactive oxygen species being formed. To achieve this goal, nearly all parenteral iron products contain iron in a stable ferric state mostly in the form of a polynuclear iron(III)-hydroxide core surrounded by a carbohydrate polymer. These complexes are designed to enable controlled, systemic release of iron within the cells of the reticuloendothelial system (RES), with little risk of release of large amounts of iron in the circulation.

Ferinject has been designed to provide high iron utilisation and to have a better benefit to risk profile than iron dextran and iron sucrose therapy. In the case of iron dextran, a key

risk is the reaction with anti-dextran antibodies leading to the well-known dextran-induced anaphylactic reactions. In the case of iron sucrose, the negative characteristics include the high pH, high osmolarity, low dosage limits (maximum 500 mg iron once per week, not exceeding 7 mg iron/kg body weight [bw]), and the long duration of administration (100 mg iron over at least 5 minutes as an injection; 500 mg iron over at least 3.5 hours as a drip infusion).

The following indication is proposed by the sponsor:

Ferinject is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

The diagnosis must be based on laboratory tests.

Regulatory Status

A similar application has been approved in the European Union (EU) via the Decentralised Procedure (approved March 2006), followed by a Mutual Recognition Procedure for a second wave to include remaining EU member states. The reference member state was the UK. The approved indication in Europe is the same as the proposed indication in this application.

A similar application has been lodged in the USA (June 2006) and Canada (November 2007). The status in these countries is pending.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Introduction

In Australia iron polymaltose injections **(**Aspen's *Ferrum H* and Sigma's *Ferrosig*) and iron sucrose injection (Aspen's *Venofer*) are registered. It appears *Inferon* iron dextran injection and Astra's *Jectofer* iron sorbitol injection were registered in the past. Products are variously administered intravenously or intramuscularly (affecting the *in vivo* release of iron).

Ferinject injection is a colloidal complex of a polynuclear iron(III)-oxyhydroxide core with carboxymaltose ligands.

Intravenous iron preparations are not simple iron solutions. All of them contain colloidal nanoparticles consisting of a polynuclear iron-oxy/hydroxide gel core with a ligand shell of carbohydrates. The sizes of the iron core and ligand chemistry differ between the species; the differences can affect *in vivo* iron release, clearance etc.

Different products may have different safety profiles.[1] The sponsor claims ferric carboxymaltose "*has the advantages of a 'robust and strong' iron complex in giving a slow, controlled systemic release of bioavailable iron to the iron-binding proteins, with little risk of release of free iron*". The application letter claims superiority over iron dextran and faster administration than iron sucrose or iron gluconate in sucrose. It is stated to have a terminal elimination half-life (7-12 hours) between those of iron sucrose (6 hours) and

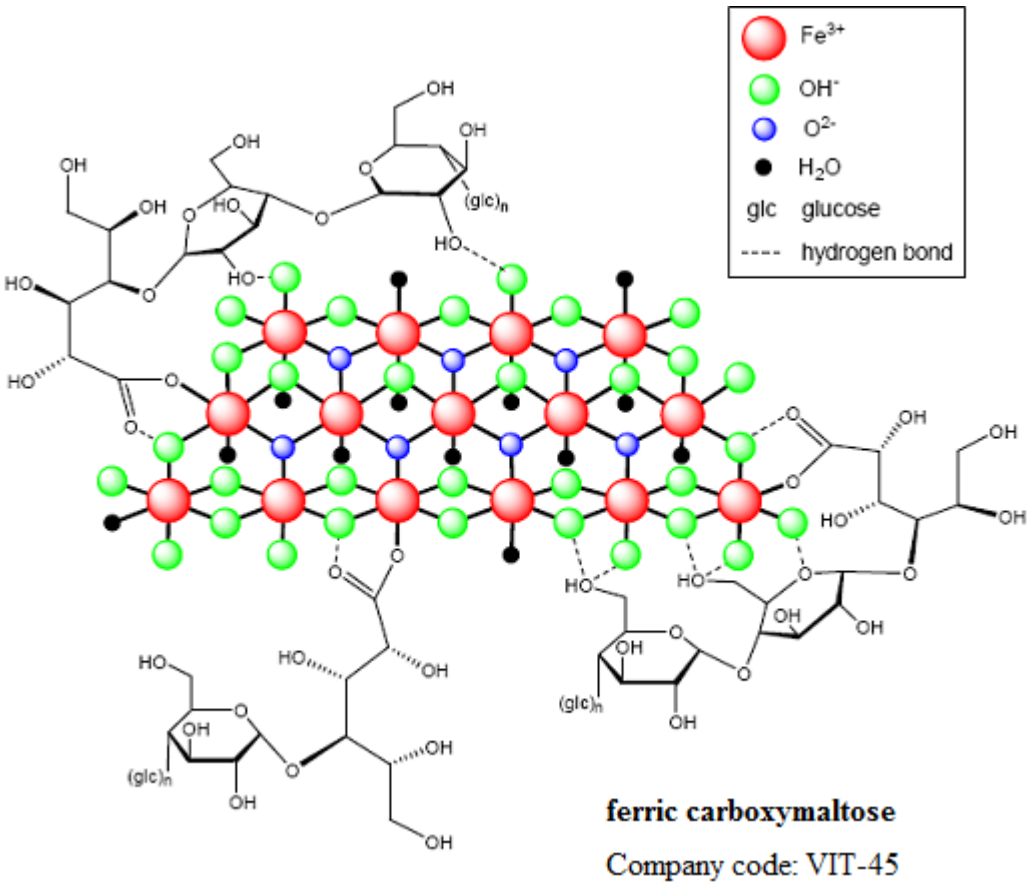
[1] For example: Hayat A. Safety issues with intravenous iron products in the management of anemia in chronic kidney disease. Clin Med Res 2008; 6: 93-102. Available at http://www.clinmedres.org/cgi/content/full/6/3-4/93

iron dextran (3-4 days). The sponsor claims that iron preparations with molecular weights above 100,000 have lower 'undue toxicity' than preparations with lower molecular weights.

Notwithstanding, or because of the nature of the complexes for these iron injections (polymeric compounds), the chemical characterisation and performance controls on these registered products in official standards are limited.

Drug Substance (active ingredient)

Ferric carboxymaltose is a brown, amorphous powder. It is freely soluble in water but insoluble in most organic solvents. It contains 24-32% m/m of iron, 25-50% m/m of 'dextrin', some sodium chloride (<6% m/m), and not more than 10% m/m water. The sponsor describes ferric carboxymaltose as "a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. The relative molecular weight is approximately 150 000 Da". A model for the proposed molecular structure can be depicted as follows:



ferric carboxymaltose

Company code: VIT-45

$[FeO_X(OH)_Y(H_2O)_Z]_n$ $[\{(C_6H_{10}O_5)_m$ $(C_6H_{12}O_7)\}_l]_k$ with n ≈ 10^3, m ≈ 8, l ≈ 11, and k ≈ 4

The control of the dextrin starting material is considered poor. The oxidation process does not appear to be a reaction which will necessarily give a well defined polymer. It is not established that the oxidation process used is necessarily consistent. The oxidised dextrin is not considered well characterised.

The chemical nature of a batch of ferric carboxymaltose is thus dependent on the batch of dextrin, the consistency of control of the oxidation process, and possibly on variables during the colloid formation and its storage. The evaluator did not consider that sufficient

data have been provided to be sure that these aspects will be consistently controlled in future batches.

Drug Product

Both 2 mL and 10 mL Ferinject vials, containing 100 mg or 500 mg of iron (as ferric carboxymaltose) respectively, are proposed for registration. The product is for intravenous administration only (either as a bolus injection, after dilution in 0.9% saline, or during dialysis).

Finished product manufacture simply involves dissolution in hot water for injections, filtration, vial filling and steam sterilisation. The resulting drug product is a dark brown, non-transparent, colloidal solution (5% iron m/v) in water for injections. It contains "not more than 1.4% m/m NaCl" and has a pH between 5.0 and 7.0. The two vials contain different fill volumes of the same solution (5% ≡ 5 g/100 mL Fe).

The finished product manufacturing validation data were not considered sufficient to establish whether there could be relevant variation in iron colloid characteristics (for example, colloidal size) between batches.

Ferinject is not formulated with chloride. Only an *upper* limit for chloride is proposed with no control of osmolarity. The osmolarity is reported to be chiefly dependent on the sodium chloride content. Thus tonicity is not well controlled for use as a bolus injection.

The proposed finished product specifications controlling future batches have very limited controls on the colloidal species, essentially only a gel permeation molecular weight distribution test. Other tests involve assays after decomposition of the complex.

Animal Tests

Some iron injection monographs in the British Pharmacopoeia and in the United States Pharmacopeia include animal tests as routine batch requirements, or direct that the "*method of manufacture is validated to demonstrate that, if tested, the injection would comply with [the test]*". The tests are for '*Absorption from Injection Site*' (pertinent for intramuscular injections) or '*Acute Toxicity*'/'*Undue Toxicity'* (tested via intravenous injections in mice, with observation for deaths).

No such tests are proposed in the Ferinject specifications.

Toxicological advice was sought within the TGA. It was considered that the acute toxicity of ferric carboxymaltose had been characterised in the nonclinical data. Using mouse death was considered an insensitive test for any changes in batch variation. Such tests are outdated and do not meet current standards for acute toxicity testing. *Routine* acute toxicity testing was not considered useful so physico-chemical testing of batches was recommended.

It was unclear what manufacturing controls would be appropriate, or whether there are chemical tests which can obviate such testing. The only pertinent test in the Ferinject specification is the test for molecular weight distribution. The evaluator did not consider that the sponsor has provided sufficient data to establish that this test and limits are adequate for that purpose.

Stability

Stability has been poorly studied. For example the batches of 2 mL vials investigated were made from a single drug substance batch, with the injection batches all made at a manufacturing site not proposed for registration. Dextrin assays appear to be confounded by problems of the accuracy of the assays. The characterisation of stored samples did not test for chemical changes in the colloid except for molecular weight distribution.

Bioavailability

The product is administered intravenously. Bioavailability data are not required for the formulation. Pharmacokinetic data were not reviewed by the quality evaluator.

Pharmaceutical Subcommittee Consideration

The application was considered at the 133rd meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC recommended that there should be no objection on quality and pharmaceutic grounds to approval of the application provided all outstanding issues are addressed to the satisfaction of the TGA.

The Committee considered that the sponsor should be asked to provide:

- Recent batch analyses and updated stability data.
- Information on the particle size of the colloidal iron and the toxicological ramifications of this.

As suggested by the evaluator, the PSC considered that iron carboxymaltose is a more appropriate name for the drug substance.

No updated stability data were provided by the sponsor. The toxicological ramifications of the particle size were considered separately. Given the adoption of ferric carboxymaltose as the international non-proprietary name (INN), this is likely to be adopted as the Australian generic name.

Quality Summary and Conclusions

Registration was not recommended with respect to chemistry and quality control aspects because consistency of the product is not considered assured.

III. Nonclinical Findings

Introduction

A relatively comprehensive package of nonclinical pharmacology, pharmacokinetic and toxicology studies was provided in support of the registration application for ferric carboxymaltose. All pivotal studies were performed according to Good Laboratory Practice (GLP). Toxicity studies were generally performed in an appropriate number and type of animal species. The duration and general conduct of toxicity studies, the selection of dose levels and route of administration were generally appropriate for the investigation of a new chemical entity proposed for intermittent human use. However, it should be noted that a deficiency identified in all toxicity studies was the absence of adequate toxicokinetic data. In the repeat dose toxicity studies, blood was sampled for plasma iron only at 24-48 hours post-dose for clinical chemistry analyses. This is inadequate for a rapidly cleared intravenous (IV) administered substance. Thus, no toxicokinetic data could be utilised for determining clinical safety margins.

Nonetheless, nonclinical studies performed with ferric carboxymaltose adequately characterised the pharmacological and toxicological profile of this drug.

Pharmacology

The nonclinical pharmacology submission for ferric carboxymaltose focused on the primary pharmacodynamic properties of ferric carboxymaltose, namely its ability to deliver iron in an effective manner to the intended target tissue (red blood cells; RBC) in iron deficient animals. Since this was the only inherent pharmacological property of the

compound and the complex was shown to be degraded to simple endogenous molecules *in vitro* (glucose, maltose, maltotriose, maltotetraose and iron), more detailed secondary pharmacodynamic and drug interaction studies were not considered necessary or appropriate. Safety pharmacology studies provided evaluated the effects of ferric carboxymaltose on the central nervous system (CNS), cardiovascular, respiratory and renal systems.

Primary pharmacology

Two GLP compliant primary pharmacology studies were submitted examining the efficiency of ferric carboxymaltose in delivering iron to the RBC in 'anaemic' rats. It is important to note that while both studies maintained rats on an iron deficient diet, only one study employed rats reaching defined anaemia criteria (haemoglobin values <100 g/L for males and <130 g/L for females attained after 3 and 6 weeks, respectively based on strain background data). Despite the defined criteria, methodological difficulties were reported to "preclude producing a marked anaemia in the rats in this study using an iron deficient diet". Given the 12 day acclimatisation period of rats in the second study, significant anaemia in these animals was also unlikely to be attained.

Nevertheless, in both studies, a radiolabelled dose of ^{59}Fe-carboxymaltose at either 35 or 10-20 mg/kg IV was shown to be rapidly cleared from plasma, with 87% (males only employed), 91% (males) and 67% (females) of the administered iron recovered in the RBC four weeks after IV administration, respectively. Overall, these studies demonstrated that ferric carboxymaltose was an effective IV iron preparation at delivering iron to the intended target tissue (red blood cells) in at least partially 'anaemic' rats. The doses employed in these studies were similar to or below the maximum recommended human dose (MRHD) of 15 mg/kg/week on a mg/kg and body surface area (BSA) basis, respectively.

Safety pharmacology

The safety pharmacology package for ferric carboxymaltose included a core battery of GLP compliant studies of the central nervous, cardiovascular, respiratory and renal systems of rats or dogs *in vivo*. All studies were conducted using the clinical (IV) administration route. No studies examining the gastrointestinal system were performed; however this is not considered a significant deficiency.

Ferric carboxymaltose had no remarkable effect on any of the major organ systems investigated in *in vivo* animal models up to 90 mg/kg IV (1-4-fold the MRHD based on BSA). There was clinical, biochemistry and histopathological evidence of iron overload at 90 mg/kg IV in dogs in one of two cardiovascular studies. It is unclear why toxicity was only observed at 90 mg/kg in one study, however it should be noted that animals were investigated more thoroughly in the second study. No adverse effects were observed at 30 mg/kg IV in either study (equivalent to the MRHD based on BSA).

In addition, no remarkable or consistent effects on cardiovascular (electrocardiogram [ECG] and blood pressure) parameters was observed in either the 3 or 6 month repeated dose toxicity studies in dogs at IV doses up to 90 mg/kg/week (3-4 fold the MRHD based on BSA).

Pharmacokinetics

The pharmacokinetic profile of ferric carboxymaltose was characterised, at least to some extent, in two pivotal species (rats and dogs) employed for toxicity testing. Pharmacokinetic studies (examining absorption, tissue distribution and/or excretion) were performed in rats (iron-deficient and normal) and dogs using IV administered ^{59}Fe-carboxymaltose. Tissue distribution/iron utilisation data were also collected as part of a

single IV pharmacology study in anaemic rats with ^{59}Fe-carboxymaltose. An *in vitro* degradation study was conducted to simulate metabolism of ferric carboxymaltose *in vivo*. No repeat dose pharmacokinetic data, conventional toxicokinetic data in repeat dose toxicity studies nor repeat dose tissue distribution studies were performed. However, tissue (liver, spleen and kidney) iron levels were examined in the 3 and 6 month repeated dose toxicity studies in rats and dogs to examine potential cumulative effects. With the exception of the *in vitro* and preliminary studies, all studies were conducted in compliance with GLP. The key findings from the absorption, distribution and excretion (ADE) studies performed in rats and dogs are summarised below:

- After IV administration, radioactivity was rapidly cleared from the plasma in all species with levels being very low or undetectable by 6 hours post-dose in dogs and about 16 hours in rats (normal and iron-deficient). The plasma elimination half-life was short at around 2.0-2.8 hours in rats, 3.1 hours in dogs and 7-12 hours in humans.
- Whole blood radioactivity levels showed a similar fall over the first 24 hours after IV dosing as that seen in plasma but steadily increased thereafter until peak levels were seen at 3-4 weeks post-dose as iron was incorporated into the blood cells.
- The relative uptake of radioactivity into blood cells of rats fed an iron deficient diet was greater than in normal rats, with a corresponding decrease in the fraction of the dose retained in the storage tissues (liver and spleen) of the iron deficient rats.
- A possible gender difference in the utilisation of iron was noted in the rat studies where both genders were examined. However, this may in part have been due to the differing ages and, more importantly, differing anaemic status of the rats used in this study as difficulty was reported in rendering the female rats anaemic through feeding of the iron deficient diet.
- Significant uptake of radioactivity occurred in the liver (between 27-67 % of the administered IV dose within first 7 days), spleen and lymph nodes. In humans, radioactivity from ^{52}Fe/ ^{59}Fe-carboxymaltose was also shown to be distributed to the liver, spleen and bone marrow.
- Virtually no (up to 3%) radioactivity was excreted in the urine or faeces of both species in the 28 day period after IV dosing. There was also negligible renal elimination of administered iron in humans following IV dosing.

Overall, these data showed that ferric carboxymaltose was an efficient iron complex in terms of delivering utilisable iron to the target tissue (blood cells) and the normal storage sites for iron in the body (liver and spleen) in all species examined. Comparison of kinetic and tissue distribution data for ferric carboxymaltose with other iron preparations when administered IV to male rats fed an iron-deficient diet suggest that ferric carboxymaltose behaves in a very similar manner with respect to efficiency and effectiveness of incorporation into blood cells and distribution to the principal storage tissues (Table 1).

Table 1: Kinetic and tissue distribution data for ferric carboxymaltose and other iron preparations

Tissue	% Dose recovered in tissues at 14 days after IV dosing					
	Iron sucrose (Venofer)	Iron polymaltose	Iron Dextran[a]	Iron Dextran (BP/USP)[b]	VIT-45 #	VIT-45 @
Blood	80.2	84.6	65.1	63.6	82.6	79
Liver	5.1	8.5	4.8	2.7	10.8	16.8
Kidney	0.8	0.9	0.7	0.4	1.0	1.0
Spleen	1.2	1.2	3.5	3.9	1.7	2.0
Faeces	2.2	3.0	3.1	3.4	2.5	ND
Urine	1.5	0	0	0.2	0.7	ND
Plasma $t_{½}$ h	1.2	1.2	5.0	5.3	1.5	2.7

ND – not determined
From Vifor study SR-1075/E01
@ From study VFR061/043161
[a] – A preparation containing 5 % w/v iron with up to 6 % w/v dextran.
[b] - A preparation containing 5 % w/v iron with up to 20 % w/v dextran, in accordance with the US and British Pharmacopoeia specifications for iron dextran preparations.

No *in vivo* metabolic analysis was conducted. However, an *in vitro* metabolism study suggests that the carbohydrate ligand part of ferric carboxymaltose is rapidly degraded to simple sugars *in vivo*, largely through the action of the enzyme α-amylase, while iron is cleared. All of the major breakdown products identified (maltose, maltotriose, maltotetraose, glucose) were of limited toxicological concern.

The effect of ferric carboxymaltose on liver CYP450 enzymes was not assessed. Iron loading has been shown to decrease the levels of hepatic P450 cytochromes in rats (Bonkovsky & Lambrecht, 2000).[2]

Toxicology

The toxicological profile of ferric carboxymaltose was characterised by acute toxicity studies in rodents, repeat-dose toxicity studies in rats (≤3 months) and dogs (≤6 months), genotoxicity studies *in vitro* and *in vivo*, reproductive toxicity studies in rats and rabbits, local irritancy studies in rabbits and piglets and an antigenicity study in guinea pigs. Pivotal studies were performed in accordance with GLP, in an appropriate number and type of species, using the intended clinical (IV) administration route. The duration of toxicity studies (≤6 months) and doses selected (based on the maximum tolerated dose (MTD) in pilot or acute studies or maximum feasible dose in definitive studies) were generally considered appropriate for a product intended for potential long term intermittent administration. No carcinogenicity studies were conducted. However, this is acceptable given the chemical structure of the drug and its use as 'replacement' therapy.

[2] Bonkovsky HL, Lambrecht RW. Iron-induced liver injury. *In* Clinics in liver disease *Ed* Herrera, JL. WB Saunders Company, Philadelphia, USA, 2000.

Relative exposure

Conventional toxicokinetic data were not collected for any repeated dose toxicity studies. Blood samples were taken at 24-48 hours post-IV injection for plasma iron (and total iron binding capacity) in both chronically iron deficient rat and dog studies as part of clinical chemistry analyses. Given the rapid plasma clearance of iron (half-life [$t_{1/2}$], 2-3 hours) in both species, it is therefore not unexpected that iron levels at the highest doses employed in any of these studies (90 mg/kg/week) were barely elevated (≤2-fold) over vehicle control values by 1-2 days post-injection. These samples are therefore of limited toxicokinetic relevance. The sponsor has suggested that tissue iron levels may be a more relevant index of total iron exposure in the chronic iron deficient situation than plasma measurements. Tissue (liver, spleen and kidney) iron levels were examined in the 3 and 6 month repeat dose toxicity studies in rats and dogs, respectively. However, while this approach might describe relative exposure and potential for accumulation in the storage organs it does take into account iron incorporated into the red blood cells (target tissue). Tissue iron levels will only reflect part of the animals iron exposure.

Clinical safety margins for ferric carboxymaltose, therefore, were based on body surface area (BSA) comparisons between animal doses employed in pivotal toxicity studies and the maximum recommended human dose (MRHD; 15 mg iron/week). The relative BSA exposures are tabulated in Table 2 with No Observable Adverse Effect Levels (NOAELs) indicated in bold.

Table 2: Relative exposures of species based on BSA

Species	Study details	IV Study Treatment	IV Doses (mg/kg/week)	IV Doses (mg/m^2/week)	Relative BSA exposure
Human	MRHD	once weekly infusion	15	510[1]	-
Rat	Repeat-dose	3 months once weekly infusion	**9** 30 90	**54** 180 540	**0.1** 0.4 1.1
	Repeat-dose	3 months thrice weekly bolus	3 **9** 30 90	18 **54** 180 540	0.04 **0.1** 0.4 1.1
	Repeat-dose	6 months thrice weekly bolus	**3** 9 30	**18** 54 180	**0.04** 0.1 0.4
Dog	Repeat-dose	3 months once weekly infusion	**9** 30 90	**180** 600 1800	**0.4** 1.2 3.5
	Repeat-dose	6 months thrice weekly bolus	3 **9** 30	60 **180** 600	0.1 **0.4** 1.2
Rat	Fertility	7-10 weeks M; 8 weeks F (pre-, during & post-mating) thrice weekly infusion	9 **27**$^{\#}$ **90**$^{\varphi}$	54 **162**$^{\#}$ **540**$^{\varphi}$	0.1 **0.3**$^{\#}$ **1.1**$^{\varphi}$
	Embryofetal	12 days (GD6-17) daily infusion	**21**$^{\#}$ **63**$^{¥}$ 210	**126**$^{\#}$ **378**$^{¥}$ 1260	**0.2**$^{\#}$ **0.7**$^{¥}$ 2.5
	Pre- & postnatal	14 days (GD6-19) daily infusion* → thrice weekly (PPD1-14)	21* **63***$^{\#¥}$ 126*	126 **378**$^{\#¥}$ 756	0.2 **0.7**$^{\#¥}$ 1.5
Rabbit	Embryofetal	14 days (GD6-19) daily infusion	**31.5**$^{¥}$ 63 94.5 126	**347**$^{¥}$ 693 1040 1386	**0.7**$^{¥}$ 1.4 2.0 2.7
	Embryofetal	14 days (GD6-19) daily infusion	7 15.75 **31.5**$^{\#¥}$ 63	77 173 **347**$^{\#¥}$ 693	0.1 0.3 **0.7**$^{\#¥}$ 1.4

[1]Based on a 50 kg person; *Weekly IV dose calculated based on the daily dosing during embryogenesis; $^{\#}$Maternal NOAEL; $^{\varphi}$Fertility/Reproduction NOAEL; $^{¥}$Fetal NOAEL; GD = gestation day; PPD = post-partum day; M= male; F = female; "-" = not applicable

Even at the highest dose administered in each study, relative BSA exposures were generally similar or only slightly higher than (0.4-3-fold) those expected in humans at the maximum recommended dose. It is important to note that while the safety margins were low, these studies were performed in iron-replete animals that bear little relation to the clinical situation whereby ferric carboxymaltose is only intended for patients with proven iron deficiency and the dose is tailored to the individual patient's iron replenishment needs. In these toxicity studies, healthy, normal animals were iron overloaded to varying degrees at all dose levels, so it is therefore not surprising that No Observable Effect Levels (NOELs) could not be determined in any study nor that exposure margins were low such that further dose escalation was generally prevented already by inherent clinical toxicity

at upper dose levels. Similar dose limiting toxicity and associated low clinical safety margins have been observed in toxicity studies of other iron complexes conducted in iron-replete animals.

Toxicity profile

The toxicological profile of ferric carboxymaltose showed the expected pattern of changes associated with iron overload in mice, rats, rabbits and dogs. There was uptake and retention of iron in the cells of the reticulo-endothelial system (RES) in the major storage organs, with toxicity observed only when the RES storage capacity was exceeded and significant accumulation of iron occurred in the tissue parenchyma. In the case of ferric carboxymaltose, toxicity was observed when organ dysfunction occurred as a result of parenchymal iron accumulation. This may have been manifested as adverse clinical signs, reduced body weight gain, food consumption, disturbances in clinical pathology parameters (for example anaemia, prolonged clotting time, elevated serum liver enzymes or decreased albumin indicating liver dysfunction, or increased urea and urinalysis disturbances indicating renal dysfunction), and/or evidence of parenchymal tissue damage at histopathological examination (for example hepatocyte necrosis or fibrosis).

Single Dose Toxicity

The acute IV toxicity of ferric carboxymaltose in rodents and dogs was low. In single IV bolus dose studies in mice and rats, a dose of up to 1000 mg/kg ferric carboxymaltose was generally well tolerated with only transient clinical signs including piloerection and dark and swollen extremities which resolved after 3 days. Also observed were enlarged spleens which are reflective of effective removal and storage of the excess iron by the RES observed at 1000 mg/kg (6-12-fold the MRHD based on BSA). At a lower single IV bolus dose in mice (250 mg/kg), there were no clinical responses to treatment and histological studies showed iron was mainly detected in the liver and the spleen. Nearly all of the iron was localised within the reticulo-endothelial cells in these organs with very little present in the parenchymal cells or evidence of necrosis seen.

Single dose IV infusion studies in rats and dogs showed that a dose of up to 240 mg/kg was generally tolerated (9-fold the MRHD based on BSA). However, the highest doses in these studies (120 and 240 mg/kg) were associated with signs of disturbed liver function (elevated serum transaminases), decreased weight gain, food consumption and/or organ discolouration, suggesting possible exposure of the liver parenchyma to excess iron, resulting in toxicity. Based on these observations, the maximum weekly dose employed in the repeated dose toxicity studies in rats and dogs was limited to 90 mg/kg/week.

Repeat Dose Toxicity

Repeated dose (13 and 26 week) IV toxicity studies in rats and dogs showed clear evidence of toxicity associated with iron overload at dosages of 30 or 90 mg/kg/week (1-4-fold the MRHD based on BSA). In rats, body weight gain and food intake decreased at these doses and there was reduction in red cell parameters observed in both species. The liver was the primary target organ in both species, with alterations observed in serum enzyme activities (alanine transaminase [ALT], aspartate transaminase [AST] and alkaline phosphatase [ALP]). At histopathological examination, widespread iron deposition was observed in several tissues in both species and in dogs, in particular, toxic changes in the liver (perivascular fibrosis and one animal with hepatocyte necrosis at 90 mg/kg/week) were observed 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 60 times that of control animals being recorded at the higher dose level (90 mg/kg/week). Some toxicological changes were also noted in the spleen and kidneys as a result of iron accumulation in these tissues. The ferric carboxymaltose formulation produced no

evidence of local irritation at the injection site in dogs. However, some changes were seen at the injection sites in rats that were possibly associated with the restraint and infusion methods used.

The NOAEL for ferric carboxymaltose in these studies was 9 mg/kg/week in both species after 13 weeks, irrespective of whether ferric carboxymaltose was given as a once weekly infusion or as a thrice weekly bolus injection. NOAEL values after 26 weeks treatment were 3 mg/kg/week and 9 mg/kg/week in rats and dogs, respectively. These values provided no apparent safety margin over the MRHD (based on BSA). Whilst these NOAEL values were below the MRHD, it should be remembered that the toxicity studies were performed in normal healthy, iron replete animals, All the pivotal changes seen at high doses (30 and 90 mg/kg/week) in these studies are well documented effects of iron overload in animals. Moreover, the nature of the changes seen in animals dosed on a repeated basis with ferric carboxymaltose are expected based on data for other approved parenteral iron preparations (such as iron sucrose).

Studies in which other parenteral iron complexes (iron dextran, iron polymaltose or iron sorbitol) given long term to various species (rabbits, dogs, rats and baboons) have all demonstrated a characteristic pattern of liver toxicity and hepatic fibrosis when iron overload has been induced. This follows the initial distribution of the excess iron into cells of RES, then into the parenchymal cells, as seen in the repeated dose toxicity studies with ferric carboxymaltose. The findings in the repeated dose toxicity studies with ferric carboxymaltose are very similar to those reported in identical studies performed with iron sucrose. In both rats and dogs, IV doses of iron sucrose at 30 or 90 mg/kg/week for 13 weeks were associated with reduced weight gain, a macrocytic anaemia and widespread evidence of iron deposition in the reticulo-endothelial system of several tissues. Evidence of hepatocellular toxicity was observed at the high dose level (90 mg/kg/week) in rats and all dose levels in dogs (9-90 mg/kg). As with ferric carboxymaltose, clinical exposure margins at the NOAEL for iron sucrose based on BSA were below the MRHD. Thus, any concerns regarding an apparent lack of a safety margin for ferric carboxymaltose from the repeated dose toxicity studies should be weighed against its intended clinical use as a replacement therapy product. Providing therapy with ferric carboxymaltose is carefully titrated against iron studies monitoring the iron status for individual patients, the apparent lack of a safety margin for ferric carboxymaltose from these studies conducted in healthy iron replete animals should be of no greater toxicological concern than other parenteral iron preparations.

The lack of reversibility of ferric carboxymaltose induced liver and kidney dysfunction at six weeks after completion of dosing in the 26 week toxicity studies is not surprising, given the nature and extent of the iron overload induced. Tissue distribution studies have shown retention of administered iron at 28 days after a single dose and combined with the low turnover rates for storage iron (particularly in iron replete animals). Experimental studies demonstrating the very slow reversal of liver changes in iron overloaded animals (Iancu *et al*, 1985) indicate that it would take many months or years for the iron overload state in animals chronically dosed with ferric carboxymaltose (or any other iron preparation) to be reversed.[3] This lack of reversibility of the toxicity findings is therefore not unique to ferric carboxymaltose.

Genotoxicity and carcinogenicity

Ferric carboxymaltose was tested for potential genotoxic effects in a standard battery of *in vitro* (bacterial reverse mutation, forward gene mutation and chromosomal aberration)

[3] Iancu TC, Rabinowitz H, Brissot P, Guillouzo A, Deugnier Y, Bourel M. Iron overload of the liver in the baboon. An ultra-structural study. J Hepatology 1985; 1: 265-275.

and *in vivo* (mouse micronucleus) test systems. All studies were conducted according to GLP utilising appropriate doses/concentrations. Ferric carboxymaltose was neither mutagenic in bacterial nor mammalian cells *in vitro* nor clastogenic in mouse erythrocytes *in vivo*.

No carcinogenicity studies were conducted with ferric carboxymaltose. According to the TGA-adopted EU guideline on the need for carcinogenicity studies of pharmaceuticals, "carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (that is physiological levels), particularly where there is previous clinical experience with similar products".[4] Given the lack of evidence for genotoxicity, the nature of the ferric carboxymaltose complex, its ready breakdown into innocuous simple sugars as well as its use solely as a replacement therapy product, carcinogenicity studies were not performed. This was considered acceptable.

Reproductive toxicity

A comprehensive reproductive toxicology assessment of ferric carboxymaltose was conducted in rats and rabbits after daily and/or thrice weekly IV administration. All pivotal studies were conducted according to GLP, utilising adequate animal numbers and appropriate high doses (based on toxicity endpoints). Rats and rabbits were considered adequate models for human reproductive toxicity testing. As with other toxicity studies with clinical exposure comparisons based on BSA (see *Relative Exposure* section) no toxicokinetic data were obtained in these studies.

Maternotoxicity was observed in both species given IV ferric carboxymaltose in all reproductive toxicity studies. Doses of 90 mg/kg/week when administered thrice weekly to rats (prior to mating and during early embryonic development) and from 9 mg/kg/day when given to rats or rabbits during organogenesis and/or during post-partum periods were associated with clinical signs of weight loss, reduced food consumption, and/or necropsy findings consistent with iron overload toxicity. NOAELs for maternotoxic effects were below (0 .2-0.7-fold)) the MRHD, based on BSA in all studies.

There were no effects on fertility or reproductive performance in rats given IV doses up to 90 mg/kg/week (1.1 times the MRHD, based on BSA). In embryofetal development studies, fetotoxic effects (decreased weights, increased resorptions and/or increased implantation loss) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV doses from 9 or 30 mg/kg/day in rabbits and rats, respectively given during embryogenesis (1.4- and 2.5 times the MRHD, based on BSA, respectively; at the NOAEL, doses were 0.7 times the MRHD, based on BSA). The types of skeletal changes seen (for example thickened/kinked ribs in rat fetuses, unossified phalanges in rabbits) are generally regarded as temporary disturbances of maturation of the skeleton and are commonly reported findings at maternally toxic dose levels in rodent embryo-fetal toxicity studies (Khera, 1985; Nishimura *et al*, 1982).[5,6] In addition, skeletal abnormalities have been reported for other parenteral iron preparations including iron poly(sorbitol-gluconic acid) complex (Flodh *et al*, 1977).[7] Thus, an inability to replicate these skeletal

[4] pp. 73 - 78 of the Rules Governing Medicinal Products in the European Union - EudraLex - Medicinal products for human use, 1998 Edition: Volume 3B - Safety and the Environment - 3BS8A. The Need for Carcinogenicity Studies of Pharmaceuticals.

[5] Khera KS. Maternal toxicity: A possible etiological factor in embryo-foetal deaths and foetal malformations in rodent-rabbit species. Teratology 1985; 31: 129-153.

[6] Nishimura M, Izuka M, Iwaki S, Kast A. Repairability of drug-induced wavy ribs in rat offspring. Arznei Forsch Drug Res 1982; 32: 1518-1522.

[7] Flodh H, Magnusson G, Malmfors T. Teratological, peri- and post natal studies on Ferstral, and iron poly (sorbitol-gluconic acid) complex. Scand J Haematol 1977; 32 (suppl.): 69-83.

abnormalities in a second rabbit embryofetal development study using a lower dose range, together with the skeletal changes seen in another species (rats) as well as evidence of similar findings in other parenteral preparations would argue for a likely treatment relationship. Placental transfer of administered iron was also demonstrated in rats. Caution should therefore be exercised when ferric carboxymaltose is used in pregnant women.

In the pre- and post-natal development study in rats, reduced fetal bodyweight gain was observed in the offspring of rats given IV ferric carboxymaltose at 18 mg/kg/day during organogenesis and 18 mg/kg thrice weekly during post-partum days 1-14 (1.5 times the MRHD, based on BSA; at the NOEL, the dose was 0.7 times the MRHD, based on BSA). Milk transfer of administered iron was also demonstrated in rats. Caution should therefore be exercised when ferric carboxymaltose is used in lactating women.

Use in children

No toxicity studies were conducted in neonatal or juvenile animals. It was noted that the product is not intended to be used in patients under 14 years.

Local tolerance

Local tolerance studies performed in rabbits and piglets demonstrated that the clinical formulations of ferric carboxymaltose (5% or 10%) are relatively well tolerated by the intended IV dosing route and accidental exposure routes (peri-venous (PV) or intra-arterial (IA)).

Antigenicity

Ferric carboxymaltose did not cross react with anti-dextran antibodies in a guinea pig passive cutaneous anaphylaxis (PCA) study suggesting that it may be acceptable to administer this product to patients that have previously been sensitised to iron dextran. The structure and breakdown products of ferric carboxymaltose also suggest it is unlikely to be immunogenic in its own right.

Nonclinical Summary and Conclusions

Two primary pharmacology studies in partially iron deficient rats demonstrated effective delivery of iron to red blood cells at doses less than or similar to the MRHD (based on mg/kg or BSA, respectively).

Ferric carboxymaltose had no effect on the central nervous, cardiovascular, respiratory and renal systems of rats or dogs *in vivo* at single IV doses up to 90 mg/kg (1-4-fold the MRHD, based on BSA).

Pharmacokinetic studies in rats, dogs (pivotal species used in toxicity testing) and humans suggest that ferric carboxymaltose has a relatively short plasma half-life ($t_{1/2}$: 2.0-2.8 hours in rats, 3.1 hours in dogs and 7-19 hours in humans, respectively) and is rapidly distributed from the blood to the RBC and iron storage tissues. There was negligible excretion of administered iron in all species. An *in vitro* metabolism study indicated that the anticipated carbohydrate breakdown products of ferric carboxymaltose following IV administration *in vivo* are simple sugars and, therefore, unlikely to be of toxicological concern.

The acute IV toxicity of ferric carboxymaltose in rodents and dogs was low. Single IV bolus doses of up to 1000 mg/kg in rodents and IV infusions of up to 240 mg/kg in rats and dogs were tolerated.

The repeated dose IV toxicity of ferric carboxymaltose in rats and dogs showed the expected pattern of iron overload toxicity consistent with that of other parenteral iron

preparations. Toxicity was observed at doses of 30 and 90 mg/kg/week in rats and dogs, principally impaired hepatic function and histopathological changes in the liver and evidence of macrocytic or non-regenerative anaemia. Some adaptive changes were also noted in the spleen and kidneys as a result of iron accumulation in these tissues. The NOAEL was 9 mg/kg/week in both species over 13 weeks, and 3 mg/kg/week and 9 mg/kg/week in rats and dogs, respectively after 26 weeks treatment. Whilst these NOAEL values were below the MRHD (based on BSA), any concerns regarding an apparent lack of a safety margin for iron toxicity of ferric carboxymaltose should be weighed against its intended clinical use as a replacement therapy product only. Thus, it was recommended that careful calculation of the required iron dose be performed in each patient administered ferric carboxymaltose and response to therapy be carefully monitored to prevent iron overload occurring.

Ferric carboxymaltose was neither mutagenic nor clastogenic in an adequate battery of genotoxicity assays.

No carcinogenicity studies were conducted with ferric carboxymaltose. However, this is acceptable given the chemical structure of the drug and its use as 'replacement' therapy.

There were no effects on fertility or reproductive performance in rats given IV doses up to 90 mg/kg/week (1.1 times the MRHD, based on BSA). In embryofetal development studies, fetotoxicity and increases in fetal skeletal abnormalities were observed at maternally toxic IV doses from 9 or 30 mg/kg/day in rabbits and rats, respectively given during organogenesis (1.4 and 2.5 times the MRHD, based on BSA, respectively). In the pre- and post-natal development study in rats, reduced fetal bodyweight gain was observed in the offspring of rats given IV ferric carboxymaltose at 18 mg/kg/day during organogenesis and 18 mg/kg thrice weekly during post-partum days 1-14 (1.5 times the MRHD, based on BSA). Although limited, significant placental and milk transfer of administered iron was demonstrated in rats. Reproductive toxicity studies highlighted embryofetal, pre- and post-natal effects of ferric carboxymaltose at maternotoxic doses which provided no apparent safety margin. This suggests its use in pregnancy should be avoided unless clearly necessary.

Local tolerance studies in rabbits and piglets demonstrated that the ferric carboxymaltose formulation is relatively well tolerated by the IV route and that misadministration (via peri-venous or intra-arterial routes) is unlikely to result in significant irritation.

Ferric carboxymaltose does not cross react with anti-dextran antibodies suggesting that it may be acceptable to administer this product to patients that have previously been sensitised to iron dextran.

There were no nonclinical objections to the registration of ferric carboxymaltose (ferric carboxymaltose) for the proposed indication provided the clinical evaluator is satisfied with the proposed dosing and monitoring regime for ferric carboxymaltose to ensure iron overload does not occur.

IV. Clinical Findings

Introduction

The aim of the clinical program was to demonstrate the safety and efficacy of parenteral ferric carboxymaltose (FCM) in the treatment of iron deficiency anaemia (IDA). The following clinical data were gathered:

- Data on ferrokinetics and iron utilisation and preliminary safety data in patients

- Dose finding studies to provide data on pharmacokinetics, pharmacodynamics (efficacy) and safety after single and multiple dose administration in iron deficiency patients

- Confirmatory clinical studies generating data on the efficacy and safety of ferric carboxymaltose in appropriate iron deficiency anaemia patient populations.

Studies submitted for evaluation included three Phase I/II studies (with IV administration of ferric carboxymaltose) in patients with IDA or renal anaemia. One of these studies was of double-blind, placebo-controlled design. The aim of these studies was to determine the pharmacokinetics, red blood cell (RBC) utilisation and the optimum dose regimen to be taken forward into the Phase III studies. Bioavailability was assessed in one Phase I/II study (VIT-IV-CL-001).

The Phase III program on FCM in IDA of different aetiologies comprised ten studies undertaken in patients with IDA associated with regular haemodialysis, IDA associated with non-dialysis dependent chronic kidney disease, IDA secondary to inflammatory bowel disease (IBD) or heavy uterine bleeding, post-partum IDA and IDA in patients with chronic heart failure and iron deficiency.

During development ferric carboxymaltose was known as VIT-45 and has been described as such in all tables and in the case study reports. In this evaluation VIT-45 will also be used to refer to ferric carboxymaltose. The studies will be referred to by the last digits in their titles eg study VIT-IV-CL-02 will be referred to as study 02.

All studies were conducted in accordance with International Council on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). The dosing in all studies was based on the individual iron deficit requirements, as established at baseline. Clinically, the efficacy of iron replacement therapy is reflected in terms of changes in haemoglobin (Hb) levels and replenished iron stores.

Pharmacodynamics

Study VIT-IV-CL-02

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 IV doses of iron as iron carboxymaltose (VIT-45) at iron doses ranging from 100 to 1000 mg 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)
- 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), % transferrin saturation ($TSAT_{post}$), Hb, reticulocyte count and soluble transferrin receptor (sTfR) concentration.

In addition, safety parameters were assessed.

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 IV

administration of VIT-45 or placebo in the fasted state each morning, starting on Day 1. The doses under investigation were 100 mg, 500, 800, and 1000 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 Hb levels and body weights (bw) 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:

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

* 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 100 mg iron as VIT-45 undiluted within one 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 IV 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.

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 TSAT<16% were eligible for enrolment. The four dose groups were well balanced with regards to demographic characteristics. Most of the included patients were female (N=30; 94%), while only 2 male patients (6%) participated in the study. Hb 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 TSAT>16%, all patients complied with the inclusion criteria for this study.

Pharmacodynamic results

Pharmacodynamic results from this study will be presented in this section and pharmacokinetic results will be presented in the next section.

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 1000 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 in Table 3.

Table 3: Study 02 - Pre-dose and maximum serum ferritin concentrations after administration of VIT-45

Serum ferritin	Statistics	Treatment / Iron as VIT-45 (mg)				
		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

max. = maximum; SD = standard deviation

Transferrin levels showed a trend towards lower concentrations after IV administration of different doses of VIT-45, compared to pre-dose levels. These changes were also seen in the placebo group. The overall decline in all treatment groups was small and changes were not clinically relevant and no clear relationship with treatment was noted. Transferrin receptor (TfR) concentrations showed minor fluctuations after IV application of VIT-45 and no clear trend was observed.

Administration of VIT-45 led to a steep decline in unsaturated iron binding capacity (UIBC), in particular after the 800 mg and 1000 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 mg and 1000 mg groups. 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 mg and 1000 mg groups.

The percentage of transferrin saturation (TSAT) was clearly increased following VIT-45 injection, while no changes were observed after placebo dosing. Maximum changes from baseline after 24 to 36 hours of treatment are summarised in Table 4. At these assessment points, TSAT 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 1000 mg iron as VIT-45) of the protein was still utilised for iron binding at the end of the observation period.

Table 4: Study 02 – Maximum mean changes in transferrin saturation from baseline at 24 to 36 hours after administration of VIT-45

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

max. = maximum; SD = standard deviation

Hb 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. Hb 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 eight days after dosing (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 post-study visit compared to 12% in the placebo group.

Study VIT-IV-CL-03

This Phase I/II study was a multicentre, open-label, uncontrolled multidose study. The study objectives were to evaluate safety and tolerability of VIT-45 following IV administration of 500 mg (Cohort 1) or 1000 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 Hb 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

Treatment began with the first dose of VIT-45 (Day 1). In Cohort 1, all patients received 500 mg iron as VIT-45 IV infusions, once weekly for up to 4 weeks. In Cohort 2, all patients received 1000 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. VIT-45 was infused IV over 15 minutes into a peripheral vein at a total volume of 250 mL.

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 1000 mg were eligible for enrolment. At least 50% of patients in each cohort should require ³ 1500 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 Hb 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. Thirty-six females were included, 15 in Cohort 1 and 21 in Cohort 2, while only 10 men in total were enrolled (5 per cohort). All patients reported a medical history in the abdominal and GI system, as expected for this patient population. Serum iron, Hb and serum ferritin levels were below NR in both cohorts. TSAT levels were below normal range (NR) and transferrin levels were generally within or above the limits of NR, as expected for patients with IDA.

Pharmacodynamic results

Pharmacokinetic results will be discussed in the next section. At baseline, almost all patients had Hb levels below the lower limit of the NR. At all time points from Day 7 onwards, mean Hb levels were elevated compared to baseline in both cohorts (Table 5).

By Day 14, 27% and 44% of patients, respectively, in Cohorts 1 and 2 had achieved a ³ 20 g/L increase in Hb on at least one occasion. Mean Hb 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 time point, 37% and 48% of patients, respectively, had achieved normal Hb levels, and 75% and 73%, respectively, in Cohorts 1 and 2 had achieved a ³ 20 g/L increase in Hb on at least 1 occasion. Over 97% of patients showed a medicinally meaningful response in terms of Hb level increase.

Table 5: Study 03 - 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]

NR=140-180 g/L for males, 120-160 g/L for females

In both cohorts, serum ferritin increased rapidly from baseline and was significantly elevated at all time points from Day 4 onwards (Table 6). Mean serum ferritin values were within the target range of 100-500 mg/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.

Table 6: Study 03- 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]

NR=20-500 µg/L

At screening, all but one patient had TSAT values below the lower limit of NR (<16%). In both cohorts, serum TSAT 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 TSAT values were 41% and 39.1% for Cohort 1 and 2, respectively (NR: 16-45%).

Evaluator comment

Analysed parameters showed a trend towards normalisation during the treatment period. Hb 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 Hb levels. Serum ferritin and TSAT values showed that iron stores were successfully filled up during study participation.

Pharmacokinetics

Biopharmaceutic studies

Study VIT-IV-CL-001

This Phase I/II study was an open-label, controlled isotope the objective of which was to assess iron pharmacokinetics after a single IV dose of VIT-45 labelled with $^{52}Fe/^{59}Fe$ as a tracer in patients with IDA or renal anaemia. Primary variables were the distribution of ^{52}Fe and incorporation of ^{59}Fe into RBCs. In addition, parameters of iron status and safety parameters were assessed. The study medication was administered as an IV injection bolus of 20 mL, containing 100 mg iron as ^{52}Fe and ^{59}Fe-labelled VIT-45, delivered over 10 min using a constant infusion pump.

Three patients with IDA and 3 patients with renal anaemia were selected for the study. Main criteria for inclusion were haemoglobin (Hb) concentrations between 90 and 130 g/L, serum ferritin <30 µg/L (IDA patients) or <200 µg/L (patients with renal anaemia), serum cyanocobalamin <115 pmol, serum folate <3.7 nmol/L, serum aluminium <20 µg/L, and age between 18 and 75 years.

Pharmacokinetic results

Pharmacokinetic evaluation of VIT-45 showed a rapid distribution in the circulation. During the observation 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 tissues) reflects its safety. Incorporation of radioiron into RBC increased rapidly during the first 6 to 9 days indicating the potential efficacy of VIT-45 in iron supplementation treatment. After 24 days, iron utilisation was greater in IDA (91-99%) than in renal anaemia patients (61-84%). The transient increase in serum ferritin levels illustrated the replenishment of the depleted iron stores. VIT-45 was generally well-tolerated.

Clinical pharmacology studies

Study VIT-IV-CL-02

The study objectives, design and patient population were described in the previous section.

Pharmacokinetic results

Pharmacokinetic parameters of total serum iron are summarised in Table 7. 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 time to maximal serum concentration (T_{max}) that was approximately 1 hour or longer at doses of 800 to 1000 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. The maximal serum concentration (C_{max}) and the area under serum concentration time curve (AUC) increased with ascending doses in a non-proportional manner, in particular regarding AUC. Based on non-compartmental analysis, mean residence time (MRT) was less than 24 hours on average. The study drug was cleared from serum with a $t_{½}$ 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).

Table 7: Study 02 - Pharmacokinetic parameters of total serum iron (168 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-t} (µg•h/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} (µg•h/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} (µg•h/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)

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 1000 mg groups, to better characterise the pharmacokinetic profile of total serum iron after IV injection/infusion, thereby excluding a "new" post-treatment baseline after replenishment of the iron stores. Estimates for $t_{½}$ (7.4-12.1 hours), MRT (11.2-16.6 hours), the volume of distribution at steady state ($V_{d,ss}$) and the volume of distribution based on trapezoid AUC (area) and elimination rate ($V_{d,area}$) were slightly lower compared to non-truncated data. The elimination pattern for VIT-45 appeared to be mono-exponential. Two elimination phases, as required by the 2-compartment model, could not be separated if the post-treatment baseline was excluded from consideration. Therefore, a calculation by the 2-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, hence the true amount and renal clearance of total iron could not be reliably determined.

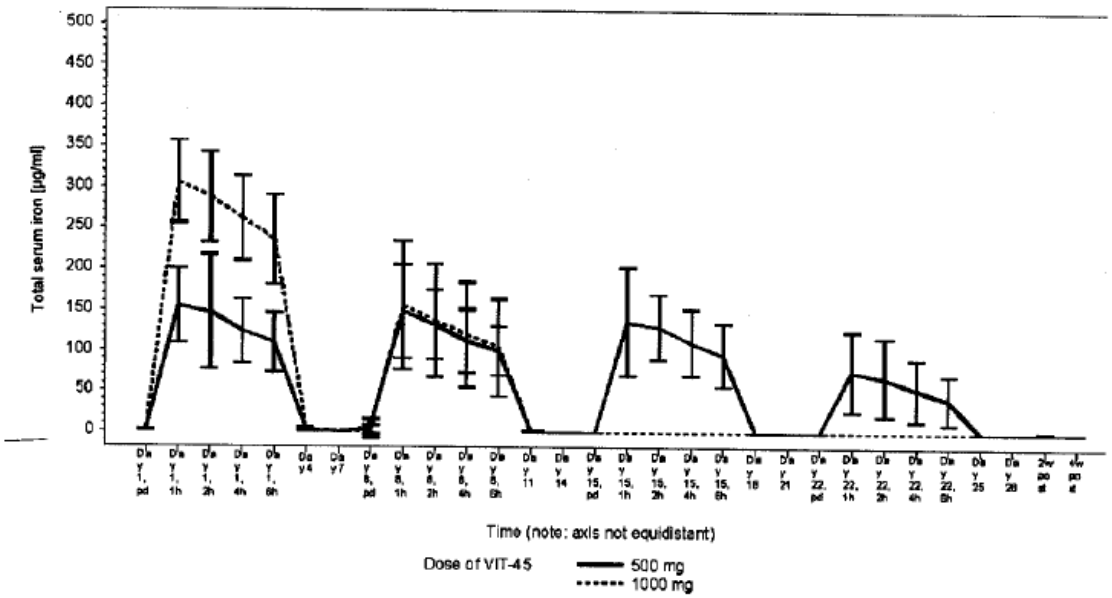
Study VIT-IV-CL-03

The study objectives, design and patient population were described in the previous section**.**

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 IV 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 (Figure 1). Mean serum iron levels in Cohort 2 were almost double compared to those in Cohort 1, reflecting the larger doses given in this group (1000 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).

Figure 1: Study 03- Mean (SD) total serum iron in blood over time (full analysis set)



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.

Evaluator Comment

In this study, at all times, serum iron levels immediately prior to the next dosing stayed within the NR and did not increase with repeated infusions, demonstrating that administration of VIT-45 did not result in accumulation of serum iron.

Study 1VIT05006

This Phase III study was a multicentre, randomised, blinded, placebo-controlled, crossover multiple dose study to investigate the safety and tolerability of VIT-45 in patients with IDA. In addition 12 subjects were enrolled in an unblinded and non-randomised, pharmacokinetic arm of the study investigating the pharmacology following single IV doses of VIT-45 at iron doses of 1000 mg in IDA, post partum.

On Day 0, patients received an unblinded dose of 1000 mg of iron as VIT-45 over 15 minutes intravenously in 250 mL normal saline.

The pharmacokinetic endpoints were:

· Total serum iron levels at approximate time of T_{max} and at trough time points

· C_{max}

· T_{max}

· The area under the serum concentration curve from time zero to the last sampling time ($AUC_{0\text{-time last measured conc.}}$)

· The extrapolated area under the serum concentration time curve from zero to infinity ($AUC_{0-\infty}$)

· Half-life ($t_{1/2}$) estimate

· The apparent serum clearance (CL).

These parameters were to be assessed based on total serum iron concentrations.

The study was conducted in 12 female, post-partum patients. Patients ≥18 years, ≥66 kg with IDA, defined as Hb ≤120 g/L within the 3 months prior to and at the screening visit, serum ferritin< 100 ng/mL, and TSAT< 25%, were eligible for enrolment.

Pharmacokinetic results

A summary of pharmacokinetic parameters for total serum iron concentrations is presented in Table 8. All 12 patients completed the study. Two subjects were excluded from the analysis due to a pre-dose outlier value (> 150 times that of other subjects) and missing data at Hours 2 and 4, respectively. The mean pre-dose total serum iron concentration was 46.8 mg/dL. Following VIT-45 dosing, a rapid increase in (total) serum iron levels was seen. Mean peak concentrations (C_{max}) were approximately 21,987 mg/dL (219.9 mg/dL) for baseline corrected and 22,034 mg/dL (220.3 mg/dL) for measured total serum iron and were associated with a coefficient of variation of 18.2% for both baseline corrected and measured serum iron values.

The elimination half-life calculated from baseline corrected serum iron was 22.8 (±2.7) hours. Serum clearance values showed limited variation, ranging from 1.4 to 4.2 dL/h (2.3 to 7.0 mL/min), with a median value of 2.15 dL/h (±1.76) (3.58 mL/min).

Table 8: Pharmacokinetic parameters with summary statistics for total serum iron in 10 patients after VIT-45 administration IV in Study 1VIT05006

Parameter	Baseline corrected	Measured Total Serum Iron
C_{max} [µg/dL]		
Mean±SD	21,987.2 ± 4003.09	22,034.0 ± 4012.09
Min	15526	15550
Max	29101	2914018.2
CV [%]	18.2	
AUC_{0-t} [µg•h/dL]		
Mean±SD	518,159.00 ± 162,201.378	543,889.45 ± 169,067.852
Min	236,680.1	246,063.0
Max	710,055.6	740,247.2
CV [%]	31.3	31.1
$AUC_{0-\infty}$ [µg•h/dL]		
Mean±SD	521,555.93 ± 163,572.253	-
Min	238,223.0	-
Max	711,597.9	-
CV [%]	31.4	-
$T_{1/2}$ [h]		
Mean±SD	22.784 ± 2.7212	-
Min	18.76	-
Max	27.0	-
CV [%]	11.9	-
CL [dl/h]		
Mean±SD	2.154 ± 0.8810	-
Min	1.41	-
Max	4.20	-
CV [%]	40.9	-

CV = coefficient of variation

Efficacy

Introduction

Studies were conducted in patients with the following conditions:

- Chronic renal failure (CRF) – study 53214 and VIT-IV-CL-015
- Non-dialysis dependent chronic kidney disease (NDD-CKD) – 1VIT04004 and 1VIT05005 (long term safety extension of 1VIT04004)
- Congestive heart failure (CHF), renal failure, iron deficiency – FER-CARS
- Inflammatory bowel disease – VIT-IV-CL-008
- Post-partum – VIT-IV-CL-009, 1VIT03001, 1VIT06011
- Secondary to heavy uterine bleeding (HUB) – 1VIT04002/4003

Studies in chronic renal failure

Study 53214: Open-label, single-arm study

Study 53214 was a multicentre, open-label, single-arm, multiple dose Phase II study in patients on haemodialysis with iron deficiency anaemia (IDA) associated with chronic renal failure (CRF). The primary objective of this study was to evaluate the safety of intravenous VIT-45 therapy. The secondary objective was to assess the efficacy of

intravenous VIT-45 therapy in terms of the correction of iron deficiency and Hb concentration in these patients.

Patients had a therapeutic period for a maximum of up to 6 weeks and an observation period for one month after the last study medication administration. They received 200 mg iron (4 mL of VIT-45) at the applicable haemodialysis session. The cumulative dosage was determined according to the patient's individual iron requirement using the formula of Ganzoni. The maximal cumulative dose was limited to 2400 mg of iron.

Main criteria for inclusion were as follows:

- Male and female patients with IDA undergoing maintenance haemodialysis.

- 18-65 years of age (inclusive)

- Iron deficiency anaemia defined as: Hb ≤110 g/L and TSAT < 20% or serum ferritin ≤200 µg/L.

- Clinically stable, without a history of admission to hospital due to renal decompensation during the 4 weeks preceding the inclusion date.

- Patients who were being treated with erythropoietin (EPO), should have received this treatment for at least one month prior to inclusion in the study and had to remain on stable doses during participation in the study.

- Permanent vascular access appropriate for haemodialysis.

Efficacy endpoints

Efficacy was assessed through the correction of iron deficiency and Hb concentration of the patient. Variables measured every 2 weeks included: Hb, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), serum iron, serum transferrin, serum ferritin and transferrin saturation (TfS). Treatment responders were defined as patients who had an increase of Hb > 10 g/L from baseline at any point during the study.

Statistical methods

Descriptive statistics included N, Mean, Standard Deviation (SD), Standard Error of the Mean, Minimum (min), Lower Quartile, Median, Upper Quartile, Maximum (max). For categorical data summary, frequency tables present N and percentages. Since this was a one armed study, statistical summaries were presented (if not specified differently) without stratification. Analysis was done on observed values. Missing values were not replaced.

Study population

The date of screening for the first patient enrolled was 16 July 2003, and the last patient observation during the follow-up on 11 May 2004. A total of 163 patients were enrolled into the study and included in the Safety set (SS). One patient did not receive study medication, therefore the full analysis set, which was used for the efficacy results, consisted of 162 patients. A total of 162 patients comprised the Full Analysis set (FAS) and 157 patients were enrolled in the Per Protocol set (PPS).

A total of 150 patients (92.0%) in the SS and FAS completed the study, while 147 patients (93.6%) in the PPS completed the study.

A total of 159 patients (98.1%) had an ongoing medical/surgical history. The most commonly reported histories were in the cardiovascular system (139 patients [85.8%]), as arterial hypertension is the most common complication of chronic renal disease and is a major risk factor for other cardiovascular disease. The next most commonly reported

histories were in the endocrine and metabolic systems (60 patients [37.0%]) and genitourinary system (33 patients [20.4%]).

Efficacy results

Haemoglobin

Hb values over time and change from baseline for the intent to treat (ITT) set are summarised in Table 9. Mean Hb levels increased from baseline to 2 weeks post-baseline during the therapeutic period and continued to slowly increase during the observation and follow-up period. The mean change from baseline was > 10 g/L for all visits from 4 weeks post-baseline onwards, indicating a meaningful response in Hb increase.

Table 9: Haemoglobin over time and change from baseline (ITT set, Study 53214)

	Baseline	Therapeutic period[a]	Observation period[b]	Follow-up[c]
N	159	129	157	152
Hb [g/L] (Mean [95% CI])	90.6 [88.6; 92.6]	94.8 [92.5; 97.2]	100.7 [98.4; 103.0]	103.2 [100.6; 105.8]
Hb change from baseline [g/L] (Mean [95% CI])	-	5.3 [4.0; 6.7]	10.1 [8.2; 11.9]	12.4 [10.1; 14.7]

[a] 2 weeks after first study medication administration
[b] 2 weeks after last study medication administration
[c] 1 month after last study medication administration (end of observation period)

In patients with chronic renal failure the target range for Hb is 110-130 g/L. In many centres patients are maintained at lower Hb levels (for example in a range of 100-120 g/L) because of economic issues (high price of EPO medications). In this study, treatment with VIT-45 resulted in an increase of the mean Hb level in participating patients and reached a range slightly below the internationally recommended target level but in a range acceptable to many clinicians. It should be noted that the EPO dose was stable in study participants and the increase in Hb was not due to increase in EPO dose.

Treatment responders were defined as patients with a Hb increase by ≥10 g/L from baseline at any point during the study. A total of 100 patients (61.7%) were classified as treatment responders. This indicates that the majority of patients experienced a medically significant increase in Hb values after start of treatment with VIT-45.

Serum ferritin

Mean serum ferritin levels increased from baseline to 2 weeks post-baseline during the therapeutic period, then slowly decreased during the observation and follow-up periods. The target range for serum ferritin in dialysis patients is 100-800 µg/L. The mean serum ferritin, which was suboptimal at baseline (67.31 µg/L), was moved into the target range within 2 weeks after start of study medication and remained in the target range up to the last follow-up visit.

Serum transferrin

Serum transferrin values over time are summarised in Table 10. Mean serum transferrin levels decreased from baseline to 2 weeks post-baseline during the therapeutic period, and remained below baseline value during the observation period and post treatment follow-up. The decrease of serum transferrin in this study can be interpreted as a sign of successful iron treatment.

Table 10: Serum transferrin over time (ITT set, Study 53214)

	Baseline	Therapeutic period[a]	Observation period[b]	Follow-up[c]
N	145	125	139	141
Serum transferrin [g/L] (Mean [95% CI])	2.31 [2.24; 2.39]	1.89 [1.82; 1.95]	1.75 [1.69; 1.80]	1.71 [1.66; 1.76]

[a] 2 weeks after first study medication administration
[b] 2 weeks after last study medication administration
[c] 1 month after last study medication administration (end of observation period)

Serum transferrin saturation

Transferrin saturation (TSAT) increased from baseline to 2 weeks post-baseline during the therapeutic period, and then decreased slightly, but remained elevated during the observation period and post treatment follow-up. The target range for TSAT in dialysis patients is 20-50%. The mean TSAT, which was suboptimal at baseline (17.36%), was moved into the target range within 2 weeks after start of study medication and remained in the target range up to the last follow-up visit.

Serum iron

As shown in Table 11, the mean serum iron levels increased considerably from baseline to 2 weeks post-baseline during the therapeutic period, then decreased, but remained elevated during the observation period and the post treatment follow-up period. Mean serum iron levels were within the normal ranges (NR males 9.5-29.9 µmol/L, females 8.8-27.0 µmol/L) for all visits after baseline. The increase in serum iron levels demonstrates the effects of successful iron treatment.

Table 11: Serum iron over time (ITT set, Study 53214)

	Baseline	Therapeutic period[a]	Observation period[b]	Follow-up[c]
N	146	125	139	141
Serum iron [µmol/L] (Mean [95% CI])	8.98 [8.12; 9.85]	16.12 [14.83; 17.41]	12.85 [12.06; 13.64]	11.87 [11.15; 12.58]

[a] 2 weeks after first study medication administration
[b] 2 weeks after last study medication administration
[c] 1 month after last study medication administration (end of observation period)

Mean corpuscular volume (MCV)

Mean MCV increased very slowly but steadily throughout the course of the study and the follow-up period. The values were within the NRs for all visits (82-98 fL).

Mean corpuscular haemoglobin (MCH)

Mean MCH increased very slowly, but steadily throughout the course of the study and the follow-up period (NR 27-33 pg).

Mean cell haemoglobin concentration (MCHC)

Mean MCHC increased very slowly but steadily throughout the course of the study and the follow-up period (NR 31-35 g/L).

Evaluator comment

In study 53214 the efficacy parameters showed that IV iron supplementation with VIT-45 was successful in anaemic haemodialysis patients. The majority of patients achieved a medically significant increase in Hb during study participation, and serum ferritin and TSAT values showed that iron stores were successfully repleted. Mean serum ferritin and TSAT values, which were below the target range at baseline, were moved into the target range within 2 weeks after start of therapy with VIT-45 and remained in the target range up to the last follow-up visit.

Study VIT-IV-CL-015

Study VIT-IV-CL-015 was a multicentre, open-label, randomised, parallel-group, Phase III study in patients on haemodialysis or haemodiafiltration with IDA secondary to chronic renal failure. The primary objective of the study was to compare the efficacy of VIT-45 injections and Venofer (iron-sucrose complex formulation for parenteral use) injections in patients on haemodialysis with IDA associated with chronic renal failure. The secondary objectives were to compare the safety of VIT-45 injections and Venofer injections in patients on haemodialysis with IDA associated with chronic renal failure.

At baseline, eligible patients were randomised (1:1) to receive VIT-45 or Venofer. Randomisation was stratified according to screening haemoglobin (Hb) concentration (≤100 g/L or >100 g/L to ≤115 g/L) and by country. Patients were assigned to 200 mg iron (except for the final dose, which may have been 100 mg iron depending on the individual iron deficit) as intravenous (IV) VIT-45 or Venofer two or three times weekly (depending on the timing of dialysis sessions), until their individual calculated cumulative dose had been reached. VIT-45 was administered as a 5% m/V iron solution without dilution by IV bolus injection directly into the haemodialysis venous line one hour after the start of a dialysis session. Venofer was administered as a 2% m/V iron solution without dilution by IV injection over 10 minutes directly into the haemodialysis venous line one hour after the start of a dialysis session. The final dose was administered over 5 minutes if it was 100 mg iron (in the case of Venofer). Efficacy and safety assessments were performed at Weeks 1, 2, and 4 and a follow-up visit was performed 4 weeks after the final dose of study medication. The visits were on the same day as the haemodialysis.

The main criteria for inclusion were as follows:

- Adult, male or female, between the ages of 18 and 80 years (inclusive) requiring haemodialysis/hemodiafiltration with iron deficiency secondary to chronic renal failure.

- IDA defined as: Hb ≤115 g/L and at least one of the following: TSAT < 20% and/or serum ferritin < 200µg/L.

- Initially, a total of 120 patients (60 in each treatment group) were enrolled with a Hb value of ≤100 g/L. Following amendment 2, this was adjusted such that in each treatment group at least 50% of patients (at least 60 in each treatment group) were enrolled with a Hb value of ≤100 g/L.

- Patients treated with Erythropoietin (EPO) (including epoetin alfa, epoetin beta, and darbepoetin alfa) must have received this treatment for at least 8 weeks prior to inclusion in the study. The EPO dose may have been decreased during the study at the discretion of the investigator; increases in the dose of EPO were not permitted.

- Permanent vascular access appropriate for haemodialysis/haemodiafiltration.

Efficacy endpoints

The primary efficacy endpoint was the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks after baseline.

Secondary Efficacy Endpoints were:

- Maximum increase in Hb, ferritin and TSAT during study participation.
- Change from baseline levels of Hb, serum ferritin, and TSAT, at Weeks 1, 2 and 4 and the follow-up visit (4 weeks after the final dose of study medication).
- The number and proportion of patients who, at Weeks 1, 2, and 4, and the follow-up visit, achieved target levels of:
    - 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
    - TSAT: 20 to 50%.
- The individual area under the plasma concentration time curve (AUC) of change from baseline levels of Hb, serum ferritin and TSAT, standardised per day of study participation.

Statistical methods

Descriptive statistics included the number (N), mean, standard deviation (SD), standard error of the mean, minimum, lower quartile, median, upper quartile, and maximum. For summaries of categorical data frequency tables with counts and percentages were presented. Efficacy endpoints were analysed using the PPS (primary set for analysis) and the ITT set (secondary analysis). Summaries of efficacy variables were provided by treatment group, stratified by severity of IDA at baseline, by country and overall. A descriptive comparison between treatment groups was performed by means of 2 sided chi squared test, and while these analyses were not considered as confirmatory analyses, p values not exceeding the 5% level were considered as indicative of a treatment difference. Additional exploratory analyses to compare the two treatment groups were performed by means of the Cochran Mantel-Haenszel test allowing for severity of anaemia (Hb ≤100 g/L versus >100 g/L to ≤115 g/L) and country. The confidence intervals (CIs) were derived from analysis of covariance (ANCOVA) with 'treatment', 'severity of anaemia' and 'country' as fixed effects, baseline values as a covariate, and including all interactions. Baseline was the last measurement obtained before the first dose of study medication on Day 1.

Study population

Out of 240 randomised patients, 237 were included in the SS, as they had received a dose of study drug. A total of 234 patients for whom any efficacy data were available were included in the FAS/ITT set, while 183 patients were included in the PPS.

Most patients were Caucasian (98.9% overall). There were slightly more males than females in the study. The patients' demographic data between the two treatment groups were similar.

Most patients (approximately 70%) had Hb ≤100 g/L at baseline. The most commonly reported history was in the cardiovascular system as reported by 166 patients. Arterial hypertension is known to be the most common complication of chronic renal disease and is a major risk factor for other cardiovascular disease. The reported medical history was similar between the treatment groups. Overall, almost half of the patients (47.0%) had glomerulopathy, with 30 patients (16.4%) having interstitial nephropathy as aetiology for renal insufficiency. More than three-quarters of the patients (89.1%) had three haemodialysis sessions per week. There were no significant differences observed between the two treatment groups.

Within the PPS 60.8% of the patients receiving VIT-45 were on EPO treatment while 61.6% of the patients receiving Venofer. The most commonly reported prior medications (not ongoing at baseline) for the PPS were Vitamin B12 (13 patients [7.1%]). The most commonly reported medications ongoing at baseline were calcium carbonate (102 patients [55.7%]), EPO preparations (100 patients [54.6%]), folic acid (36 patients [19.7%]) and calcitriol (29 patients [15.8%]). The ongoing medications reported at baseline and the medications not ongoing at baseline were similar for both treatment groups and by severities of IDA at baseline.

The most commonly reported concomitant medications were epoetin alfa (13 patients [5.5%]), glucose and vitamin B12 (11 patients each [4.6%]). All other concomitant medications were reported in less than 4% of the total patient population.

The most commonly reported prior medications in the PPS during haemodialysis were heparin (131 patients [71.6%]), glucose (24 patients [13.1%], enoxaparin (21 patients [11.5%]) and ascorbic acid (20 patients [10.9%]). The prior medications during haemodialysis and additional therapy during haemodialysis were similar for both treatment groups and by severities of IDA at baseline.

There was no difference between the VIT-45 and Venofer groups in the calculated iron deficit, overall and by severity of IDA at baseline.

Efficacy results

Primary endpoint

In this study the primary response rate was defined as the percentage of patients reaching an increase in Hb of ≥10 g/L at 4 weeks after baseline. The estimate of the primary response rate, presented by severity of IDA at baseline, is summarised in Table 12. The percentage of responders was higher in the VIT-45 group than in the Venofer group, overall and by severity of IDA at baseline. However, there were no statistically significant differences for the estimated response rate between the two treatment groups. The primary response rate was higher in patients with Hb ≤100 g/L at baseline compared to patients with Hb > 100 to ≤115 g/L at baseline. This effect could be seen in patients treated with VIT-45 and Venofer and in both the PP and ITT sets.

Table 12: Primary response rate – increase in haemoglobin ≥10 g/L at 4 weeks after baseline (ITT and PP set, Study VIT-IV-CL-015)

N of responders (%)	VIT-45		Venofer®	
	ITT[a] (N = 118)	PP (N = 97)	ITT (N = 116)	PP (N = 86)
All patients	52 (44.1)	45 (46.4)	41 (35.3)	32 (37.2)
Hb ≤ 100 g/L	39 (48.8)	34 (50.0)	33 (44.0)	26 (45.6)
Hb > 100 to ≤ 115 g/L	13 (34.2)	11 (37.9)	8 (19.5)	6 (20.7)

[a] 5 patients with a baseline Hb value > 115 g/L are included in Hb > 100 to ≤ 115 g/L.

Secondary endpoints

Maximum increase in haemoglobin values

The mean maximum increase of Hb was higher in the VIT-45 group than in the Venofer group, overall and by severity of IDA at baseline for the ITT and PP sets (see Table 13). The mean maximum increase of Hb in patients with Hb ≤100 g/L at baseline was higher compared to patients with Hb >100 to ≤115 g/L at baseline for both treatments and for

the ITT and PP sets. The Hb value at baseline had a statistically significant ($p<0.05$) effect on the maximum increase of Hb for the PP set. Treatment had a statistically significant ($p<0.05$) effect favourable for VIT-45 on the maximum increase of Hb for the ITT set.

Table 13: Maximum increase of haemoglobin (ITT and PP set, Study VIT-IV-CL- 015)

Mean maximum increase of Hb (SD) [g/L]	VIT-45		Venofer®	
	ITT[a] (N = 117)	PP (N = 97)	ITT (N = 116)	PP (N = 86)
All patients	14.2 (11.1)	14.9 (11.5)	11.3 (11.6)	12.6 (12.0)
Hb ≤ 100 g/L	16.0 (11.8)	16.3 (12.4)	14.1 (12.4)	15.7 (12.4)
Hb > 100 to ≤ 115 g/L	10.4 (8.6)	11.6 (8.2)	6.4 (8.1)	6.4 (8.3)

[a] 5 patients with a baseline Hb value > 115 g/L are included in Hb > 100 to ≤ 115 g/L.

Change from baseline levels of haemoglobin values

Mean Hb levels slowly increased from baseline up to the follow-up period. The mean change from baseline at all visits (except Week 1) was slightly higher in the VIT-45 group compared to the Venofer group.

Secondary response rate for haemoglobin

The secondary response rate for Hb was defined as follows: Patients had to achieve target levels of Hb ≥110 g/L (in patients with a baseline of Hb ≤100 g/L) or achieve ≥120 g/L (in patients with a baseline Hb > 100 g/L to ≤115 g/L). No patients in the VIT-45 group had a secondary response for Hb at Week 1. At Week 2 the response for Hb was similar for both treatment groups, while at Week 4 the response rate for patients receiving VIT-45 was higher than for the patients who received Venofer. At the follow-up visit, 30.9% and 30.5% of the patients in the VIT-45 group and 23.3% and 17.2% of the patients in the Venofer group achieved the secondary response criteria for Hb increase in the PP and ITT sets, respectively.

Standardised AUC of haemoglobin

Mean AUC of Hb was higher in the VIT-45 group than the Venofer group, irrespective of the severity of IDA at baseline. Mean standardised AUC of Hb was higher in patients with Hb ≤100 g/L at baseline than patients with Hb > 100 to ≤115 g/L at baseline. Baseline Hb had a statistically significant ($p<0.05$) effect on standardised AUC of Hb.

Maximum increase of serum ferritin

The mean maximum increase of serum ferritin was higher in the VIT-45 group than in the Venofer group, overall and by severity of IDA at baseline for the ITT and PP sets. The mean maximum increase of serum ferritin in patients with Hb >100 to ≤115 g/L at baseline was slightly higher compared with patients with Hb ≤100 g/L at baseline for VIT-45 for the ITT and PP sets and for Venofer for the PP set only. Treatment had a statistically significant ($p<0.01$) effect favourable for VIT-45 on the maximum increase of serum ferritin for the ITT and PP sets.

Change from baseline levels of serum ferritin

Mean serum ferritin levels increased markedly from baseline to Weeks 1 and 2 and decreased to the follow-up, but were notably higher than baseline. The target range for serum ferritin in dialysis patients is 100 – 800 µg/L. Mean serum ferritin levels were below the target range at baseline and were within the target range for dialysis patients

from Week 1 to the follow-up. Mean serum ferritin changes from baseline were higher in the VIT-45 group than in the Venofer group at all visits.

Secondary response rate for serum ferritin

The secondary response rate for serum ferritin was defined as achieving serum ferritin levels of 200 – 800 µg/L. Response rate was > 80% at Week 1 in both groups. The response rate decreased slightly at Weeks 2 and 4 for both treatments and the follow-up (for Venofer only). At the follow-up visit approximately three-quarters of patients in both treatment groups still had target levels of serum ferritin.

Standardised AUC of serum ferritin

Mean AUC of serum ferritin was higher in the VIT-45 group than the Venofer group, irrespective of the severity of IDA at baseline. Mean standardised AUC of serum ferritin was similar for patients with Hb ≤100 g/L at baseline and patients with Hb > 100 to ≤115 g/L at baseline. Treatment had a statistically significant ($p<0.01$) effect on standardised AUC of Hb, for VIT-45 compared to Venofer.

Maximum increase of serum transferrin saturation

The mean maximum increase of TSAT was higher in the VIT-45 group than in the Venofer group, overall and by severity of IDA at baseline for the ITT and PP sets. For VIT-45, the mean maximum increase of TSAT in patients with Hb ≤100 g/L at baseline was higher compared with patients with Hb > 100 to ≤115 g/L at baseline for the ITT and PP sets.

Change from baseline levels of transferrin saturation

Mean TSAT levels doubled from baseline to Week 2 for VIT-45 and increased slightly from baseline to Week 4 for Venofer. Mean TSAT decreased from Week 2 to the follow-up for VIT-45 and decreased from Week 4 to the follow-up for Venofer. Mean TSAT changes from baseline were higher in the VIT-45 group than the Venofer group. The target range for TSAT in dialysis patients is 20-50%. The mean TSAT was in the low target range at baseline and was moved within the target range during the treatment and follow-up.

Secondary response rate for transferrin saturation

The secondary response rate was defined as achieving target levels of TSAT of 20-50%. Response rates were 58.8% and 57.6% for VIT-45 and 70.9% and 63.8% for Venofer at Week 1 for the PP and ITT sets, respectively. Response rate increased over time for VIT-45, but for Venofer it decreased from baseline to Weeks 2 and 4 and then increased again at the follow-up. The response rate was similar for both treatments (approximately 70%) at the follow-up.

Standardised AUC of transferrin saturation

Mean AUC of TSAT was higher in the VIT-45 group than the Venofer group, irrespective of the severity of IDA at baseline. Treatment had a statistically significant ($p<0.05$) effect on standardised AUC of TSAT, for VIT-45 compared to Venofer. Baseline TSAT values had a statistically significant ($p<0.01$) effect on standardised AUC of TSAT.

Evaluator Comment

All pharmacodynamic parameters (Hb, serum ferritin and TSAT) showed response to IV iron treatment in anaemic haemodialysis patients. Hb, serum ferritin values together with TSAT values demonstrated successful increase in iron stores for both treatment groups. The increase in iron stores translated into a medically meaningful increase in Hb of > 8 g/L at any point during the study in over 60% of the participating patients.

Studies in chronic kidney disease

Study 1VIT04004

Study 1VIT04004 was a multicentre, randomised, open-label, controlled Phase III study to compare the safety and efficacy of intravenous infusions of VIT-45 and oral ferrous sulphate (FS), independent of haemoglobin response to erythropoietin (EPO) in treating anaemia in non-dialysis dependent chronic kidney disease (NDD-CKD).

Eligible patients were stratified separately within the EPO treated group and the non-EPO treated group by degree of renal failure and by baseline Hb, and randomised 2:1 ratio (VIT-45 to oral iron) within each combination of strata. The original objective for the 2:1 randomisation was to recruit sufficient VIT-45 subjects to meet an FDA-agreed safety population target. That target was met for the VIT-45 project and enrolment for this protocol had been slower than expected. Therefore, a reduction in the VIT-45 sample size with a 1:1 ratio ensured the feasibility of the study in face of enrolment obstacles, reduced the number of subjects exposed to an experimental protocol, and maintained the original power specification.

An initial dose (Day 0) of 15 mg/kg VIT-45 for weight ≤66 kg (up to a maximum of 1000 mg) was administered in 250 mL normal saline solution (NSS) over 15 minutes IV. On Day 17±1 and Day 31±1 doses of 15 mg/kg up to a maximum of 500 mg were given in 100 mL normal saline over 15 min IV if TSAT was ≥30% or ferritin was ≥500 ng/mL on Days 14 and 28, respectively. Ferrous sulphate (FS) was dispensed as 325 mg tablets, one tablet to be taken orally 1 hour before meals, three times daily with water. The first dose was administered on Day 0. During the treatment phase, patients returned to the clinic for assessment of efficacy and safety and dosing if applicable on Days 14, 17±1, 28, 31±1, 42 and 56. Patients were treated for a maximum of 56 days.

Main criteria for inclusion were:

- Male or female NDD-CKD patients ≥12 years of age

- Anaemia in NDD-CKD with GFR ≤45 mL/min/1.73m^2 using the MDRD calculation (based on the initial BL 1 Visit creatinine result.

- IDA defined by the average Hb of 2 consecutive BL central laboratory Hb results drawn on different days ≤110 g/L, with the difference between the 2 results ≤7.0 g/L, a latest baseline TSAT ≤25% and ferritin of ≤300 ng/mL, respectively.

- Fixed dose of EPO over 8 weeks (a dose of 0 is permitted) and no parenteral iron for 12 weeks.

Efficacy endpoints

The primary efficacy endpoint was the percentage of patients achieving an increase in haemoglobin of ≥10 g/L anytime between baseline and end of study or time of intervention.

Secondary endpoints were:

- Clinical response, defined as an increase in haemoglobin ≥10.0 g/L and increase in ferritin ≥160 ng/mL (not necessarily simultaneous).

- Percentage of patients achieving an increase in haemoglobin of ≥10.0 g/L in the EPO vs the non-EPO users.

- Change to each visit in haemoglobin, ferritin and TSAT

- Change from baseline to highest haemoglobin, ferritin and TSAT

- Change from baseline to highest haemoglobin, ferritin and TSAT on or before Days 14, 28, 42, and 56.

- Comparison in changes from baseline in various laboratory combinations to support clinical response.

Statistical methods

The primary endpoint was assessed with Fisher's exact test, performed on the unstratified success rate. Major secondary efficacy endpoints were tested with Fisher's exact test and the t-test in a hierarchical order with all tests done at an alpha-level ≤0.05. Efficacy analyses were performed for the Modified Intent to Treat (mITT) population and the Evaluable Population (EP). The mITT was defined as patients from the safety population (patients dosed at least once) who received at least one dose of study medication, had stable EPO for at least 8 weeks before randomisation, had at least one post-baseline haemoglobin assessment and had NDD-CKD defined by a GFR ≤45 mL/min/1.73m^2. The EP was defined as those patients from the mITT population who completed ≥28 days of the study, received at least 67% of the required study drug, and had no major protocol violations.

Study population

A total of 255 patients were randomised at 47 centres to receive VTI-45 (152 patients) or oral ferrous sulphate (103 patients); 147 patients were treated in the VIT-45 group and 103 in the ferrous sulphate group, respectively (safety population). In the VIT-45 group, 134 of the 147 patients completed the study (91.2%) and 84 out of 103 (81.6%) in the ferrous sulphate group.

Mean haemoglobin, TSAT, and ferritin values at baseline were similar between the VIT-45 (10.13 g/dL, 15.39%, and 111.81 ng/mL, respectively) and oral iron (10.04 g/dL, 15.77%, and 104.84 ng/mL, respectively) treatment groups. The proportion of subjects with a baseline haemoglobin ≤9.0 g/dL was 10.2% in the VIT-45 group and 13.6% in the oral iron group. The majority of subjects in both treatment groups were not taking EPO at randomization (VIT-45: 76.2%; oral iron: 74.8%). The most common degree of CKD was a GFR between 15.1 - 30.0mL/min/1.73m^2. Over half of the subjects in the oral iron group had received previous iron therapy (56.3%), whereas, over half of the subjects in the VIT-45 group had not received previous iron therapy (55.8%).

Efficacy results

Among the patients in the mITT population a statistically significant difference was observed between the VIT-45 and the FS groups in the proportion of patients who achieved an increase in haemoglobin ≥10.0 g/L (60.4% vs 34.7%, p<0.001). Logistic regression analyses indicated that higher baseline TSAT values were associated with decreased odds of achieving an increase in haemoglobin ≥10.0 g/L during the study. The superiority of VIT-45 to FS was unaffected by baseline TSAT.

When the proportion of patients who achieved an increase in Hb ≥10.0 g/L was analysed by baseline subgroups, statistically significant differences were observed between the VIT-45 and FS groups for the majority of subgroups.

Secondary efficacy endpoints

A summary of the major secondary efficacy endpoints is presented in Table 14. Among patients in the mITT population a statistically significant difference was observed between the VIT-45 group and the FS group for each of the major secondary efficacy endpoints. A statistically significantly greater proportion of patients in the VIT-45 group achieved a Hb change ≥10.0 g/L, a ferritin change ≥160 ng/mL and a Hb change ≥10.0 g/L before Day 42

compared to the FS group. In addition, the VIT-45 group achieved a statistically significantly higher mean Hb change at the end of the study period (Day 56), change to Day 42 and change to highest Hb compared to the oral iron group. When analysed per subgroup, the change to highest Hb was statistically significantly higher in the VIT-45 group for EPO use at baseline, no EPO use at baseline, CKD degree 30.1 to 45.0 mL/min/1.73 m^2, baseline Hb 101 to 110 g/L, baseline ferritin <100 ng/mL, age <65years, female patients, Caucasians, and patients in Australia and the US.

Statistically significant mean increases from baseline in Hb, ferritin and TSAT values were observed at Days 14, 28, 42, and 56 in both the VIT-45 and oral iron groups. The mean increases from baseline in haemoglobin in the VIT-45 group were statistically significantly greater than those observed in the oral iron group at Days 28, 42, and 56.

Table 14: Summary of Major Secondary Efficacy Endpoints (mITT Population)

Endpoint	Number (%) Subjects		Fisher's Exact p-value	95% CI
	FCM	Oral Iron		
Hemoglobin Change ≥ 1.0 g/dL at any Time and Ferritin Change ≥ 160 ng/mL n/N (%)	87/144 (60.4%)	0/101 (0.0%)	< 0.001	48.2, 72.6
Hemoglobin Change ≥ 1.0 g/dL on or Before Day 42 n/N (%)	78/144 (54.2%)	29/101 (28.7%)	< 0.001	12.8, 38.1
Mean Hemoglobin Change to Day 56/End of Study N Mean (SD) Median	133 1.0 (1.10) 0.8	84 0.7 (1.25) 0.5	0.034	0.0, 0.7
Mean Hemoglobin Change to Day 42 N Mean (SD) Median	132 1.0 (1.12) 0.8	87 0.5 (1.23) 0.3	0.005	0.1, 0.8
Mean Change to Highest Hemoglobin N Mean (SD) Median	44 1.3 (1.11) 1.2	101 0.8 (1.18) 0.6	0.001	0.2, 0.8

n = number of subjects with response, N = number of subjects in group, % = 100 x (n divided by N), SD = standard deviation
CI = confidence interval based on normal approximation to the binomial under the null hypothesis for superiority

Evaluator Comment

VIT-45 was shown to be efficacious for the treatment of IDA in EPO- and non-EPO treated NDD-CKD patients.

Study 1VIT05005

Study 1VIT05005 was a multicentre, non-randomised, open-label, longitudinal study in patients who were enrolled in Study 1VIT04004. No control group was necessary for this interventional study. The study was focussed on safety; however, efficacy parameters were included as secondary evaluation parameters. The dose of VIT-45 for all patients was based on the TSAT and the ferritin values from the last scheduled visit. For TSAT that was ≥25% and ferritin that was <300 ng/mL an initial dose of 15 mg/kg VIT-45 for weight ≤66 kg (up to a maximum of 1000 mg) was administered in 250 mL normal saline solution (NSS) over 15 minutes IV within 7 days of qualifying visit. Patients with > 66 kg bw received a dose of 1000 mg iron as VIT-45 on the first dosing occasion. If patients did not qualify for the 1000 mg dose but their TSAT was <30% and ferritin < 500 ng/mL, a maximum dose of 500 mg was administered in 100 mL of NSS over 15 minutes within 7 days of qualifying visit. During the treatment phase, patients returned to the clinic for

assessment of efficacy and safety and dosing if applicable on Days (±3) 28, 56, 84, 112, 140, 168, 196, 224, 255, 280 and 308.

The main criteria for inclusion were:

- Patients who completed Study 1VIT04004 (VIT04) through Day 56 or

- Patients who were discontinued from VIT04 for requiring intervention with an increase in dose of EPO, or the addition of EPO

- Patients who required the use of iron outside the protocol

Efficacy endpoints

No primary efficacy parameters were defined as this study was focussed on long-term tolerability and safety. Secondary efficacy parameters included:

- Percentage of patients at with "Clinical Success", defined as Hb ≥110 g/L, TSAT between 30 and 50%, and ferritin between 100 and 800 ng/mL

- Number and proportion of patients who achieved sustained clinical success (defined as achievement of clinical success at 50% or more of the assessments) (that is, TSAT between 30 and 50% and ferritin between 100 and 800 ng/mL),

- Percentage of patients with Hb ≥110 g/L

- Change from baseline to highest Hb, TSAT, and ferritin

- Change from baseline to each scheduled visit in Hb, TSAT, and ferritin

- Change from baseline in the average weekly dose of EPO in the EPO treated population.

Study population

A total of 145 patients were randomised at 28 centres to receive VTI-45. A total of 104 of the 145 patients completed the study (71.7%). A total of 127 of the 145 patients enrolled were included in the safety population (87.6%) and a total of 140 patients in the efficacy population (96.9%). The majority of patients who were treated with VIT-45 in this study had previously received VIT-45 in Study 1VIT04004 (59.1%). Mean patient's age was 65.6 years; the majority of patients were female (66.9%) and most were Caucasian (52.0%) in the safety population.

Efficacy results

A tabular summary of results is provided in Table 15. Of the 140 patients in the EP, 72 (51.4%) achieved clinical success and 14 (10%) had sustained clinical success during the treatment phase. Clinical success was reached independently from prior treatment with VIT-45 or oral FS in 52.3% and 50% of patients, respectively.

The proportion of patients who achieved clinical success and had sustained success was greater among those who had baseline Hb levels between 101 and 110 g/L. No remarkable differences were observed for the proportions of patients who achieved clinical success when analysed according to baseline GFR, EPO use, race and gender. The proportion of patients who had sustained clinical success was greater among those who had baseline GFR≤15.0 mL/min/1.73m^2.

A Hb level ≥11.0 g/L at any time during the study was achieved by 87.9% of patients. The percentage of patients achieving this criterion at a given visit ranged from 55% (Day 84) to 64.3% (Day 308). The proportion of patients achieving ferritin between 100 and 800 ng/mL at a given study visit ranged from 83.3% (Day 28) to 93% (Day 84), and the overall proportion of patients achieving ferritin between 100 and 800 ng/mL at any time during the study was 99.3%. The proportion of patients achieving TSAT between 30% and 50%

ranged from 23.5% (Day28) to 35.8% (Day 255), and the overall proportion of patients achieving TSAT between 30% and 50% at any time during the study was 75.7%.

Mean changes from baseline in Hb, TSAT and ferritin were observed at each visit. For Hb the range was 0.92 g/L at Day 28 to 1.21 g/L at Day 112. For TSAT the range was 9.28% at Day 168 to 12.35% at Day 112, and for ferritin the range was 397.85 ng/mL at Day 84 to 704.22 ng/mL at Day 280.

Table 15: Summary of the Proportion of Patients Who Achieved Clinical Success and Sustained Clinical Success in Study 1VIT05005

Subgroup	Clinical Success[a] n/N (%)	Sustained Clinical Success[b] n/N (%)
Overall 95% CI	72/140 (51.54) (43.1, 59.7)	14/140 (10%) (5.0, 15.0)
Treatment in VIT04		
Oral Iron	26/52 (50)	4/52 (7.7)
VIT-45	46/88 (52.3)	10/88 (11.4)
Baseline Haemoglobin		
≤ 90.0 g/L	6/16 (37.5)	0/16 (0)
91-100 g/L	18/38 (47.4)	2/38 (5.3)
101-110 g/L	48/86 (55.8)	12/86 (14.0)
CKD Degree (GFR)		
≤ 15.0 mL/min/1.73m²	9/17 (52.9)	4/17 (23.5)
15.1-30.0 mL/min/1.73m²	38/73 (52.1)	8/73 (11.0)
30.1-45.0 mL/min/1.73m²	25/50 (50.0)	2/50 (4.0)
Receiving EPO		
No	33/72 (45.8)	7/72 (9.7)
Yes	39/68 (57.4)	7/68 (10.3)
Race		
Caucasian	40/70 (57.1)	11/70 (15.7)
Non-Caucasian	32/70 (45.7)	3/70 (4.3)
Gender		
Female	51/94 (54.3)	8/94 (8.5)
Male	21/46 (45.7)	6/46 (13.0)
Age		
< 65 years	28/66 (42.4)	4/66 (6.1)
≥ 65 years	44/74 (59.5)	10/74 (13.5)
Baseline Ferritin		
< 100 ng/mL	47/70 (67.1)	9/70 (12.9)
≥ 100 ng/mL	25/70 (35.7)	5/70 (7.1)

N=Number of patients in group, n=number of patients with response

a Hb ≥ 110 g/LL, ferritin between 100 and 800 ng/ml inclusive, and TSAT between 30% and 50% inclusive on the same day

b Achievement of clinical success at 50% or more of the assessments

Evaluator Comment

The study results support that efficacy of VIT-45 was demonstrated during long-term treatment of up to 44 weeks.

Studies in chronic inflammatory bowel disease (IBD)

Study VIT-IV-CL-008

Study VIT-IV-CL-008 was a multicentre, open-label, randomised, and controlled Phase III study in patients with iron deficiency anaemia (IDA) secondary to chronic inflammatory bowel disease (IBD). Patients were randomised in a 2:1 (VIT-45 : ferrous sulphate) ratio to receive one of two treatments: VIT-45 intravenous (IV) on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached, or oral ferrous sulphate capsules 100 mg twice daily (bd) for 12 weeks.

The primary objective of the study was to evaluate the non-inferiority in efficacy in reducing IDA of infusions of VIT-45 compared to oral ferrous sulphate capsules in patients with IDA secondary to chronic IBD. The secondary objectives were to assess the safety of infusions of VIT-45 in patients with IDA secondary to chronic IBD and to evaluate the quality of life (QoL) of patients with IDA secondary to chronic IBD treated with infusions of VIT-45 versus oral ferrous sulphate capsules.

The main criteria for inclusion were:

- Male and female, inpatient or outpatient, aged 18 to 80 years (inclusive).

- Have IDA secondary to chronic IBD (Crohn's disease or ulcerative colitis).

- IDA defined as: Hb ≤110 g/L and at least one of the following: Serum transferrin saturation (TSAT) < 20% and/or serum ferritin < 100 µg/L.

- Required treatment with at least 1000 mg total iron, based on individual assessment of iron deficiency.

Efficacy endpoints

The primary efficacy endpoint was the change from baseline levels of Hb to Week 12.

Secondary efficacy endpoints were:

- change from baseline levels of Hb at Weeks 2, 4 and 8 and serum ferritin and TSAT at Weeks 2, 4, 8 and 12;

- the maximum increase in Hb, serum ferritin and TSAT;

- the number and proportion of patients who, at Weeks 2, 4, 8 and 12, achieved: Hb levels of 135 to 180 g/L for males and 120 to 160 g/L for females; serum ferritin levels of 100 to 800 µg/L; TSAT levels of 20 to 50%;

- the number and proportion of patients who had, at Weeks 2, 4, 8 and 12, Hb levels >20 g/L higher than their baseline level, and whether the patient discontinued due to lack of response;

- change from baseline to Weeks 4, 8 and 12 in SF-36v1 questionnaire and Crohn's Disease Activity Index (CDAI)/Colitis Activity Index (CAI).

Statistical methods

For categorical data summary, frequency tables present counts and percentages. Analysis was done on observed values. Missing values were not replaced. Presentation of efficacy parameters was based on both the FA/ITT set and the PP set. Efficacy was assessed through the correction of iron deficiency and Hb concentration of the patient. For the change in Hb from baseline to Week 12, the analysis was performed by calculating the 2 sided 95% CI for the difference "VIT-45 minus ferrous sulphate" in Hb change, and noninferiority was concluded if the lower bound was ≥–5g/L. Superiority of VIT-45 was established if the lower bound was ≥0. A descriptive comparison between the two

treatment groups was performed by means of a 2 sided chi-squared test, and p values not exceeding the 5% level was considered as indicative of a treatment difference as these analyses were not considered confirmatory.

A total of 200 patients were included in the safety set, 196 patients were included in the intention to treat (ITT)/full analysis set and 160 patients in the PP set.

Study population

Out of 422 screened patients, 200 were included in the safety set, as they had received at least one dose of study drug. A total of 196 patients for whom any efficacy data were available were included in the full analysis/ITT set, while 160 patients were included in the PP set.

Most patients were Caucasian (98.8% overall). Overall, there were more females (61.3%) than males (38.8%) in the study. There were more patients who were diagnosed with ulcerative colitis (72.5%) than Crohn's disease (27.5%). Overall, seven patients (4.4%) used alcohol and 13 patients (8.1%) used tobacco. The patients' demographic data between the two treatment groups were similar, except that patients in the ferrous sulfate group were slightly older than patients in the VIT-45 group (mean age 47.2 years versus 40.7 years).

There was no significant difference between the two treatment groups in terms of the proportion of patients with medical and surgical history.

Overall, the most commonly (≥5% of patients) reported prior medications (not ongoing at baseline) for the PP set were sulfasalazine (18 patients [11.3%]), Vitamin B_{12} (15 patients [9.4%]), prednisolone (13 patients [8.1%]), mesalazine (10 patients [6.3%]), folic acid (9 patients [5.6%]) and prednisone (8 patients [5.0%]). Overall, the most commonly reported medications ongoing at baseline were mesalazine (57 patients [35.6%]), sulfasalazine (52 patients [32.4%]), prednisolone (19 patients [11.9%]), folic acid (11 patients [6.9%]), prednisone (10 patients [6.3]%), omeprazole and sulfasalazine (8 patients each [5.0]%). Azathioprine was used by only 6 patients (5.4%), and they were all in the VIT-45 group (medication use of clinical relevance). All other ongoing medications were reported in less than 4% of the total patient population. The ongoing medications reported at baseline and the medications not ongoing at baseline were similar for both treatment groups.

There was no difference between the VIT-45 and ferrous sulfate groups in the calculated iron deficit.

Efficacy Results

Primary efficacy endpoint: haemoglobin change from baseline levels to Week 12

Hb values by visit are summarised in Table 16. The mean increase in Hb concentration from baseline to Week 12 in the PP and ITT sets respectively was 38.3 g/L and 36.0 g/L in the VIT-45 group and 37.5 g/L and 32.9 g/L in the ferrous sulphate group. The mean Hb concentrations at Week 12 were 123.9 g/L and 121.5 g/L in the VIT-45 group and 125.1 g/L and 122.6 g/L in the ferrous sulphate group in the PP and ITT sets, respectively.

The lower limit of the 95% CI for difference of Hb changes between VIT-45 and ferrous sulphate is –5.00 for the PP set and –4.35 for the ITT set; thus non-inferiority of VIT-45 versus ferrous sulphate can be concluded. Superiority cannot be concluded, since the lower limits of the CIs are below zero. While sex, country and treatment had no significant effect on the primary endpoint, the Hb value at baseline had a statistically significant ($p < 0.001$) effect on change in Hb from baseline to Week 12.

Table 16: Haemoglobin by visit (ITT and PP set, Study VIT-IV-CL-008)

Hb (SD) [g/L]	Values by visit			
	VIT-45		Ferrous sulphate	
	ITT (N = 136)	PP (N =111)	ITT (N = 60)	PP (N = 49)
Baseline	85.4 (15.4)	85.6 (15.2)	89.7 (15.1)	87.6 (15.4)
Week 2	105.7 (13.0)	106.8 (12.1)	103.0 (15.8)	101.4 (16.1)
Week 4	117.6 (14.6)	118.6 (12.5)	113.9 (15.1)	113.0 (15.6)
Week 8	124.4 (14.5)	124.5 (14.6)	121.8 (15.3)	121.5 (15.4)
Week 12	121.5 (17.9)	123.9 (16.4)	122.6 (18.4)	125.1 (18.5)

Secondary efficacy endpoints for haemoglobin

Haemoglobin: Change from baseline

The mean Hb values increased in both treatment groups after 2, 4 and 8 weeks, but the VIT-45 group showed a more robust response to iron treatment than the ferrous sulphate group.

The mean Hb in the VIT-45 group showed a faster increase compared to the ferrous sulphate group (in the PP set, the mean increase in Hb was 21.3 g/L versus 13.9 g/L after 2 weeks, 33.0 g/L versus 25.4 g/L after 4 weeks and 39.0 g/L versus 33.9 g/L after 8 weeks).

The lower limit of the 95% CI for difference of Hb changes at Week 2 between VIT-45 and ferrous sulphate is 3.41 for the PP set and 1.26 for the ITT set; and at Week 4 is 2.48 for the PP set and 0.20 for the ITT set, thus superiority of VIT-45 versus ferrous sulphate can be concluded at these two time points. The difference in lower limit of 95% CI between treatment groups at Week 8 was –0.76 for the PP set and –1.50 for the ITT set, thus non-inferiority of VIT-45 versus ferrous sulphate can be concluded, but not superiority (the lower limits of the CIs are below zero).

Haemoglobin: Maximum increase

The mean maximum increase in Hb was 43.8 g/L and 41.9 g/L in the VIT-45 group and 40.4 g/L and 36.0 g/L in the ferrous sulphate group in the PP and ITT sets, respectively. The Hb value at baseline had a statistically significant ($p<0.001$) effect on the mean maximum increase of Hb, but no other statistically significant difference between the results in the two treatment groups was found.

Haemoglobin: Secondary response rate for measured haemoglobin values

The estimate of the response rate for measured Hb was defined as the percentage of patients reaching Hb target levels of 135-180 g/L for males and 120-160 g/L for females. The percentage of responders was higher in the VIT-45 group than in the ferrous sulphate group for all visits. At Week 4, the percentage of responders was statistically significantly higher for VIT-45 than for ferrous sulphate ($p<0.05$ for both the Chi-squared test and the Cochran-Mantel-Haenszel test) for the PP set indicating a more rapid response to therapy in the VIT-45 group.

Haemoglobin: Secondary response rate for changes from baseline of haemoglobin

In this study the estimate of the response rate for changes from baseline of Hb values was defined as the percentage of patients who had Hb > 20 g/L higher than their baseline Hb values. The percentage of responders was higher in the VIT-45 group than in the ferrous sulphate group for all visits, except for Week 12 where it was similar. At Week 12, 81.1%

and 76.5% of patients were responders in the VIT-45 group and 81.6% and 68.3% of patients in the ferrous sulphate group were responders in the PP and ITT sets, respectively. At Weeks 2 and 4 the percentage responders was statistically significantly higher for VIT-45 compared to ferrous sulphate ($p<0.01$ at Week 2 and $p<0.5$ for Week 4, for both the Chi-squared test and the Cochran-Mantel-Haenszel test) for the PP set. This indicates the more rapid response to treatment in the VIT-45 group and confirms that the response is sustained to the Week 12 time point.

There were no patients who discontinued from the study due to a lack of response.

Serum ferritin: Change from baseline

Serum ferritin values by visit and change from baseline are summarised in Table 17. Mean serum ferritin levels for the patients receiving VIT-45 increased markedly from baseline to Week 2, and although levels decreased at the assessment at Weeks 4, 8 and 12, serum ferritin levels remained elevated compared to baseline. Mean serum ferritin levels for patients receiving ferrous sulphate increased slightly from baseline to Weeks 2 and 4, then decreased slightly to Week 8 and increased again slightly to Week 12. In the PP set, the mean serum ferritin value at baseline was higher for the ferrous sulphate group compared to the VIT-45 group (21.7 µg/L versus 9.9 µg/L), while at Week 12 the mean values were 42.1 µg/L and 82.3 µg/L. In the ITT set the difference between baseline values was less pronounced (12.7 µg/L versus 19.8 µg/L) and the mean values at week 12 for the ITT sets were 80.2 µg/L and 38.6 µg/L, respectively. The mean serum ferritin value at Week 12 for patients in the VIT-45 group was therefore twice the value compared to patients receiving oral ferrous sulphate.

Table 17: Serum ferritin by visit and change from baseline (ITT and PP set, Study VIT-IV-CL-008)

Mean serum ferritin (SD) [µg/L]	Values by visit		Change from baseline	
	VIT-45	Ferrous sulphate	VIT-45	Ferrous sulphate
ITT population	**(N = 136)**	**(N = 60)**		
Baseline	12.7 (36.4)	19.8 (54.8)		
Week 2	413.1 (339.9)	33.1 (34.2)	403.2 (337.0)	12.7 (52.1)
Week 4	170.2 (148.6)	41.5 (85.0)	157.3 (150.2)	21.1 (99.9)
Week 8	95.1 (100.9)	36.0 (33.3)	82.0 (104.4)	14.8 (52.3)
Week 12	80.2 (102.8)	38.6 (42.5)	67.3 (104.2)	18.3 (55.2)
PP population	**(N = 111)**	**(N = 49)**		
Baseline	9.9 (14.9)	21.7 (60.5)		
Week 2	424.6 (362.4)	35.2 (36.0)	414.8 (359.3)	13.5 (55.7)
Week 4	178.0 (155.1)	44.8 (90.4)	168.2 (151.1)	23.0 (106.8)
Week 8	97.4 (97.4)	37.4 /33.7)	87.4 100.5)	15.7 (53.8)
Week 12	82.3 (105.8)	42.1 (44.9)	72.4 (100.0)	20.4 (56.9)

Although VIT-45 was administered for a shorter period of time (1-3 weeks) than ferrous sulphate (12 weeks), the effect was long lasting, as can be seen from the Week 12 mean serum ferritin values that stayed elevated compared to baseline several weeks after the last dose of study medication was administered.

Mean serum ferritin changes from baseline were higher in the VIT-45 group than the ferrous sulphate group at all visits, with a factor of approximately 30 at Week 2 and a factor of approximately 3 at Week 12.

Serum ferritin: Maximum increase

The mean maximum increase of serum ferritin was approximately 10 times higher in the VIT-45 group than in the ferrous sulphate group. This large difference was statistically significant ($p<0.0001$) in the ANCOVA.

Serum ferritin: Secondary response rate

In this study the estimate of the response rate for serum ferritin was defined as the percentage of patients who achieved target levels of 100-800 µg/L. The percentage of responders was much higher in the VIT-45 group than in the ferrous sulphate group for all visits. The percentage responders for serum ferritin statistically significantly differed between the two treatments for all visits with patients in the VIT-45 group having a higher response rate for serum ferritin than patients in the ferrous sulphate group.

Transferrin saturation: Change from baseline

In this study the estimate of the response rate for TSAT was defined as the percentage of patients who achieved target levels of 20-50%. The percentage of responders was higher in the VIT-45 group than in the ferrous sulphate group for all visits, except Week 12, where the response rates were similar. The percentage of responders decreased with each visit from Week 2 (61.3% and 55.9%) to Week 12 (43.2% and 40.4%) for the patients in the VIT-45 group in the PP and ITT group, respectively. The percentage of responders increased from Week 2 (30.6% and 28.3%) to Week 12 (46.9% and 43.3%) for patients in the ferrous sulphate group. However, the percentage of responders was similar between the two treatment groups at Week 12 (43.2% and 40.4% in the VIT-45 group and 46.9% and 43.3% in the ferrous sulphate group in the PP and ITT sets, respectively). The differences between the two treatment groups with respect to the percentage of responders at Weeks 2 and 4 was statistically significant with patients in the VIT-45 group having a higher response rate than patients in the ferrous sulphate group. The VIT-45 group showed a more rapid response than the ferrous sulphate group, which was sustained up to Week 12.

The Quality of Life Questionnaire SF-36[8]

Mean SF-36 total scores increased over the study in both treatment groups indicating improvement in quality of life (QoL), although mean change from baseline scores were higher in the VIT-45 group than the ferrous sulphate group at all time points. In both treatment groups the percentage of patients whose health as compared to one year ago was "much better now" increased in both treatment groups in a similar way (from 9.0% to 26.1% in the VIT-45 group and from 12.2% to 26.5% in the ferrous sulphate group).

Overall, the patients' QoL improved from baseline to Week 12 for both treatment groups.

Evaluator Comment

All efficacy parameters showed that iron treatment was successful in treating IDA in patients with IBD. Based on the primary efficacy variable (increase in Hb from baseline to Week 12), VIT-45 was non-inferior to ferrous sulphate in treating patients with IDA

[8] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

secondary to IBD. Moreover, patients treated with VIT-45 showed a significantly higher increase in mean Hb at Week 2 and Week 4 and also higher response rates of Hb at the early time points. This demonstrates that VIT-45 leads to a faster response to treatment when compared to ferrous sulphate. The values of serum ferritin and TSAT demonstrated a successful repletion of the iron stores in patients treated with VIT-45.

Studies in heavy uterine bleeding (HUB)

Study 1VIT04002/1VIT04003

Study 1VIT04002/1VIT04003 was a multicentre, randomised, open-label, controlled Phase III study to compare the safety and efficacy of intravenous infusions of VIT-45 and oral ferrous sulphate (FS) in improving haemoglobin in females with IDA secondary to heavy uterine bleeding (HUB). Originally two identical studies were designed, but due to slow enrolment, studies 1VIT04002 and 1VIT04003 were discontinued before complete enrolment and combined for analyses. All eligible patients were stratified by Hb levels (96-110, 81-95 g/L and <80 g/L), degree of uterine bleeding (mild/moderate, severe, very severe) and by past response to oral iron (poor/yes/no), and randomised in a 1:1 ratio to the treatment groups. Patients were treated for a maximum of 42 days.

The main criteria for inclusion were:

- Female patients ≥18years of age, with a history of HUB

- Baseline HB must have been ≤114 g/L with an average of 2 consecutive central laboratory baseline Hb values drawn on different days within a 7 day period of ≤110 g/L and a difference between the values of ≤70.0 g/L.

- TSAT must have been ≤25% and ferritin ≤100 ng/mL.

Efficacy endpoints

The primary endpoint for efficacy was the proportion of patients achieving success, defined as an Hb increase from baseline of ≥20.0 g/L anytime between baseline and end of study or time of intervention.

Major secondary endpoints included:

- The number and proportion of patients with an increase in Hb ≥20 g/L at any time between baseline and the end of study or time of intervention.
- Number and proportion of subjects requiring intervention.
- Time to intervention, defined as the days between randomisation and the day of intervention or end of study, whichever came first
- Mean changes from baseline in Hb, TSAT and ferritin at each visit were assessed together with other secondary endpoints.

Statistical methods

For efficacy analyses patients were analysed under treatment actually received. The statistical tests were done at 0.05 alpha levels, two-tailed (unless stated otherwise). The effect of baseline characteristics on the primary efficacy endpoint was examined by means of logistic regression. Efficacy analyses were performed for the mITT population and the evaluable population (EP). The mITT was defined as patients from the safety population (at least dosed once) who received at least 1 dose of study medication, an average baseline Hb ≤110 g/L, TSAT ≤25%, ferritin ≤100 ng/mL, HUB and at least one post-baseline Hb assessment. The EP was defined as those patients from the mITT population who were followed until Day 42, received at least 67% of the required study drug and had no major protocol violations.

Study population

A total of 477 patients were randomised at 84 centres to receive VTI-45 (246 patients) or oral ferrous sulphate (231 patients), 230 patients were treated in the VIT-45 group and 226 in the ferrous sulphate group, respectively (safety population). In the VIT-45 group 211 of the 230 patients completed the study (91.7%) and 212 out of 226 (93.8%) in the ferrous sulphate group respectively (EP). A total of 456 patients were included in the safety population (VIT-45: 230, FS: 226), 453 (VIT- 45. 228, FS: 225) in the mITT population and 420 (VIT-45: 213, FS: 207) in the EP.

Patients in the safety population were comparable regarding to demographic and other baseline characteristics except for a statistically significant difference in the pattern of menstrual cycle at screening: A greater proportion of patients in the FS group had regular menstrual cycles at screening (74.3%) compared with the patients in the VIT-45 group (65.1%). Mean patient age was 38.7 years in the VIT-45 and 39.5 in the FS group, respectively. The most common race was African American, the next common Caucasian (VIT-45: 50.0% and 27.4%, respectively, FS: 46.5% and 26.5% respectively).

Efficacy results

Primary efficacy endpoint

Among the patients in the mITT population a statistically significant difference was observed between the VIT-45 and the FS groups in the proportion of patients who achieved success, defined as an increase in haemoglobin ≥20 g/L (82.0% vs 61.8%, p<0.001); similar results were observed in the EP.

In the mITT population, statistically significantly greater proportions of VIT-45 patients achieved an increase in Hb ≥20 g/L at any time during the study compared with oral iron patients for each of the subgroups, except for patients with a baseline Hb ≤80 g/L, Caucasian patients, and patients from Mexico. The superiority of VIT-45 versus oral iron for an increase in haemoglobin of ≥2.0 g/dL was consistent across baseline haemoglobin level, degree of uterine bleeding at baseline, baseline levels of TSAT and ferritin, history of poor response to oral iron, total dose of iron, and race.

Major secondary endpoints

Among patients in the mITT population a statistically significantly greater proportion of VIT-45 patients attained a Hb value > 120 g/L at any time between baseline and the end of study or time of intervention: 166/288 (72.8%) in the VIT-45 group versus 112/225 (49.8) in the FS group (p<0.001). Similar results were observed in the EP with 75.1% (VIT-45) and 51.2% (FS), respectively). The proportion of patients with an increase in Hb ≥30 g/L at any time between baseline and the end of study or time of intervention in the mITT population was statistically significantly greater in the VIT-45 group (121/128; 53.1%) compared to the FS (80/225; 35.6%) group p<0.001). Similar results were observed in the EP with 53.5% (VIT-45) and 27.1% (FS), respectively.

The median time to success among the 187 patients who achieved success in the VIT-45 group was 26 days compared to 28 days among the 139 patients who achieved success in the FS group in the mITT population. Similar results were observed in the EP with 27 days in the VIT-45 group and 28 in the FS group.

Statistically significant mean increases from baseline in haemoglobin values were observed at Days 7, 14, 28, and 42 in both the VIT-45 and oral iron groups. The mean increases from baseline in haemoglobin in the VIT-45 group were statistically significantly greater than those observed in the oral iron group at each visit, except at Day 7.

Statistically significant mean increases from baseline in TSAT values were observed at Days 7, 14, 28, and 42 in both the VIT-45 and oral iron groups. The mean increase from baseline in TSAT in the VIT-45 group was greater than that observed in the oral iron group at Day 28, though the results was not statistically significant.

Statistically significant mean increases from baseline in ferritin values were observed at Days 7, 14, 28, and 42 in both the VIT-45 and oral iron groups. The mean increases from baseline in ferritin in the VIT-45 group were statistically significantly greater than those observed in the oral iron group at each visit.

Evaluator Comment

In this study VIT-45 was superior to oral iron in restoring Hb levels, and was therefore shown to be effective in treating IDA in patients with HUB.

Studies in post-partum anaemia

Study VIT-IV-CL-009

Study VIT-IV-CL-009 was a multicentre, randomised, open-label, parallel-group Phase III study in women suffering from post-partum anaemia. The primary objective of the study was to evaluate the non-inferiority in efficacy of IV VIT-45 in comparison with oral ferrous sulphate in reducing iron deficiency anaemia in women with post-partum anaemia. The secondary objectives were to investigate the safety and tolerability of VIT-45 in comparison with comparator drug and to investigate the safety of VIT-45 in lactating mothers (safety of mother and breast-fed infant).

The main criteria for inclusion were:

- Adult women (≥18 years old) with post-partum anaemia within 6 days after delivery.

- Post-partum anaemia defined as Hb ≤100 g/L. After implementation of amendment 4 this was changed to Hb ≤105 g/L as calculated from the average of two assessments taken on separate days within 48 to 96 hours post-partum; to be eligible, both values had to be ≤105 g/L or, if one of the two Hb values was greater than 105 g/L, the average of both Hb values had to be ≤105 g/L and the difference between the two samples could not be> 10 g/L. Patients who met all criteria, except the last condition could be re-screened (that is, two further Hb assessments on separate days) within 6 days post-partum.

Efficacy endpoints

The primary efficacy endpoint was the change in Hb from baseline to Week 12.

Secondary efficacy endpoints were:

- Change from baseline in Hb at Weeks 2 and 4.

- Change from baseline in serum ferritin at Weeks 2, 4, and 12.

- Change from baseline in transferrin saturation (TSAT) at Weeks 2, 4, and 12.

- Number and proportion of women achieving target Hb levels (120 to 160 g/L) at Weeks 2, 4, and 12.

- Number and proportion of women achieving target serum ferritin levels (50 to 800 µg/L) at Weeks 2, 4, and 12.

- Number and proportion of women achieving target TSAT (20 to 50%) at Weeks 2, 4, and 12.

- Number and proportion of women receiving transfusions.

Statistical methods

For the change in Hb from baseline to Week 12, the analysis was performed by calculating the 2 sided 95% CI for the difference "VIT-45 minus ferrous sulphate" in Hb change from an analysis of covariance (ANCOVA), and non inferiority was concluded if the lower bound was ≥5g/L. Descriptive statistics were tabulated for measured values and for absolute changes from baseline to all subsequent time points, including 95% CIs for changes from baseline.

Study population

Overall, the mean gestational age was 39.49 weeks for the safety set and 39.52 weeks for the PP set. Most patients had only one infant (98.8% of patients in the safety set and 98.9% of patients in the PP set), and live births (99.7% of patients in the safety set and 99.6% of patients in the PP set). Delivery method in most patients was vaginal (63.0% of patients in the safety set and 62.5% of patients in the PP set). There was no clinically relevant difference between the two treatment groups or between the safety and PP sets overall, by severity of anaemia, by country or by enrolment in terms of the proportion of patients with medical and surgical history.

Efficacy results

Primary efficacy endpoint: haemoglobin change from baseline levels to Week 12

Hb values by visit for the ITT and PP set are summarised in Table 18. In the PP set, the mean Hb concentration at baseline was increased from 96.7 g/L (VIT-45) and 96.0 g/L (ferrous sulphate) to 130.4 g/L (VIT-45) and 128.9 g/L (ferrous sulphate) at Week 12, which resulted in a mean increase of Hb of 33.7 g/L in the VIT-45 group and a mean increase of 32.9 g/L in the ferrous sulphate group.

Table 18: Haemoglobin by visit (ITT and PP set, Study VIT-IV-CL-009)

Hb [g/L] Mean (SD)	Values by visit			
	VIT-45		Ferrous sulphate	
	ITT (N = 227)	PP (N = 179)	ITT (N = 117)	PP (N = 89)
Baseline	96.6 (14.6)	96.7 (14.7)	97.6 (15.8)	96.0 (12.8)
Week 2	119.2 (12.8)	119.5 (12.9)	119.7 (11.9)	118.6 (10.1)
Week 4	126.2 (10.4)	126.2 (10.6)	125.1 (8.6)	125.3 (8.5)
Week 12	129.6 (12.0)	130.4 (10.7)	128.7 (10.4)	128.9 (10.4)

For the primary efficacy endpoint "Hb change from baseline to Week 12", the lower bound of the 95% CI difference "VIT-45 versus ferrous sulphate" was –0.69 for the PP set and –1.47 for the ITT set and thus above the pre-specified non-inferiority margin of –5 g/L; thus non-inferiority of VIT-45 versus ferrous sulphate can be concluded. However, superiority cannot be concluded because the lower limits of the CIs are below zero.

Mean Hb levels increased in both treatment groups from baseline to Week 12 for patients enrolled both before and after amendment 4. Mean Hb levels at each visit were similar between treatment groups, although mean baseline Hb levels were slightly higher after amendment 4 (as expected) and mean Hb levels at Week 12 were slightly higher before amendment 4 for VIT-45 versus after amendment 4.

ANCOVA of the primary efficacy variable (Hb change from baseline to Week 12) showed that there was a statistically significant effect of "enrolment" (p=0.0014 for the PP set),

that is, results for the primary efficacy endpoint in the two sub-populations of patients enrolled before versus after the implementation of amendment 4 were different. In the PP set, the mean increase of Hb was greater in patients enrolled before implementation of amendment 4 (36.9 g/L for VIT-45 and 37.5 g/L for ferrous sulphate) compared to patients enrolled after implementation of amendment 4 (28.2 g/L) compared to ferrous sulphate (24.0 g/L).

Secondary efficacy endpoints for haemoglobin

Haemoglobin: Change from baseline

The mean Hb values increased in both treatment groups after 2, 4, and 12 weeks. For the change from baseline of Hb including interactions at Weeks 2 and 4 the lower bound of the 95% CI for the difference "VIT-45 – ferrous sulphate" at Week 2 was –2.21 for the PP set and –3.10 for the ITT set; and at Week 4 was –1.45 for the PP set and –0.89 for the ITT set, and thus above the pre-specified non-inferiority margin of –5 g/L. Therefore non-inferiority, but not superiority (the lower limits of the CIs are below zero) of VIT-45 versus ferrous sulphate can be concluded at these two time points. However, it should be noted that the non-inferiority analyses for the secondary efficacy endpoints are not part of the confirmatory analysis, but have to be considered as descriptive analyses.

Haemoglobin: Secondary response rate for measured haemoglobin values

The estimate of the response rate for measured Hb was defined as the percentage of patients reaching Hb target levels of 120-160 g/L. The percentage of responders was higher in the VIT-45 group than in the ferrous sulphate group for Weeks 2, 4 and 12. At Week 2 approximately half of the patients responded to treatment. There were no statistically significant differences in the percentage of responders between the two treatments.

Secondary efficacy endpoints for serum ferritin

Serum ferritin: Change from baseline

Mean serum ferritin changes from baseline were higher in the VIT-45 group than in the ferrous sulphate group at all visits (Table 19). Mean serum ferritin change from baseline to Week 12 was 123.9 µg/L and 115.1 µg/L in the VIT-45 group and 11.2 µg/L and 8.1 µg/L in the ferrous sulphate group in the PP and ITT sets, respectively.

Table 19: Serum ferritin by visit and change from baseline (ITT and PP set, Study VIT-IV-CL-009)

Mean serum ferritin (SD) [µg/L]	Values by visit		Change from baseline	
	VIT-45	Ferrous sulphate	VIT-45	Ferrous sulphate
ITT population	(N = 227)	(N = 117)		
Baseline	45.5 (110.9)	33.4 (27.7)		
Week 2	490.3 (305.9)	35.8 (29.6)	456.5 (313.1)	1.9 (34.8)
Week 4	305.7 (216.0)	37.5 (25.8)	272.5 (208.8)	2.8 (32.4)
Week 12	158.3 (133.4)	42.0 (32.7)	115.1 (163.7)	8.1 (43.2)
PP population	(N = 179)	(N = 89)		
Baseline	39.9 (63.7)	32.4 (21.7)	-	-
Week 2	501.9 (302.6)	34.8 (29.6)	473.1 (298.5)	2.1 (30.5)
Week 4	313.5 (212.4)	35.7 (23.4)	279.4 (210.2)	2.3 (26.2)
Week 12	161.2 (120.0)	43.3 (34.0)	123.9 (126.0)	11.2 (38.7)

Mean serum ferritin levels for the patients receiving VIT-45 increased markedly from baseline to Week 2. Although levels decreased at the assessment at Weeks 4 and 12, serum ferritin levels remained elevated above the lower target limit compared to baseline. Mean serum ferritin levels for patients receiving ferrous sulphate increased slightly from baseline to each visit. The mean serum ferritin value at baseline was higher for the VIT-45 group compared to the ferrous sulphate group (39.9 µg/L versus 32.4 µg/L in the PP set and 45.5 µg/L versus 33.4 µg/L in the ITT set), while at Week 12 the mean values were 161.2 µg/L (158.3 µg/L in the ITT set) and 43.3 µg/L (42.0 µg/L in the ITT set), respectively. The mean serum ferritin value at Week 12 for patients in the VIT-45 group was therefore more than three times the value compared to patients receiving oral ferrous sulphate.

Although VIT-45 was administered for a shorter period of time (1-3 weeks) than ferrous sulphate (12 weeks), the effect was long lasting as can be seen from the Week 12 mean serum ferritin values that stayed elevated compared to baseline several weeks after the last dose of VIT-45 was administered. At all visits the increase of serum ferritin in the PP set was statistically significantly higher after treatment with VIT-45 as compared to treatment with ferrous sulphate ($p < 0.0001$ at Weeks 2, 4 and 12).

Serum ferritin: Secondary response rate

In this study the estimate of the response rate for serum ferritin was defined as the percentage of patients who achieved target levels of 50-800 µg/L. The percentage of responders was much higher in the VIT-45 group than in the ferrous sulphate group for all visits. In the PP set, at Week 2 it was 70.9% for patients in the VIT-45 group and 13.5% for patients in the ferrous sulphate group. The percentage of responders increased to Week 4 (83.3%) and decreased to Week 12 (77.7%) for patients in the VIT-45 group. The percentage of responders in the ferrous sulphate group increased from Week 2 (13.5%) to Weeks 4 and 12 (16.9% and 32.6%, respectively). In the ITT set, at Week 2 it was 63.9% for patients in the VIT-45 group and 14.5% for patients in the ferrous sulphate group. The percentage of responders increased to Week 4 (72.2%) and decreased to Week 12 (69.2%) for patients in the VIT-45 group. The percentage of responders in the ferrous sulphate group increased from Week 2 (14.5%) to Weeks 4 and 12 (17.1% and 27.4%, respectively). Patients in the ferrous sulphate group received treatment for 12 weeks, while the patients in the VIT-45 group received treatment for only up to 3 weeks. The low response rate for ferrous sulphate at Weeks 4 and 12 indicates that iron absorbed from the intestines does not lead to a fast build up of iron stores due to continuous iron utilisation by the bone marrow. The percentage responders for serum ferritin was statistically significantly different between the two treatments for Weeks 2, 4 and 12 with patients in the VIT-45 group having a higher and faster response rate for serum ferritin than patients in the ferrous sulphate group.

Secondary efficacy endpoints for transferrin saturation

Transferrin saturation: Change from baseline

Mean TSAT levels increased from baseline to Weeks 2 and 4, but decreased at Week 12 for both treatment groups (Table 20). The mean TSAT levels were higher in the VIT-45 group at all visits (except baseline) than for the ferrous sulphate group. At Week 12, TSAT was 34.4% and 34.5% for VIT-45 and 26.5% and 27.2% for ferrous sulphate in the PP and ITT sets, respectively. Enrolment before versus after amendment 4 had no statistically significant effect on the change in TSAT from baseline to all visits.

Table 20: Transferrin saturation by visit and change from baseline (ITT and PP set, Study VIT-IV-CL-009)

TSAT (SD) [%]	Values by visit		Change from baseline	
	VIT-45	Ferrous sulphate	VIT-45	Ferrous sulphate
ITT	(N = 227)	(N = 117)		
Baseline	12.1 (9.9)	12.8 (9.5)		
Week 2	35.2 (20.0)	26.6 (24.4)	22.8 (19.8)	14.2 (23.3)
Week 4	39.1 (17.6)	27.9 (19.3)	26.7 (18.4)	14.8 (17.1)
Week 12	34.5 (14.3)	27.2 (12.8)	22.2 (18.0)	14.5 (14.3)
PP	(N = 179)	(N = 89)		
Baseline	11.7 (8.8)	12.2 (9.0)	-	-
Week 2	36.0 (20.3)	26.2 (24.6)	24.2 (19.4)	14.2 (22.7)
Week 4	40.1 (17.6)	27.9 (20.1)	28.3 (17.8)	15.7 (16.9)
Week 12	34.4 (13.7)	26.5 (12.3)	22.7 (16.5)	14.3 (14.0)

Transferrin saturation: Secondary response rate

In this study the estimate of the response rate for TSAT was defined as the percentage of patients who achieved target levels of 20-50%. The percentage of responders was higher in the VIT-45 group than in the ferrous sulphate group for all visits. The percentage of responders increased with each visit from Week 2 (69.8% and 63.0%, PP and ITT set, respectively) to Week 12 (77.7% and 69.2%, PP and ITT set, respectively) for the patients in the VIT-45 group. The percentage of responders increased from Week 2 (36.0% and 34.2%, PP and ITT set, respectively) to Week 12 (66.3% and 59.8%, PP and ITT set, respectively) for patients in the ferrous sulphate group. The differences between the two treatment groups with respect to the percentage of responders at Weeks 2, 4 and 12 were statistically significant with patients in the VIT-45 group having a higher response rate than patients in the ferrous sulphate group. The VIT-45 group showed a more rapid response than the ferrous sulphate group, which was sustained up to Week 12. In the PP set, the response rate for the ferrous sulphate group at Week 4 was higher for patients included before versus after amendment 4 (70.0% versus 40.7%). Response rates for other visits were similar for patients included before versus after amendment 4.

Breastmilk substudy

Mean iron values in breastmilk for the VIT-45 group increased from baseline from a pre dose value of 0.500 mg/kg to 1.447 mg/kg 24 hours post-dose. Iron values decreased to 48 hours post-dose (0.601 mg/kg) and Week 1 pre-dose (0.513 mg/kg), increasing again at Week 1, 1-3 hours post-dose (0.615 mg/kg) and Week 2 pre-dose (0.991 mg/kg). Mean iron values in breastmilk for the ferrous sulphate group decreased from a pre-dose baseline value of 0.407 mg/kg to 0.347 mg/kg 24 hours post-dose. The values increased during Week 1 and to 0.779 mg/kg pre-dose at Week 2. The iron values 24 and 48 hours post-dose at baseline and pre-dose Week 1 were higher in the VIT-45 group than for the ferrous sulphate group. The maximum iron level observed in breastmilk samples was 9.96 mg/kg by only one patient in the VIT-45 group, 24 hours post-baseline. At 48-hours post-baseline, the change from baseline of iron breastmilk was statistically significantly higher (p=0.0052) in the VIT-45 group (0.101 mg/kg) compared to the ferrous sulphate group (-0.075 mg/kg). The values for the other visits were similar for the two treatment groups.

Evaluator Comment

Based on the primary response parameter of change in mean Hb from baseline to Week 12, the results of this study demonstrated that VIT-45 was non inferior to ferrous sulphate. Results of secondary endpoints further supported efficacy of ferric carboxymaltose.

Study 1VIT03001

Study 1VIT03001 was a multicentre, randomised, open-label, active control, Phase III study in women suffering from post-partum anaemia. The primary objective of this study was to evaluate the non-inferiority in efficacy of IV VIT-45 in comparison with oral ferrous sulphate in improving Hb in post-partum anaemia. The secondary objective was to evaluate the safety and tolerability of parenteral VIT-45 in comparison with oral ferrous sulphate in post-partum anaemia.

The main criteria for inclusion were:

- Female patients able to give informed consent.

- Post-partum within 10 days after delivery.

- Hb ≤100 g/L at baseline, based on an average of 2 Hb values drawn 18 hours post-partum. Baseline Hb No. 2 must have been drawn ≥12 hours from baseline Hb No. 1. The difference between the Hb values must have been ≤10 g/L. The first dose of study drug must have been given within 32 hours of the baseline Hb No. 2 being drawn. A third baseline Hb may have been allowed.

- Patients must have agreed to practice an acceptable form of birth control once sexual activity was resumed.

- Demonstrated the ability to understand the requirements of the study, willingness to abide by study restrictions, and to return for the required assessments.

Efficacy endpoints

The primary efficacy endpoint was 'success' defined as number of patients with an increase in Hb levels of ≥20 g/L anytime between baseline and Week 6 (end of study).

Secondary measures of efficacy included:

• Number and proportion of patient attaining a Hb > 120 g/L at any time.

• Proportion of patients with an increase in Hb ≥30 g/L anytime between baseline and end of study or time of intervention.

• Time to success.

• Highest change in Hb over baseline.

• Time to highest Hb, defined as the days between first dose and the day when the highest on study Hb was reached.

• Change from baseline to highest ferritin, TSAT, reticulocyte count, and reticulocyte Hb content during the study.

• Number of patients requiring intervention.

• Time to intervention, defined as the days between randomisation and the day of intervention or end of study, whichever came first. The observation was censored if no intervention was necessary.

• Number and percent of patients with change from baseline in Hb ≥20 g/L and change from baseline in ferritin ≥160 µg/L.

• Comparison in changes of iron indices from baseline in various combinations.

• Improvement based on the Quality of Life assessments.

Statistical methods

The primary assessment of the non-inferiority of VIT-45 to oral iron was assessed at the 0.025 alpha level, 1-tailed. All other statistical tests were at the 0.05 alpha level, 2-tailed, unless stated otherwise. The non-inferiority of the proportion of patients 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%. If noninferiority was established as described above, superiority of VIT-45 compared to ferrous sulphate was assessed and was declared if the lower bound of the CI was greater than zero.

The effect of baseline characteristics on the primary efficacy endpoint was examined by means of logistic regression. Covariates included baseline Hb, baseline ferritin, baseline TSAT, age, race, method of delivery (vaginal, C-section), estimated blood loss from delivery, and number of neonates delivered.

Change from baseline to highest haemoglobin, to highest TSAT, to highest reticulocyte count, to highest reticulocyte haemoglobin content, and to highest ferritin was assessed for treatment group differences with the t-test for independent groups. Change from baseline to each visit was similarly assessed for Hb, TSAT, ferritin, reticulocyte count, and reticulocyte Hb content and Fatigue Linear Analogue Scale. Missing data were not estimated for this analysis.

The proportion of patients achieving each of the previously defined efficacy and quality of life criteria at any time during the study was assessed for treatment differences with Fisher's exact test. Time to intervention was characterised by means of Kaplan-Meier for each treatment group and was analysed for treatment group differences using the log-rank test incorporating a life table approach.

Study population

A total of 352 patients were included in the safety set, 337 patients in the modified ITT set and 312 patients in the EP set. The modified ITT set was defined as patients from the safety population who received at least one dose of study medication and had at least one post-baseline Hb assessment and had post-partum anaemia characterised by an average of the two baseline Hb being < 110 g/L. The EP which was defined as those patients from the modified ITT population who received at least 67% of the required study drug and were followed until the Day 42 (end of study) evaluation and had no major protocol violations.

A statistically significant difference was observed between the treatment groups in the Safety Population for weight at screening; subjects in the oral iron group had a greater mean weight at screening (80.78 kg) compared with subjects in the VIT-45 group (76.44 kg). No other statistically significant differences were observed between the treatment groups in the Safety Population for any of the demographic characteristics. Mean subject age was 26.93 years in the VIT-45 group and 26.03 years in the oral iron group. The mean estimated blood loss from delivery was 534.70 cc in the VIT-45 group and 558.27 cc in the oral iron group. Mean haemoglobin, TSAT, and ferritin values at baseline were similar between the VIT-45 (9.00 g/dL, 10.54%, and 25.99 ng/mL, respectively) and oral iron (9.02 g/dL, 9.74%, 23.70 ng/mL, respectively) treatment groups. The proportion of subjects with a baseline haemoglobin ≤8.0 g/dL at randomisation was 19.0% in the VIT-45 group and 17.4% in the oral iron group.

Efficacy results

Primary efficacy endpoint: 'Success' - number of patients with an increase in Hb levels of ≥20 g/L anytime

The proportions of patients who achieved success anytime during the study, defined as a ≥20 g/L increase in Hb, were similar between the VIT-45 (96.4%) and oral ferrous sulphate (94.1%) treatment groups and non-inferiority of VIT-45 relative to oral ferrous sulphate was demonstrated. Similar results were observed for the modified ITT and the EP analysis set. The primary efficacy analysis was the non-inferiority of the proportion of patients who achieved success for VIT-45 relative to oral ferrous sulphate based on a 1-sided 97.5% CI on the treatment difference with a non-inferiority margin of 15%. The CI for the difference in success rates demonstrated the non-inferiority of VIT-45 relative to ferrous sulphate.

Secondary efficacy endpoints for haemoglobin

Hb: Proportion of patients who achieved success by study visit

Among patients in the modified ITT population, greater proportions of VIT-45 patients compared with oral ferrous sulphate patients achieved success on or before each visit (Table 21). The differences between the treatment groups were statistically significant at Days 7 and 14 using both the last observation carried forward and observed cases methods, and at Day28 using the observed cases method. The proportions of patients who achieved success on or before Day 42 were comparable between the treatment groups.

Table 21: Proportion of patients who achieved success (≥20 g/L increase from baseline in Hb) on or before each visit during the study (modified ITT set, Study 1VIT03001)

Visit	N/N (%) patients		p-value
	VIT-45	Ferrous sulphate	
Last observation carried forward			
Day 7	98/168 (58.3%)	65/169 (38.5%)	0.0003
Day 14	147/168 (87.5%)	122/169 (72.2%)	0.0006
Day 28	160/168 (95.2%)	151/169 (89.3%)	0.0644
Day 42	162/168 (96.4%)	159/169 (94.1%)	0.4433
Observed Cases			
Day 7	98/168 (58.3%)	65/164 (39.6%)	0.0007
Day 14	144/167 (86.2%)	111/162 (68.5%)	0.0001
Day 28	153/163 (93.9%)	139/163 (85.3%)	0.0174
Day 42	151/163 (92.6%)	143/161 (88.8%)	0.2556

Hb: Time to success achieving ≥20 g/L increase from baseline in haemoglobin

Patients in the VIT-45 group achieved success earlier compared with patients in the oral 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 VIT-45 patients (7.0 days) compared with oral ferrous sulphate (14.0 days) patients. Similar results were observed in the EP analysis set.

Hb: Change from baseline

Statistically significant mean increases from baseline in Hb values were observed at Days 7, 14, 28 and 42 in both the VIT-45 and oral ferrous sulphate groups. The mean increases from baseline in Hb in the VIT-45 group were statistically significantly greater than those observed in the oral ferrous sulphate group at each visit. Additionally, a statistically

significantly greater increase from baseline to the highest Hb value attained during the study was observed in the VIT-45 group (42 g/L) compared with the oral ferrous sulphate group (34 g/L). Similar results were obtained for mean changes from baseline in Hb to each visit and to the highest Hb value attained during the study in the EP analysis set.

Secondary efficacy endpoints for serum ferritin

Serum ferritin: Change from baseline

Statistically significant mean increases from baseline in ferritin values were observed at Days 7, 14, 28, and 42 in the VIT-45 group. In the oral ferrous sulphate group, a small increase in ferritin was noted at Day 7, with small decreases noted at Days 14, 28, and 42. The mean increases from baseline in ferritin in the VIT-45 group were statistically significantly greater than those observed in the oral ferrous sulphate group at each visit. Statistically significant increases from baseline to the highest ferritin value attained during the study were observed in both the VIT-45 (622.7 µg/L) and oral ferrous sulphate (10.0 µg/L) groups; the difference between the treatment groups was statistically significant. Similar results were also obtained for mean changes from baseline in ferritin to each visit and to the highest ferritin value attained during the study in the EP analysis set.

Secondary efficacy endpoints for transferrin saturation

TSAT: Change from baseline

Statistically significant mean increases from baseline in TSAT values were observed at Days 7, 14, 28, and 42 in both the VIT-45 and oral ferrous sulphate groups. The mean increases from baseline in TSAT in the VIT-45 group were statistically significantly greater than those observed in the oral ferrous sulphate group at Days 14, 28 and 42. Additionally, a statistically significantly greater increase from baseline to the highest TSAT value attained during the study was observed in the VIT-45 group (34.1%) compared with the oral ferrous sulphate group (29.8%). Similar results were obtained for mean changes from baseline in TSAT to each visit and to the highest TSAT value attained during the study in the EP analysis set, except that the mean change from baseline to the highest TSAT value attained during the study only approached statistical significance (p=0.0531).

Additional haematological secondary efficacy endpoints

Statistically significantly greater increases from baseline to the highest value attained during the study for reticulocyte count (1.7% vs 0.6%), and reticulocyte Hb (4.7 pg vs 2.3 pg) were also observed in the VIT-45 group compared with the oral ferrous sulphate group. In addition, a statistically significantly greater proportion of patients in the VIT-45 group had an increase in Hb ≥20 g/L and ferritin ≥160 µg/L compared with the oral ferrous sulphate group at each visit and at anytime during the study.

Secondary efficacy endpoint Quality of Life

In the analyses of the Fatigue Linear Analog Scale and SF-36 data (modified ITT analysis set), no statistically significant differences were observed between the treatment groups. The mean decrease from baseline to the lowest score on the Fatigue Linear Analog Scale was – 35.9 in the VIT-45 group and –35.4 in the oral ferrous sulphate group. The difference between the treatment groups in the mean change from baseline to the lowest score on the Fatigue Linear Analog Scale was not statistically significant. Using the normalised SF-36 data, no statistically significant differences were observed between the treatment groups for the mean change from baseline to Days 14, 28 and 42, to the maximum value in SF-36 total score or in the health concept categories of physical functioning, role-physical, role-emotional, social function, bodily pain, mental health, vitality, and general health.

Subgroup analyses

No consistent trends were apparent among VIT-45 patients when the primary efficacy parameter and the secondary efficacy parameters of patients who achieved Hb concentrations > 120 g/L and patients who had an increase in Hb ≥30 g/L at anytime during the study were analysed according to baseline Hb, method of delivery, baseline TSAT and ferritin, age, race and centre.

Evaluator Comment

The proportions of patients who achieved success anytime during the study, defined as a ≥20 g/L increase in Hb, were similar between the VIT-45 (96.4%) and oral ferrous sulphate (94.1%) treatment groups and non-inferiority of VIT-45 relative to oral ferrous sulphate was demonstrated.

Study 1VIT06011

Study 1VIT06011 was an open-label, phase III, randomised active control study evaluating the safety and efficacy of intravenous VIT-45 and oral ferrous sulphate in improving haemoglobin levels in post-partum anaemia requiring iron supplementation. All eligible patients were stratified by Hb levels (91-100 g/L, 81-90 g/L, <80 g/L) and requirement for Caesarean section and screening iron indices (ferritin ≤25 ng/mL and ferritin > 25 ng/mL).

The main criteria for inclusion were as follows:

- Female patients, post-partum within 10 days after delivery

- Baseline HB ≤100 g/L based on the average of the last consecutive 2 Hb values drawn ≥18 hours post-partum. The difference between the Hb values had to be ≤10 g/L.

Efficacy endpoints

The primary endpoint for efficacy was the number of patients achieving success, defined as an increase to Hb values of ≥120.0 g/L anytime between baseline and end of study of time of intervention. Failure was defined as the number of patients with ≤120 g/L increase in Hb at all times between baseline and end of study or intervention.

Major secondary endpoints included:

- The number and proportion of patients attaining an Hb increase by ≥30 g/L at any time between baseline and the end of study or time of intervention.
- The proportion of patients who met the criteria for success on or before Day 42, 28 or 14.
- The proportion of patients with an increase in Hb ≥30 g/L on or before Day 42, 28 or 14.
- Time to success.

Other secondary endpoints included:

- Mean change from baseline to each visit and to highest Hb, ferritin and TSAT, respectively, during the study and improvement based on Rating of Physical Energy and on Fatigue Severity Scale.

Statistical methods

Treatment group differences were assessed with Fisher's exact test. For efficacy analyses patients were analysed under treatment actually received. Quantitative characteristics (age, pre-pregnancy weight, weight, obstetrical history and estimated blood loss from

delivery) were summarised with sample size, mean, median, standard deviation, minimum and maximum value.

Treatment group differences in the mean were assessed with the t-test for independent groups. The statistical tests were done at 0.05 alpha levels, two-tailed (unless stated otherwise). The effect of baseline characteristics on the primary efficacy endpoint was examined by means of logistic regression.

Efficacy analyses were performed for the mITT population and the EP. The mITT was defined as patients from the safety population (dosed at least once) who received at least 1 dose of study medication, and had at least one post-baseline Hb assessment. The EP was defined as those patients from the mITT population who were followed until Day 42, received at least 67% of the required study drug, and had no major protocol violations. The primary efficacy analysis was the superiority of the proportion of patients who achieved success for VIT-45 relative to oral iron based on a 2-sided Fisher's exact test on the unstratified success rate.

Study population

A total of 291 patients (ITT) were randomised at 28 centres to receive VTI-45 (143 patients) or oral ferrous sulphate (148 patients), 142 patients were treated in the VIT-45-group and 147 in the ferrous sulphate-group, respectively (total 289, safety population). A statistically significant difference was observed between the treatment groups in the Safety Population for weight at screening; subjects in the oral iron group had a greater mean weight at screening (80.78 kg) compared with subjects in the VIT-45 group (76.44 kg). No other statistically significant differences were observed between the treatment groups in the Safety Population for any of the demographic characteristics. Mean subject age was 26.93 years in the VIT-45 group and 26.03 years in the oral iron group.

Efficacy results

Primary efficacy endpoint

Among the patients in the mITT population a statistically significant difference was observed between the VIT-45 and the FS groups in the proportion of patients who achieved success, defined as haemoglobin ≥120.0 g/L ($p<0.001$); a statistically significantly greater proportion of subjects in the VIT-45 group (127/139; 91.4%) achieved success (haemoglobin >12.0 g/dL anytime during the study) compared with the FS group (98/147; 66.7%); similar results were observed in the EP.

Logistic regression analysis confirmed the superiority of VIT-45 to oral iron. Baseline Hb, race and prior intolerance to iron were statistically significant predictive factors in the mITT population. VIT-45 patients with baseline Hb concentrations of ≤00.0 g/L achieved better responses than patients treated with oral iron, while responses among the 15 patients with baseline Hb concentrations ≥100 g/L were similar between treatment groups. Similar results were also observed in the EP and ITT populations.

Major secondary endpoints

The proportion of patients with an increase in Hb ≥30.0 g/L at any time between baseline and the end of study or time of intervention in the mITT population was statistically significantly greater in the VIT-45 group (127/139; 91.4%) compared to the FS group (95/147; 64.6%), $p<0.0001$. Similar results were observed in the EP with 91.3% (VIT-45) and 64.3% (FS), respectively.

Among patients in the mITT population a statistically significantly greater proportion of VIT-45- patients attained an Hb value >120 g/L at any time between baseline and the end of study or time of intervention. The differences between the groups were statistically

significant at Days 14, 28 and 42. The proportion of patients with an increase in Hb ≥30.0 g/L on or before Day 42, 28 and 14 was statistically significantly greater in the VIT-45 group in the mITT population compared to the FS group, all p<0.0001.

The median time to success among the 127 patients who achieved success in the VIT-45 group was 14 days compared to 27 days among the 98 patients who achieved success in the FS group in the mITT population.

Other secondary endpoints

The mean change from baseline to the highest Hb-, TSAT- and ferritin value, respectively, attained during the study was statistically significantly greater in the VIT-45 group compared to oral iron. In relation to mean increases in Physical Energy VAS Scale in the study results between the treatment groups were not statistically significant.

Evaluator Comment

VIT-45 showed superior efficacy compared to oral iron in the treatment of IDA in postpartum patients treated for 42 days.

Pilot studies

Study FER-CARS-01

Study FER-CARS-01 was a randomised, double-blind, multicentre, three-arm, placebo and active-controlled, parallel-group pilot study. The study consisted of a screening phase (up to 4 weeks before randomisation), an initial phase (4 weeks), a maintenance phase (8 weeks) and a follow-up visit (2 weeks after Week 12 or earlier in case of withdrawal).

The main criteria for inclusion were as follows:

- Consenting male and female patients aged ≥18 years with CHF, renal failure and iron deficiency and without interfering concomitant conditions.

Efficacy endpoints

The primary endpoint was the change in patient global assessment (PGA) and in clinical symptom status (New York Heart Association [NYHA] status) from baseline to follow-up.

Secondary endpoints included:

- Number of patients-responders in each group (defined as improvement in PGA, at least by + 1 point and reduction in NYHA class by at least 1 class at the end of treatment compared to baseline);
- Change in exercise tolerance (6 minute walking test, peak oxygen consumption/uptake [VO2]);
- Change in Hb level from baseline to follow-up; and change in serum iron status from baseline to follow-up.

Statistical methods

Study FER-CARS-01 was a pilot study and was not powered to show superiority of VIT-45. The LOCF method was used was used for handling of missing active treatment period data (baseline values were not carried forward). Interference statistics included Fisher's exact (qualitative data) or Wilcoxon-Mann-Whitney test (ordinal data) and two-sample t-tests or Wilcoxon rank sum test (depending on distribution of the variable for quantitative data). Change in NYHA classes within treatment groups was assessed with Bowker's test of symmetry.

Efficacy analyses were performed for the ITT population (full analysis set), consisting of all patients who took at least one dose of study drug and had both a baseline and a post-baseline efficacy measurement; for the PP (patients from the ITT population who completed the study protocol, and had no significant protocol violations); as well as for the safety set (patients who took at least one dose of study drug). The allocation of patients to the PP set was carried out using a pre-defined list of significant protocol violations.

Study population

A total of 72 patients were randomised into the study (full analysis set and safety set). Thirty patients were randomised to receive VIT-45; 27 to receive Venofer; and 15 to receive placebo. All patients in the VIT-45 group completed the study, 24 of 27 in the Venofer group and 13 of 15 in the placebo group.

In the VIT-45 group, the mean (STD) age was 70.0 (10.2) years and 56.7% of the patients were female. In the Venofer group the mean age was 68.1 (13.6) years and 63.0% of the patients were female. In the placebo group the mean age was 70.1 (11.6) years and 46.7% of the patients were female. All patients were Caucasian. The treatment groups did not differ statistically with respect to demographic characteristics.

There were no clinically relevant differences between treatment groups in vital signs or physical examination at baseline. The majority of patients (≥80% in all treatment groups) had NYHA Class III at baseline. Over 70% of patients in each treatment group had chronic renal failure. Mean (STD) baseline Hb was 12.4 (1.7) g/dL in the VIT-45 group, 12.1 (1.2) g/dL in the Venofer group and 12.3 (1.4) g/dL in the placebo group. Mean baseline ferritin was between 71 and 77 µg/L across treatment groups, and mean baseline TSAT was between 16 and 19% across groups. There were no statistically significant between-group differences.

Efficacy results

An improvement in PGA score was observed in 80% of patients in the VIT-45 group and in 74% of patients in the Venofer group, and an improvement in NYHA class by 1 step, from baseline to last observation, was observed in 23% and 33% of patients, respectively. A lower proportion of patients in the placebo group showed an improvement in PGA score or improvement in NYHA class (47% and 13%, respectively). However, none of the between-group differences in change of PGA and NYHA between last observation and baseline was statistically significant.

Major secondary endpoints

None of the between-group differences in number of responders (defined as improvement in PGA at least by +1 point and NYHA class at least by -1 class at the end of treatment compared to baseline), or change of walking distance and VO2 between baseline and follow-up (Week 14) was statistically significant.

The within-group improvement in walking distance between baseline and follow-up was statistically significant in all treatment groups, whereas the within-group differences in VO2 uptake were not statistically significant in any of the treatment groups.

Other secondary endpoints

There were statistically significant differences between VIT-45 and placebo and between Venofer and placebo (and between active treatment and placebo) for the change in serum ferritin, TSAT and serum transferrin between baseline and follow-up (Week 14). These differences are in line with the within-group differences between baseline and follow-up, which were statistically significant in the VIT-45 and Venofer groups but not in the placebo group.

There were statistically significant differences only between Venofer and placebo for the change in Hb and serum iron between baseline and follow-up. The within-group differences between baseline and follow-up in Hb values were statistically significant in the VIT-45 group and the Venofer group, but not in the placebo group. The within-group differences between baseline and follow-up in serum iron values were statistically significant only in the Venofer group.

Evaluator Comment

Study FER-CARS-01 was not powered to show superiority for VIT-45 with respect to the chosen clinical efficacy parameters. In relation to the laboratory efficacy parameters (Hb, TSAT, transferrin), representative for correcting an iron deficiency status, both active treatments showed superiority versus placebo.

Efficacy - summary and conclusions

The parameters chosen to assess therapeutic response in the clinical studies showed that administration of ferric carboxymaltose (VIT-45) was effective in treating iron deficiency due to various causes. Hb levels increased significantly to expected and clinically acceptable levels.

In Study VIT-IV-CL-015 the primary response rate for haemodialysis patients, defined as an increase in Hb 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 Study 1VIT04004, in patients with NDD-CKD, erythropoietin was maintained at a stable dose during the study. For the primary efficacy endpoint a statistically significant difference was observed between the VIT-45 and the ferrous sulphate groups in the proportion of subjects who achieved an increase in haemoglobin ≥10 g/L (60.4% and 34.7%, respectively).

The long-term efficacy of continuous treatment with VIT-45 was demonstrated in the open-label study 1VIT05005, in which patients from Study 1VIT04004 were included. Here the proportion of subjects achieving haemoglobin values ≥110 g/L ranged from 55% (Day 84) to 64.3% (Day 308).

In Studies VIT-IV-CL-008 and -009, based on the primary efficacy variable (increase in Hb 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 Studies 1VIT06011 and 1VIT03001, conducted in post-partum patients with IDA, the proportion of patients who achieved an increase in Hb levels of ≥12 g/L and ≥20 g/L, respectively, was 91.4% and 96.4% in the VIT-45 group, respectively, and 66.7% and 94.1% in the ferrous sulphate group, respectively. Thus, non-inferiority of VIT-45 relative to oral iron was demonstrated.

In Study 1VIT04002/4003 in patients with heavy uterine bleeding, the proportion of patients who achieved an increase in haemoglobin of ≥20 g/L was statistically significantly greater in the VIT-45 group (82.0%) compared with the oral ferrous sulphate group (61.8%).

Overall, the changes in serum ferritin and TSAT confirmed successful repletion of deficient iron stores in patients treated with VIT-45. Serum ferritin levels were raised 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 (1VIT04004, VIT-IV-CL-008, VIT-IV-CL–009, 1VIT03001,

1VIT06011 and 1VIT04002/4003), the increase of serum ferritin was significantly higher at all visits in patients treated with VIT-45 than in patients treated with ferrous sulphate.

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

Overall, in the studies submitted for evaluation, VIT-45 was shown to be an effective treatment option for patients with iron deficiency. Based on the data from studies 1VIT04004, VIT-IV-CL-008, VIT-IV-CL–009, 1VIT03001, 1VIT06011 and 1VIT04002/4003, VIT-45 is non-inferior to ferrous sulphate for the increase in Hb levels from baseline to Week 6 (1VIT04004, 1VIT03001, 1VIT06011 and 1VIT04002/4003) or Week 12 (VIT-IV-CL-008 and -009) for effectively treating patients with IDA secondary to IBD or HUB or patients with post-partum anaemia. Data support that 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 clinical advantage in specific patients populations needing iron treatment. The evaluator believed that the data submitted for evaluation adequately supported the efficacy of Vit-45 and the indication as proposed by the sponsor.

Safety

Extent of exposure

A tabular summary of study subject drug exposure by maximal single dose during study is provided in Table 22.

Table 22: Study Subject Drug Exposure by Maximal Single Dose during Study

Study	Maximal Single Dose of VIT-45 During Study				
	0 < Dose ≤ 200 mg	200 mg < Dose ≤ 500mg	500 mg < Dose < 1,000 mg	1,000 mg = Dose	Total N
VIT-IV-CL-001	6	0	0	0	6
VIT-IV-CL-02	6	6	6	6	24
VIRD-VIT-25-IM	4	0	0	0	4
VIT-IV-CL-03	0	20	0	26	46
53214	162	0	0	0	162
VIT-IV-CL-015	119	0	0	0	119
VIT-IV-CL-008	0	1	88	48	137
VIT-IV-CL-009	0	0	124	103	227
1VIT03001	2	2	98	72	174
1VIT04002/1VIT04003	0	8	60	162	230
1VIT04004	0	1	34	112	147
1VIT05005*	1	63	8	55	127
1VIT05006	0	2	153	429	584
1VIT06011	0	1	69	72	142
FER-CARS-01	30	0	0	0	30
Total	**330**	**104**	**640**	**1,085**	**2,159**
Percent of total	15.28%	4.82%	29.64%	50.25%	100%

* Study 1VIT05005 was a safety extension of study 1VIT04004, and 75 out of the 127 patients who received VIT-45 during study 1VIT05005 had also received VIT-45 in the previous study. For the purpose of this safety summary, no distinction was made among the 127 patients with respect to the treatment they had received in study 1VIT04004.

Adverse events

Study VIT-IV-CL-001

A total of three adverse events (AEs) occurred during the study, all being of mild severity. One AE (nasopharyngitis) was considered unlikely to be related to study medication; one (dysgeusia) was considered possibly related to study medication; and the other (haematoma) was considered probably/likely related to study medication (the latter event was likely a result of the injection procedure). Due to the small number of patients no tendency in frequency of AEs could be observed. No serious adverse events (SAEs)

occurred in the study population. A dose of 100 mg iron as VIT-45 was shown to be safe and well-tolerated.

Study VIRD-VIT-45-IM

A total of 11 AEs occurred in four patients. There were no severe AEs - 5 and 6 AEs were of mild and moderate intensity, respectively. Headache was reported at two occasions by one patient. Four of the AEs were considered to be unrelated to the study drug, whereas 7 AEs were assessed as being unlikely related. A dose of 100 mg iron as VIT-45 administered as IM injection was shown to be safe and well tolerated.

Study VIT-IV-CL-02

Altogether, 19 AEs occurred in 8 patients. The most frequently observed treatment emergent adverse event (TEAE) was headache which was reported for 5 patients. No TEAEs occurred following placebo administration while 3 drug-related AEs (nausea and vomiting, and headache) were observed in 2 patients (after 100 mg and 1000 mg iron as VIT-45, respectively). There were no severe AEs and all AEs resolved without sequelae. Remedial therapy (paracetamol) due to an AE (headache) was necessary in 3 patients who received 800 to 1000 mg iron as VIT-45. There were no AEs of severe intensity. Injection/infusion of 100 to 1000 mg iron as VIT-45 was safe and well tolerated.

Study VIT-IV-CL-03

A total of 24 TEAEs occurred in 46 patients. TEAEs were experienced by a similar proportion of patients in each dosing cohort (approximately half of the patients). The most frequently reported TEAEs were haematuria (5 patients), C-reactive protein increased (5 patients) and urticaria (2 patients). All other events were reported by one patient only. The majority of TEAEs were considered by the investigator to be unrelated, or of unlikely relationship to the study medication. Only one patient in Cohort 1 reported an event of probable relationship to the study medication (infusion site pain). A total of four patients (20.0%) in Cohort 1 and four patients (15.4%) in Cohort 2 reported events of possible relationship to the study medication. These events were gamma-glutamyl transaminase (GGT) increased, AST increased and ALT increased (1 patient), blood iron and transferrin abnormal (1 patient), urticaria, thrombocythaemia in Cohort 1, and dermatitis allergic, urticaria, reticulocyte count increased and hyperthermia in Cohort 2. A total of three patients (6.5%) experienced allergic skin reactions. In all cases, the allergic rash responded well to symptomatic treatment.

A total of three patients were withdrawn from the study due to TEAEs. Two patients discontinued treatment because of allergic skin reactions (dermatitis allergic and urticaria), the third patient experienced tonsillitis. There were no TEAEs of severe intensity. Overall IV infusions of VIT-45 given weekly over 15 minutes at doses of 500 mg to 1000 mg per dose up to a total maximum dose of 2,000 mg were well tolerated.

Study 53214

More than half (54.6%) of the patients had at least one TEAE. The most frequently reported TEAEs ≥5 patients were: hypertension and headache (13 patients each [8.0%]), hypotension and muscle cramp (8 patients each [4.9%]), respiratory tract infection viral (6 patients [3.7%]) and nausea (5 patients [3.1%]). All other events were reported by less than 5 patients.

There were 8 (4.9%) patients who had at least one severe TEAE, while 12 patients (7.4%) experienced at least one serious TEAE. A total of 5 patients (3.1%) withdrew from the study due to TEAEs. Two patients (1.2%) died during the study.

Study VIT-IV-CL-015

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. The most frequently reported TEAEs in ≥2 patients were: hypotension (12 patients [10.2%] in each of the treatment groups), hypertension (7 patients [5.9%] in the VIT-45 group and 8 patients [6.8%] in the Venofer group), muscle cramp (6 patients [5.0%] in the VIT-45 group and 5 patients [4.2%] in the Venofer group), procedural hypotension (2 patients [1.7%] in the VIT-45 group and 1 patient [0.8] in the Venofer group), headache (3 patients [2.5%] in the VIT-45 group and 5 patients [4.2%] in the Venofer group), blood pressure increased (1 patient [0.8%] in the VIT-45 group and 4 patients [3.4%] in the Venofer group). All other events were reported by less than 5 patients overall.

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. Two patients (1.7%) in the VIT-45 group and five patients (4.2%) in the Venofer group withdrew from the study due to TEAEs. One patient (0.8%) in the VIT-45 group died. The event was unlikely to be related to the study medication as the study medication was withdrawn more than one week before, due to another TEAE.

Study VIT-IV-CL-008

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. The most commonly reported TEAEs in ≥3 patients were: colitis ulcerative (11 patients [8.0%] in the VIT-45 group and 9 patients [14.3%] in the ferrous sulphate group), abdominal pain (7 patients [5.1%] in the VIT-45 group and 2 patients [3.2%] in the ferrous sulphate group), headache (8 patients [5.8%] in the VIT-45 group and 1 patient [1.6%] in the ferrous sulphate group), Crohn's disease, pyrexia and back pain (5 patients [3.6%] in the VIT-45 group and 1 patient [1.6%] in the ferrous sulphate group), diarrhoea (2 patients [1.5%] in the VIT-45 group and 4 patients [6.3%] in the ferrous sulphate group) and nausea (3 patients [2.2%] in the VIT-45 group and 3 patients [4.8%] in the ferrous sulphate group). All other events were reported by less than 6 patients overall.

There were 8 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 9 patients (6.6%) in the VIT-45 group and no patients in the ferrous sulphate group reported at least one serious TEAE. There were 2 patients (1.5%) in the VIT-45 group and 5 patients (7.9%) in the ferrous sulphate group who were withdrawn from the study medication due to TEAEs. One patient (0.7%; patient 863013) in the VIT-45 group died. The serious TEAEs were reported in only the VIT-45 group; however none of the events were considered by the investigator to be related to study medication.

Study VIT-IV-CL-009

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. The most commonly reported TEAEs in ≥3 patients were: nasopharyngitis (7 patients [3.1%] in the VIT-45 group and 2 patients [1.7%] in the ferrous sulphate group), constipation (1 patient [0.4%] in the VIT-45 group and 8 patients [6.8%] in the ferrous sulphate group), ALT increased (5 patients [2.2%] in the VIT-45 group and 3 patients [2.6%] in the ferrous sulphate group), headache (6 patients [2.6%] in the VIT-45 group and 2 patients [1.7%] in the ferrous sulphate group) , infusion site burning (5 patients [2.2%] in the VIT-45 group and no patients in the ferrous sulphate group), C-reactive protein increased (4 patients [1.8%] in the VIT-45 group and none in the ferrous sulphate group), uterine haemorrhage (3 patients [1.3%] in the VIT-45

group and 1 patient [0.9%] in the ferrous sulphate group). All other TEAEs were reported by less than 4 patients overall.

There were 5 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 2 patients (0.9%) in the VIT-45 group (all considered not related to study drug by the investigator) and no patients in the ferrous sulphate group. 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 4 patients (1.8%) in the VIT-45 group and 1 patient (0.9%) in the ferrous sulphate group who were withdrawn from the study drug due to TEAEs.

Summary of adverse events in breast-fed infants

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. The most common reported TEAEs in ³ 2 infants were: constipation (3 infants [1.3%] in the VIT-45 group and 4 infants [3.4%] in the ferrous sulphate group), erythema (5 infants [2.2%] in the VIT-45 group), diarrhoea (3 infants [1.3%] in the VIT 45 group), abdominal pain (1 infant [0.4%] in the VIT-45 group and 2 infants [1.7%] in the ferrous sulphate group), nasopharyngitis (2 infants [0.9%] in the VIT 45 group and 1 infant [0.4%] in the ferrous sulphate group), upper respiratory tract infection (1 infant [0.4%] in the VIT-45 group and 2 infants [1.7%] in the ferrous sulphate group), pallor and flatulence (2 infants [0.9%] each in the VIT-45 group). All other TEAEs were reported by < 2 breast-fed infants overall.

There were 2 breast-fed infants (0.9%) in the VIT-45 group and none in the ferrous sulphate group who reported at least one severe TEAE, while 4 breast-fed infants (1.7%) in the VIT-45 group and 1 breast-fed infant (0.9%) in the ferrous sulphate group reported at least one serious TEAE. There was only one breast fed infant in the ferrous sulphate group who reported two episodes of constipation that were probably related to the study drug. There were 10 breast-fed infants (8.5%) with TEAEs that were considered to be unrelated and 3 infants (2.6%) with TEAEs that were considered unlikely related to study medication.

Study 1VIT03001

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. The only TEAEs 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 the 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 the TEAEs experienced during the study were classified by the investigator as mild or moderate. Severe TEAEs were experienced by 7 subjects (4.0%) in the VIT-45 group and 9 subjects (5.1%) in the ferrous sulphate group. One patient in the ferrous sulphate group experienced a life-threatening TEAE of major depression, and 1 patient in the VIT-45 group experienced a Grade 5 TEAE which led to death.

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%). Drug-related TEAEs that were higher in the VIT-45 group compared with the oral iron group included headache (5.7% vs 2.8%), pruritus (2.3% vs 0.0%) and rash (2.9% vs 0.6%).

Study 1VIT04002/1VIT04003

At least one TEAE was reported by 157 patients (68.3%) in the VIT-45 group and 149 patients (65.9%) in the ferrous sulphate (FS) group. The most commonly (≥5% patients) reported TEAEs were: headache (34 patients, 14.8%), blood phosphorus decreased (26 patients, 11.3%), fatigue (13 patients, 5.7%), abdominal pain and nausea (12 patients, 5.2% each) in the VIT-45 group; and constipation (35 patients, 15.5%), nausea (33 patients, 14.6%), headache (27 patients, 11.9%), nasopharyngitis (14 patients, 6.2%), and diarrhoea (13 patients, 5.8%) in the FS group. The drug-related TEAEs experienced by ≥5% patients were blood phosphorus decreased (10.9%) and headache (6.5%) in the VIT-45 group, and constipation (14.2%) and nausea (11.9%) in the FS group. The majority of TEAEs were mild (Grade 1) or moderate (Grade 2). Severe TEAEs were reported by 21 patients (9.1%) in the VIT-45 group and 6 patients (2.7%) in the FS group.

In the VIT-45 group, 20 out of the 21 severe TEAEs were of Grade 3, and one was a Grade 4 (life-threatening) TEAE (WBC count increased) which was not considered to be drug-related. No Grade 5 TEAE was reported in the VIT-45 group, and no Grade 4 or 5 TEAEs were reported in the FS group. Sixteen patients from the VIT-45 group had severe TEAEs considered to be drug-related: blood phosphorous decreased (13 patients, 5.7%), abdominal pain (1 patient, 0.4%), headache (1, 0.4%), wheezing (1, 0.4%), pruritus (1, 0.4%), rash erythematous (1, 0.4%), skin warm (1, 0.4%) and flushing (1 patient, 0.4%).

In the VIT-45 group the severe Grade 3 TEAEs considered not related to study medication were abdominal pain, chest pain, pelvic inflammatory disease, migraine, syncope, and uterine haemorrhage (each of them reported in 1 patient, 0.4%). The severe TEAEs in the FS group were abdominal pain, back pain, uterine leiomyoma, transient ischaemic attack, headache, migraine, uterine haemorrhage, asthma (each reported by 1 patient, 0.4%). None of the severe TEAEs in the FS group were considered drug-related.

Three (1.3%) patients from each group experienced at least one serious AE, none of which was considered to be related to the study medications. Six patients (2.6%) in the VIT-45 group and 8 patients (3.5%) in the FS group discontinued study medication due to AEs. Among these, 3 patients from the VIT-45 group and 5 patients from the FS group were discontinued from the study due to AEs.

Study 1VIT04004

At least one TEAE was reported by 43.5% patients (64/147) in the VIT-45 group and 59.2% patients (61/103) in the FS group; the difference was statistically significant. The most commonly reported TEAEs (≥2% patients) were: oedema peripheral (9 patients, 6.1%), hyperkalaemia (6 patients, 4.1%), urinary tract infection, hypotension (5 patients, 3.4% each), bronchitis (3 patients, 2.0%), headache, and infusion site reaction (3 patients, 2.0% each) in the VIT-45 group, and constipation (18 patients, 17.5%), nausea (5 patients, 4.9%), diarrhoea, upper respiratory tract infection (4 patients, 3.9% each), faeces discoloured and gastrointestinal haemorrhage (3 patients, 2.9% each) in the FS group. The proportion of patients who experienced constipation in the FS group (17.5%) was statistical significantly greater compared to the VIT-45 group (1.4%).

At least one drug-related TEAE (possibly or probably related) was experienced by 4 patients (2.7%) in the VIT-45 group and 27 patients (26.2%) in the FS group. No drug-related TEAEs were experienced by more than 1 patient in the VIT-45 group. In the FS

group, the drug-related TEAEs reported in more than 1 patient were constipation (17/103, 16.5%), faeces discoloured (3/103, 2.9%), abdominal pain upper, diarrhoea and nausea (2/103, 1.9% each).

The majority of TEAEs were mild or moderate. Severe TEAEs were reported by 13 patients (8.8%) in the VIT-45 group and 12 patients (11.7%) in the FS group. None of the severe TEAEs experienced by patients in the VIT-45 group were considered to be drug-related. During the study, 13 (8.8%) patients from the VIT-45 group, including 2 patients who died, and 10 (9.7%) patients in the FS group experienced at least 1 serious AE (17 SAEs in the VIT-45 group, and 11 SAEs in the FS group); however, none of the serious AEs was considered to be related to the study medications. The majority of serious AEs were severe in intensity (13/17 SAEs in the VIT-45 group, and 10/11 SAEs in the FS group). Two patients in the VIT-45 group died; the investigator considered the events unrelated to the study drug.

Five patients (3.4%) in the VIT-45 group and 7 patients (6.8%) in the FS group discontinued study medication due to AEs. Among these, 4 patients from the VIT-45 group and 3 patients from the FS group were discontinued from the study due to AEs. Safety of VIT-45 was analysed in various subgroups (dose subgroups, maximum haemoglobin achieved during study or haemoglobin change from baseline to Week 2, Week 4, Week 6, and Week 8), and no clinically meaningful differences were observed for the overall proportion of patients with TEAEs or serious AEs or for any specific event.

Study 1VIT05005

At least one TEAE was reported by 84/127 patients (66.1%) who received VIT-45 in this study. The most commonly reported TEAEs (≥5% patients) were oedema peripheral (9 patients 7.1%), hypertension (8 patients, 6.3%), and urinary tract infection (7 patients, 5.5%), followed by diarrhoea, arthralgia, and skin ulcer (6 patients, 4.7% each). At least one drug-related TEAE (possibly or probably related) was experienced by 6 patients (4.7%), and included injection site discolouration (2 patients), dizziness, infusion site pain, infusion site reaction, gastrointestinal infection, and hypertension (1 patient each). The majority of TEAEs were mild or moderate. Severe TEAEs were reported by 26 patients (20.5%). One patient experienced severe dizziness and nausea (while receiving her fourth and last dose of VIT-45) were considered to be drug-related and resolved without treatment within 2 minutes. The same patient had experienced abdominal pain (serious TEAE) after her second dose of VIT-45 (unrelated to study medication), and severe abdominal pain upper and severe diarrhoea while receiving ferrous sulphate in study 1VIT04004 (drug-related).

During the study, 23 (18.1%) patients, including the 2 patients who died, experienced at least 1 serious AE, none of which was considered to be related to the study drug. Two patients died; the investigator considered the events unrelated to the study drug.

Seven patients (5.5%) discontinued study medication due to AEs; none of these AEs was considered to be drug related. Three patients (2.4%) discontinued from the study due to AEs.

The safety of VIT-45 was analysed in various subgroups (dose groups, maximum haemoglobin achieved during study or haemoglobin change from baseline within 30 days after dosing), and once again no clinically meaningful differences were observed for the overall proportion of patients with TEAEs or the proportion of patients with any specific TEAE.

Study 1VIT05006

This study focused on the safety and tolerability of VIT-45 in comparison with placebo. Following the administration of a single dose of study drug, two categories of AEs were analysed: AEs occurring during the 7-day treatment period, and AEs occurring within the first 24 hours of the treatment period.

TEAEs reported in the 7-day treatment period in the Completer population

At least one TEAE was reported by 29.3% (164/559) of patients after receiving VIT-45 and 19.7% (110/559) after receiving placebo. The most commonly reported TEAEs (≥1% patients) were headache (30 patients, 5.4%), nausea (21 patients, 3.8%), dizziness (10, 1.8%), ALT and AST increased (9, 1.6% each), diarrhoea, pyrexia and fatigue (7, 1.3% each) and rash (6, 1.1%) in the VIT-45 group, and headache (19 patients, 3.4%), nausea (10, 1.8%) and diarrhoea (9, 1.6%) in the placebo group.

At least one drug-related TEAE (possibly or probably related) was experienced by 75 patients (13.4%) after receiving VIT-45 and 37 patients (6.6%) after receiving placebo. Each of the drug-related TEAEs reported by ≥1% patients in either treatment group was higher in the VIT-45 group compared with placebo. These events included (VIT-45 vs placebo): nausea (2.5% vs 1.1%), ALT increased (1.3% vs 0.2%), AST increased (1.3% vs 0.0%), headache (2.9% vs 1.4%), dizziness (1.6% vs 0.2%) and rash (1.1% vs 0.2%). Similar results were observed in the Safety population.

TEAEs reported in the first 24 hours of the treatment period in the Completer population

At least one TEAE was reported by 15.0% (84/559) of patients after receiving VIT-45 and 11.4% (64/559) after receiving placebo. The most commonly reported TEAEs (≥1% patients) were headache (20 patients, 3.6%), nausea (17, 3.0%) and dizziness (7, 1.3%) after receiving VIT-45, and headache (16 patients, 2.9%), nausea (8, 1.4%) and diarrhoea (6, 1.1%) after receiving placebo. At least one drug-related TEAE (possibly or probably related) was experienced by 52 patients (9.3%) in the VIT-45 group and 27 patients (4.8%) in the placebo group. Each of the drug-related TEAEs reported by ≥1% patients in either treatment group was higher in the VIT-45 group compared with placebo. These events included (VIT-45 vs placebo): nausea (2.1% vs 1.1%), headache (2.0% vs 1.3%) and dizziness (1.3% vs 0.2%). Similar results were observed in the Safety population.

During the 7-day treatment period in the Safety population, the majority of TEAEs experienced were of Grade 1 (mild) or Grade 2 (moderate) intensity. Grade 3 (severe) TEAEs were experienced by 6 patients (1.0%) after receiving VIT-45 and 9 patients (1.6%) after receiving placebo. The majority of patients experienced the Grade 3 TEAEs after the first 24 hours of the treatment period (5/6 patients in the VIT-45 group and 7/9 patients in the placebo group). Among the patients with Grade 3 TEAEs, drug-related TEAEs were experienced by 4 patients in the VIT-45 group and 5 patients in the placebo group. The drug-related Grade 3 TEAEs included headache (1 patient) and blood phosphorus decreased on study Day 7 (3 patients) after receiving VIT-45, and rash (1 patient), blood creatinine increased (1 patient), blood phosphorus decreased on study Day 7 (1 patient) and blood phosphorus decreased on study Day 0 (2 patients) after receiving placebo.

One patient was reported as having a Grade 4 (life-threatening) TEAE (intestinal obstruction) after receiving VIT-45; the event led to premature discontinuation. One patient experienced a Grade 5 (death related to AE) TEAE (pneumonia) after receiving VIT-45; the event led to death. Neither of these Grade 4 or 5 events was considered to be related to the study drug.

During the study, 2 (0.3%) patients, including the one patient who died, and 4 (0.7%) patients experienced at least 1 SAE after receiving VIT-45, and placebo, respectively. Only 1 patient (VIT-45) reported an SAE (obstruction of the ileum due to Crohn's disease) during the first 24 hours of the treatment period. None of the reported SAEs were considered to be related to study drug. The SAEs that occurred after receiving VIT-45 were of Grade 4 (1 event) and Grade 5 (1 event) intensity, whilst those occurring after receiving placebo were of Grade 2 (1 event) and Grade 3 (5 events). One (0.2%) patient prematurely discontinued from the study drug due to the occurrence of AEs after receiving VIT-45 and 2 (0.4%) patients due to the occurrence of AEs after receiving placebo. Only the premature discontinuation due to AEs after receiving VIT-45 (1 patient) occurred during the first 24 hours of the treatment period. None of the patients in either treatment group prematurely discontinued from study drug due to drug-related AEs.

Study 1VIT06011

No statistical differences were observed between the treatment groups for the overall incidence of TEAEs. At least one TEAE was reported by 45.8% patients (65/142) in the VIT-45 group and 56.5% patients (83/147) in the FS group. The most commonly reported TEAEs (≥5% patients) were headache (7 patients, 4.9%) in the VIT-45 group and constipation (18 patients, 12.2%) and headache (11 patients, 7.5%) in the FS group. A statistically significantly greater proportion of patients in the FS group experienced constipation (12.2%) compared to the VIT-45 group (1.4%).

At least one drug-related TEAE (possibly or probably related) was experienced by 15 patients (10.6%) in the VIT-45 group and 32 patients (21.8%) in the FS group. The only drug-related TEAE experienced by ≥2% patients in the VIT-45 group was urticaria (3/142); this event was experienced by more patients in the VIT-45 (2.1%) compared to the FS group (0.7%). In the FS group, the drug-related TEAEs reported by ≥2% patients were constipation (16/147, 10.9%), ALT increased (6/147, 4.1%), AST increased (3/147, 2%) and nausea (3/147, 2%), all of them at a higher incidence compared to the VIT-45 group.

The majority of TEAEs were mild (Grade 1) or moderate (Grade 2). Grade 3 (severe) TEAEs were reported by 5 patients (3.5%) in the VIT-45 group and 7 patients (4.8%) in the FS group. Two of the severe TEAEs experienced by patients in the FS group were considered to be drug-related (abdominal pain and gastrointestinal pain, respectively). Grade 4 (life-threatening) TEAEs were experienced by 3 patients (2%) in the FS group, none of them drug-related. No patient in the VIT-45 group experienced a Grade 4 TEAE, and no Grade 5 TEAEs were reported in the study in any of the treatment groups.

During the study, 4 (2.8%) patients from the VIT-45 group and 4 (2.7%) patients in the FS group experienced at least 1 serious AE, none of which was considered to be related to the study medications or requiring study drug discontinuation. Two patients (1.4%) in the VIT-45 group were prematurely discontinued from study medication due to AEs. Both patients experienced Grade 2 urticaria following first VIT-45 dosing. Both events required treatment and were considered probably related to study medication. No patient in the FS group experienced an AE leading to study drug discontinuation. No patient was discontinued from the study due to AEs.

Study FER-CARS-01

There were no relevant differences between the treatment groups in the proportion of patients with TEAEs, drug related TEAEs, severe TEAEs, TEAEs causing discontinuation of study drug, TEAEs causing withdrawal from study, serious TEAEs and TEAEs with an outcome of death. At least one TEAE was reported by 50% patients (15/30) in the VIT-45 group, 44.4% patients (12/27) in the Venofer group, and 66.7% patients (10/15) in the

placebo group. The most common TEAEs (≥5% patients) were hyperkalaemia (13.3% patients) in the VIT-45 group, cardiac failure, hyperkalaemia and hypertension (11.1% each) in the Venofer group, and cardiac failure (13.3%), hyperkalaemia and hypertension (6.7% each) in the placebo group. The relationship of the majority of TEAEs to study drug was considered unrelated or unlikely. The relationship of TEAEs to the study drug was possible, probable or certain in 6.7% patients in the VIT-45 group (2 patients, vertigo and hypersensitivity), 14.8% patients in the Venofer group (4 patients, asthenia/dizziness, dysgeusia, headache and hypertension) and no patients in the placebo group. Most TEAEs were of mild or moderate intensity. Severe TEAEs occurred in 3.3% patients (1 patient) in the VIT-45 group (cardiac failure), 7.4% patients (2 patients, cardiac failure/acute myocardial infarction and cardiac failure) in the Venofer group and 6.7% patients (1 patient, toothache) in the placebo group. None of the severe TEAEs was drug-related, and the differences between the treatment groups in TEAE intensity were not statistically significant.

Serious TEAEs occurred in 10% patients in the VIT-45 group (3 patients; unstable angina, cardiac failure and nodal osteoarthritis (2 patients; cardiac failure and urethral polyp). One patient (Venofer group) died of cardiac failure. None of the serious TEAEs was considered to be drug-related. No patient was permanently withdrawn from the study drug or from the study due to TEAE.

Summary analysis of TEAEs

A variable proportion of patients reported TEAEs depending on the treatment group and study. The proportion of patients with TEAEs was comparable between treatment groups in Studies VIT-IV-CL-015, VIT-IV-CL-009, 1VIT03001, and 1VIT04002/1VIT04003. In Studies 1VIT04004 and 1VIT06011, more patients reported TEAEs in the FS group compared to VIT-45 (1VIT04004: 59.2% vs 43.5%, 1VIT06011: 56.5% vs 45.8% for FS and VIT-45, respectively), whilst in Studies 1VIT05006 and VIT-IV-CL-008 the percentage of patients with TEAEs was higher in the VIT-45 group compared to FS (1VIT05006: 29.8% vs 20%, VIT-IV-CL-008 56.9% vs 42.9%). Differences between treatment groups were also observed in Study FER-CARS-01, the highest percentage of patients with TEAEs being reported for the placebo group (66.7%), followed by VIT-45 (50%), and Venofer (44.4%). The high proportion of patients with TEAEs observed in all treatment groups in this study may be due to the characteristics of the patient population, that is, older patients (mean age between 68.1 and 70.1 years in the three treatment groups) with cardio-renal anaemia syndrome, and most of them with associated co-morbidities.

The System Organ Classes (SOCs) most commonly affected by adverse events included (in alphabetic order): *Gastrointestinal Disorders*, *General Disorders and Administration Site Conditions*, *Infections and Infestations*, *Investigations*, *Musculoskeletal and Connective Tissue Disorders*, *Nervous System Disorders*, *Skin and Subcutaneous Tissue Disorders*, and *Vascular Disorders*.

The AEs most commonly observed (reported by ≥2% of patients in at least one study for *Gastrointestinal Disorders* included constipation, diarrhoea, nausea, and vomiting. These AEs were observed in both the VIT-45 and FS groups; however, in the controlled studies, the incidence of these AEs was generally higher in the oral ferrous sulphate group compared with VIT-45.

Among *General Disorders and Administration Site Conditions*, injection site reactions were the AEs most frequently observed (not unexpected, considering the route of administration), followed by pyrexia, oedema peripheral, and fatigue, which occurred generally more often with VIT-45 than with FS.

For *Infections and Infestations*, the incidence of TEAEs was generally slightly higher in the VIT-45 group compared to FS (controlled studies 008: 11.7% vs 7.9%, 009: 8.4% vs 3.4%, 04004: 13.6% vs 7.8%, 06011: 20.4% vs 15.0%), although in some other studies the proportion of patients with infections was comparable between VIT-45 and FS groups (controlled studies 03011: 13.8% vs 12.4%, 04002/04003: 15.7% vs 18.6%). The proportion of patients who experienced infections was comparable between VIT-45 and Venofer (study 015: 9.2 vs 8.5%).

TEAEs associated with *Investigations* were reported in most of the studies, although the number of patients and laboratory parameters affected varied. There were some cases of TEAEs which were related with increased values of ALT, AST, and GGT reported in several studies. In Studies 04002/04003 and 05006 there were patients experiencing low blood phosphate values which were reported as TEAEs (04002/04003: 26/230, 11.3% in the VIT-45 group, 0 in the FS group; cross over 05006: 5/584, 0.9% in the VIT-45, 3/569, 0.5% in the placebo group). Low phosphate levels were also reported in other studies, but there were not considered to be adverse event.

The TEAEs most commonly observed in *Musculoskeletal and Connective Tissue Disorders* included arthralgia, back pain, muscle cramp and myalgia, whilst headache was the TEAE most frequently experienced in association with *Nervous System Disorders*. TEAEs associated with *Skin and Subcutaneous Tissue Disorders* were generally more often observed with VIT-45 than with FS, and in a comparable proportion of patients in the VIT-45 and Venofer groups (although Venofer was used as comparator only in two studies with a total number of 145 patients). The TEAEs most commonly experienced with VIT-45 were rash, pruritus, and urticaria.

The TEAE most commonly observed among *Vascular Disorders* was hypotension, which occurred in only a small number of patients.

Deaths

There were no deaths in studies VIT-IV-CL-001, VIRD-VIT-45-IM, VIT-IV-CL-02, VIT-IVCL-03, VIT-IV-CL-009 and 1VIT04002/1VIT04003, and 1VIT06011. In studies 53214, VIT-IV-CL-015, VIT-IV-CL-008, 1VIT03001, 1VIT04004, 1VITT05005, 1VIT05006, and FER-CARS-01, 11 cases of death have been reported: 10 cases of death occurred with VIT-45 among 1,480 patients (0.676%) exposed to VIT-45 in these studies, (1,481 patients were randomised to receive VIT-45, however one patient in study 53214 was randomised to the VIT-45 group but did not receive VIT-45), and one with the active comparator Venofer among 145 patients (0.689%) exposed to Venofer. No deaths were considered related to study drug treatment. No deaths were reported in patients who received oral iron (344 exposed patients) or placebo (584 exposed patients).

Serious adverse events

Serious adverse events were reported variably in studies (VIT-45: 5% in 015, 6.6% in 008, 7.4% in 53214, 8.8% in 04004, 10% in FER-CARS-01 and 18.1% in 05005; comparators: 6.8% in 015, 9.7% in 04004, 13.3% and 18.5% for placebo and Venofer in FER-CARS-01). The higher incidence of SAEs observed in the latter category of studies could be explained by the different characteristics of the patients, that is, older patients with multiple associated morbidities and chronic diseases (CKD, IBD) at the origin of their iron deficiency. This is supported by the observation that in controlled studies the proportion of patients with SAEs was similar between VIT-45 and comparator, except Study 008 and Study FER-CARS-01 (proportion of patients with SAEs higher in placebo and Venofer comparators than in VIT-45, but number of patients too low to allow meaningful comparisons).

The SOCs most commonly affected by SAEs were *Infections and Infestations* (VIT-45: 19 patients with SAEs, comparators: 6 patients), *Cardiac Disorders* (VIT- 45: 17 patients with SAEs, comparators: 8 patients) and *Gastrointestinal Disorders* (VIT-45: 15 patients with SAEs, comparators: 7 patients). The higher proportion of VIT-45 patients who experienced SAEs correlates with the much higher number of patients in the VIT-45 safety populations (total 2,080 for VIT-45 and 1,379 for pooled comparators). If considering only the controlled studies (SAEs occurring in Studies 53214 and 05005 excluded), the number of patients with SAEs associated with *Gastrointestinal Disorders* is similar between VIT-45 and pooled comparators (7 patients in each group, VIT-45: 0.39%, pooled comparators: 0.50%), whilst the proportion of patients with SAEs associated with *Infections and Infestations* and *Cardiac Disorders* remained slightly higher in the VIT-45 group (12 [0.67%] vs 6 patients [0.43%] with SAEs for *Infections and Infestations*, 13 [0.72%] vs 8 patients [0.58%] with SAEs for *Cardiac Disorders* for VIT-45 and pooled comparators, respectively). None of the SAEs were considered to be related to study medication.

Considering the total number of patients who received VIT-45 and comparators (safety populations) and the total number of SAEs, a slightly higher proportion of VIT-45 patients experienced SAEs compared to the FS group (81/2,080 patients, 3.89% in the VIT-45 group, and 21/650 patients, 3.23% in the FS group). The proportion of patients who developed SAEs after receiving Venofer was much higher (13/145 patients, 8.96%), but the total number of patients who received this IV product was too low in comparison to the other treatment groups to allow a meaningful comparison (Venofer was only used in studies conducted in patients with CKD or cardio-renal anaemia).

Overall, in controlled clinical studies, the proportion of patients who experienced SAEs was similar in the VIT-45 and pooled comparator populations, with 46/1,790 patients (2.56%) treated with VIT-45, and 40/1,379 patients (2.90%) treated with comparators experiencing SAEs. In general, in studies conducted in post-partum IDA (03001, 009, 06011), IDA secondary to heavy uterine bleeding (04002/04003) and IDA of various aetiologies (05006), the incidence of SAEs was lower, compared with the studies conducted in CKD patients with haemodialysis (53214, 015), NDD-CKD (04004, 05005), or in patients with IBD (008).

Clinical laboratory evaluations

Generally, there were no consistent trends in safety laboratory abnormalities, except for phosphate levels. Individual cases of increased liver function tests (GGT, ALT, or AST) or of elevated CRP values were reported, although no clear pattern emerged. Generally, the observed differences between treatment groups with respect to clinical laboratory values were small.

Differences were observed between treatment groups with respect to haematology parameters, in line with the therapeutic effect of VIT-45, for example haematocrit, MCH, and MCHC mean values increased from baseline, showing an improvement during study participation consistent with the effectiveness of VIT-45 in treating IDA. As a result of treatment, serum ferritin and TSAT levels above the normal ranges were measured in individual patients. There were isolated reports of treatment emergent abnormal haematology parameters such as low platelet count, but no consistent pattern was observed.

Serum phosphate levels

Treatment emergent low serum phosphate values were reported in several clinical studies in various proportions of patients, predominantly in the VIT-45 group, where it ranged from 3.8% to 70.1%. The low phosphate values were considered to be treatment emergent abnormal clinical chemistry values, that is, met the NCI CTC Grade 3 or Grade 4 toxicity

criteria (levels below 2.0 mg/dL or below 0.6 mmol/L), except for study FER-CARS-01, in which values below 0.87 mmol/L were defined as low). Most of the patients with low phosphate levels were asymptomatic, and for very few of them the low phosphate level was reported as TEAE. The decrease in phosphate levels was generally transient, reached a nadir 2 weeks after dosing, and did not cause discontinuation from study medication in any of the patients.

Other significant adverse events

One of the main concerns related to the use of parenteral iron products, is their potential to cause allergic/hypersensitivity reactions, as those described for example for iron dextran. In clinical studies conducted with VIT-45 very few TEAEs associated with *Immune System Disorders* have been reported, although several TEAEs classified under other SOCs could potentially be due to an allergic or hypersensitivity reaction, for example skin rashes, pruritus or urticaria.

Hypersensitivity reactions were reported in a very limited number of patients, although skin rashes, urticaria and pruritus (AEs potentially related to allergic reactions) were observed in many clinical studies. Generally such events, especially rash, occurred more often in VIT-45 patients than in patients treated with comparators and were often assessed by the investigator as drug-related (or possibly related). The proposed PI of VIT-45 lists hypersensitivity reactions among the special warnings and precautions for use, and in the list of adverse drug reactions.

Evaluator Comment

Overall ferric carboxymaltose appeared to be reasonably well tolerated with a manageable safety profile.

Post-Marketing Experience

Post-marketing data are available from the Periodic Safety Update Reports (PSURs) (following the EU approval) pertaining to the period 18 June 2007 to 17 June 2008 and 18 June to 17 December 2008. During this period, a total of 427 patients were exposed to VIT-45 in ongoing clinical studies (FER-CARS-01-02: 394 patients with iron deficiency and chronic heart failure; ThromboVIT: 12 patients with thrombocytosis secondary to iron deficiency and chronic inflammatory bowel disease; FER-IBD-07-COR: 21 patients with IDA due to IBD), and patient exposure through the market was 40,353 patient years.

During the period covered by these two PSURs, 169 new case reports came from patients treated with the marketed product, which were associated with a total of 384 AEs. The 169 patients (total exposure: 40,353 patient years) who reported AEs correspond to a frequency of 41.9 per 10,000 patient years. Most of those reports were assessed as being "non serious", and only 28 qualified for "serious" (6.94 per 10,000 patient years) according to ICH criteria.

During the 18-months reporting period of these PSURs, 15 patients experienced 31 serious, unlisted adverse events. No new safety signals were observed.

Clinical Summary and Conclusions

A comprehensive program of clinical studies has been conducted to support registration of Ferinject (VIT-45). Pharmacokinetic evaluation of VIT-45 with the PET technique showed a rapid distribution from the blood to the target tissues. 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. RBC utilisation increased rapidly during the first 6 to 9 days indicating the efficacy of VIT-45 in iron replacement therapy.

In two Phase I/II studies in patients with mild to moderate IDA, PK analysis revealed increases in exposure roughly proportional to the iron dose administered with VIT-45.

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.

All pharmacodynamic parameters investigated in Phase I/II studies, that is, Hb and iron stores variables, showed the expected response to IV iron therapy. Serum ferritin values together with TSAT values measured 4 weeks after repeated VIT-45 infusions demonstrated a clinically effective replenishment of depleted iron stores. Transiently elevated TSAT also indicated that iron binding capacity is almost fully utilised following VIT-45 infusion. Undesired high levels of serum ferritin or TSAT indicating iron intoxication were avoided. In the multiple-dose study, the gradual decrease in transferrin over time also indicated successful iron replacement.

In the 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 iron deficiency due to various aetiologies. Hb levels were raised to expected and clinically meaningful levels.

In Study VIT-IV-CL-015, the primary response rate was 46.4% in the VIT-45 group and 37.2% in the Venofer group. In Studies VIT-IV-CL-008, -009, and 1VIT04004, 1VIT03001, 1VIT06011 and 1VIT04002/4003 based on the primary efficacy variable VIT-45 was non-inferior to oral ferrous sulphate in patients with IDA secondary to IBD or heavy uterine bleeding or in patients with post-partum anaemia. The values of serum ferritin and TSAT 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 (1VIT04004, VIT-IV-CL-008 and –009, 1VIT06011 and 1VIT04002/4003), the increase of serum ferritin was significantly higher at all visits in patients treated with VIT-45 than in patients treated with ferrous sulphate. TSAT levels moved from suboptimal levels to the clinically accepted target range (20 - 50%) within 2 weeks after start of treatment with VIT-45.

In relation to safety, a variable proportion of patients reported TEAEs during clinical studies, with the SOCs most commonly affected by adverse events being *Gastrointestinal Disorders*, *General Disorders and Administration Site Conditions*, *Infections and Infestations*, *Investigations*, *Musculoskeletal and Connective Tissue Disorders*, *Nervous System Disorders*, *Skin and Subcutaneous Tissue Disorders* and *Vascular Disorders*. Only a low number of adverse events were considered by the investigators to be related to treatment, and the number of patients who discontinued study medication due to adverse events was low.

Some of the TEAEs reported in clinical studies (rash, pruritus, and urticaria, AEs which could be caused by an allergic reaction), together with the very few cases of hypersensitivity reactions experienced during studies, as well as the allergic reactions reported in the post-marketing period may indicate that VIT-45 has the potential of inducing hypersensitivity reactions. This has been also described for other parenteral iron products.

Generally, considering the total number of patients who received VIT-45 and comparators and the total number of SAEs, a slightly higher proportion of VIT-45 patients experienced

SAEs compared to the FS group, whilst the proportion of Venofer patients who developed SAEs was higher. Overall, in controlled clinical studies, the proportion of patients who experienced SAEs was similar in the VIT-45 and pooled comparator populations. In general, in studies conducted in post-partum IDA, IDA secondary to heavy uterine bleeding and IDA of various aetiologies, the incidence of SAEs was lower, compared with the studies conducted in CKD patients with or without dialysis or in patients with IBD. The higher proportion of patients with SAEs that was observed in the studies conducted in chronically ill patients may be explained by the different characteristics of the patients, that is, older patients, with multiple associated morbidities, and chronic diseases (CKD, IBD) as the origin of their iron deficiency.

None of the reported serious adverse events or deaths were considered to be related to the study medication.

In conclusion, it was the opinion of the evaluator that the data presented in this application provide evidence of efficacy of Ferinject in treating patients with iron deficiency. The clinical studies performed with VIT-45 have demonstrated that it is an effective and safe iron complex for delivery of iron to target tissues in the treatment of patients with IDA. A comparative study between VIT-45 and iron sucrose demonstrated a good safety profile and comparable efficacy for both injectable products. VIT-45 offers the possibility to administer high doses of iron (up to 1000 mg iron once per week, not exceeding 15 mg iron/kg bw) over a short time period (200 mg iron as IV bolus injection or short-term infusion of up to 1000 mg iron over 15 minutes) and to replenish the iron stores rapidly and efficiently during a short treatment time (usually in 1-2 weeks).

Overall assessment of the benefits and risks of the use of VIT-45 in the treatment of iron deficiency demonstrates a favourable benefit-risk profile. The indication as proposed by the sponsor is appropriate and is similar to the indication approved in the EU. The evaluator recommended that the application to register Ferinject (ferric carboxymaltose) should be approved.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The important safety concerns identified by the sponsor are shown at Table 23.

Table 23: Ongoing safety concerns for ferric carboxymaltose

Important identified risks	Hypersensitivity/anaphylactoid reaction Transient decrease of serum phosphorus level
Important potential risks	Haemosiderosis Cardiotoxicity Excess of mortality
Important missing information	Use in children Use in pregnant women Use in patients with hepatic insufficiency Use in patients with infectious diseases Long-term usage

The OMSM reviewer noted that the proposed application of routine pharmacovigilance activities for all safety concerns as identified by the sponsor and the application of

additional pharmacovigilance activities for some of these safety concerns are generally acceptable.[9]

The completed and ongoing studies identified in the pharmacovigilance plan were not considered to be part of the planned clinical studies in the pharmacovigilance plan. Nevertheless an update on the progress/results/analysis of these studies, according to the milestones presented, will be expected in future PSURs and the sponsor should provide an explanation for the planned *in vitro* study (VFR/0126) being terminated.

In regard to the sponsor's discussions with the FDA to conduct additional clinical trials to address the potential risk of excess in mortality, any additional safety data from clinical studies presented to the FDA or Health Canada should also be submitted to the TGA for evaluation.

The sponsor acknowledged that the safety profile of ferric carboxymaltose is unknown in children under the age of 14 years, pregnant women, patients with hepatic insufficiency, patients with infectious diseases and in the context of long-term usage. However, the reviewer noted that there were no provisions in the pharmacovigilance plan to pro-actively obtain information regarding the incidence and nature of ADEs in these groups.

The OMSM reviewer acknowledged that use in pregnancy in the first trimester is a proposed contraindication and that use of ferric carboxymaltose in these other groups is either not recommended or a circumstance where caution is required with its use. Nevertheless it was suggested that routine pharmacovigilance is insufficient with respect to gathering information on the safety profile of ferric carboxymaltose in each of these specified patient groups. Therefore it was suggested the sponsor makes some provision to pro-actively gain such information. This may take the form of a patient register, the details of which should be agreed with the TGA.

The proposed application of routine risk minimisation activities to the safety concerns, as specified by the sponsor, is generally acceptable given the background of these risks. [10] However in relation to long-term usage, the Australian PI should state clearly in the 'Clinical Trials' section that there are no data available regarding the long term use of Ferinject.

In addition it was noted that the approved Australian PIs for iron sucrose and iron polymaltose formulations currently on the ARTG recommend giving a test dose before the therapeutic dose is administered. Given that hypersensitivity/anaphylactoid reaction has been identified as an important identified risk it was suggested that the sponsor specifically justify why such a safety directive should not be included in the PI/Consumer medicine Information (CMI).

In its response to this issue, the sponsor stated that:

The requirement for a test dose with other parental iron preparations is due to the documented IgE mediated anaphylactic reactions due to anti-dextran antibodies. Ferric carboxymaltose does not show any cross-reactivity with anti-dextran antibodies. This is due

[9] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[10] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

to its composition and the breakdown of Ferinject to endogenous sugar residues. This has been confirmed in the following animal studies:

Study VFR043/003504: guinea pigs were sensitised with iron dextran to assess potential cross reactivity of anti-dextran antibodies with Ferinject. No response to Ferinject was observed.

Study VFR072/052022: 26 week intravenous toxicity study in rats to assess if Ferinject could cause immune stimulation. Recovery group rats (previously treated with Ferinject at 30 mg Fe/kg/week) were re-challenged with a 1 mg Fe/kg dose of Ferinject post the six week recovery period. No observed evidence of hypersensitivity reactions were observed [sic].

On the basis of the above a test dose is not required for Ferinject.

The Delegate sought toxicological comments on the clinical relevance of the above animal data cited by the sponsor.

Study VFR043/003504 was a heterologous PCA test in guinea-pigs, using serum from rabbits sensitised to dextran. This study was conducted to assess possible cutaneous anaphylactic reactions due to interactions with anti-dextran antibodies, although it should be noted that formation of anti-dextran antibodies was not confirmed by serology. Ferric carboxymaltose was found to be negative in this test. Venofer (iron sucrose) was also tested in this study and was also found to be negative.

Study VFR072/052022 was a 26-week IV toxicity study in rats. The evaluation report did not refer to the re-challenge dose of Ferinject after the 6-week recovery period. A further review of the study confirmed that no hypersensitivity reactions were reported in the animals following the re-challenge dose of 1 mg Fe/kg Ferinject.

Only limited preclinical data are available for the antigenic potential of ferric carboxymaltose. The absence of hypersensitivity reactions in the 26-week study in rats does not confer a high level of evidence for the lack of antigenicity of the product, especially with regard to its potential cross-reactivity with other iron products. The potential for ferric carboxymaltose to trigger anaphylactic reactions in dextran-sensitised animals has not been investigated in an ASA animal model. Although the negative finding in the heterologous PCA test provides some indirect evidence suggesting that ferric carboxymaltose may not cross-react strongly with anti-dextran antibodies, it should be noted that the presumed formation of anti-dextran antibodies was not actually confirmed by serology in the study. It should also be noted that Venofer was also negative in this study and that Venofer currently requires a test dose prior to administration of a therapeutic dose in new patients.

Taken together, the animal data cited by the sponsor are not considered sufficient as an adequate justification for the omission of a test dose for the product in new patients. Evidence to justify such an omission should therefore be relied on clinical experience, taking into consideration *inter alia* the incidence of anaphylactic/anaphylactoid reactions reported in the clinical studies of this product. In particular, special attention should be paid to reactions in atopic patients and those with a history of anaphylactic / anaphylactoid reactions to other iron products.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The evaluator was uncertain if manufacture would produce a consistent product and also uncertain of appropriate manufacturing controls.

Tonicity was not well controlled for use of the product as a bolus injection.

Stability was poorly studied. The characterisation of stored samples did not test for chemical changes in the colloid except for molecular weight distribution.

Like the registered products, Ferinject is not a simple iron solution but contains colloidal nanoparticles. Official standards for chemical characterisation and performance controls are limited. Different products may have different safety profiles because of differences in iron release and clearance.

The evaluator did not recommend approval.

Nonclinical

The drug was well tolerated via the IV route in rabbits and piglets. Toxicity studies in rats and dogs showed iron overload effects consistent with those seen with other parenteral iron products. Effects were principally in the liver. The No Observable Adverse Effect Level (NOAEL) was below the maximum recommended human dose based on body surface area (BSA).

The drug was toxic to rat and rabbit embryos and there were fetal skeletal abnormalities at 1.4-2.5 times the maximum weekly clinical dose based on BSA. Pregnancy category B3 was recommended. Genotoxicity was not evident. Carcinogenic potential was not assessed.

The evaluator had no objections to approval.

Clinical

Pharmacology

Trial VIT-IV-CL-02 assessed single IV doses of ferric carboxymaltose in patients with mild iron deficiency anaemia. After 100 mg injected over 1 minute, serum iron concentration peaked at a mean of 15 minutes. After 500, 800 or 1,000 mg IV infused in 250 mL normal saline over 15 minutes, serum iron concentration peaked at means of 20 minutes, 1 hour and 1.2 hours respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 hours. Renal elimination was negligible.

Mean serum ferritin concentration began to rise after 6-12 hours and reached peak concentration at 48 hours in the case of the 100 mg dose and 120 hours in the case of 800-1,000 mg. The increase in serum ferritin concentration was dose-dependent.

Within 8 hours of a single radiolabelled 100 mg IV dose of ferric carboxymaltose to patients with iron deficiency or renal anaemia (trial VIT-IV-CL-001), most of the dose had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, radioiron had incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

After repeated IV doses of ferric carboxymaltose 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26) infused in 250 mL normal saline over 15 minutes to patients with moderate iron deficiency anaemia secondary to gastrointestinal disorders (trial VIT-IV-CL-03), 37% and 48% of patients respectively achieved normal Hb levels within 8 and 6 weeks respectively and 75% and 73% respectively achieved a ≥ 20 g/L increase in Hb on at least one occasion. Mean serum ferritin concentration reached the

target range of 100-500 µg/L by Day 4 and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups.

Efficacy

The efficacy of ferric carboxymaltose in iron deficiency anaemia was determined in ten trials in adults. The dosage was individualised based on calculated iron deficit according to Ganzoni except for trials 1VIT04004 and 1VIT05005 where it was based on serum transferrin saturation and ferritin.

In trial VIT-IV-CL-015, a randomised, open-label trial in patients with anaemia secondary to dialysis-dependent chronic renal failure, ferric carboxymaltose IV (n=118) was compared with Venofer IV (n=116). The products produced similar Hb responses (percentage of patients with increase in Hb ≥ 10 g/L within 4 weeks) – 44.1% for ferric carboxymaltose and 35.3 % for Venofer. The difference was not statistically significant. The serum ferritin response (percentage of patients achieving serum ferritin concentration of 200-800 µg/L) at follow-up 4 weeks after the last dose was 73.7% for ferric carboxymaltose and 68.1% for Venofer, the difference again not being statistically significant. There was support from an uncontrolled trial (53214) of ferric carboxymaltose IV in a similar population. Hb response with ferric carboxymaltose IV was 61.7% (n=162).

In trial 1VIT04004, a randomised 2:1, open-label trial in patients with anaemia secondary to non-dialysis-dependent chronic renal disease, ferric carboxymaltose IV (n=152) was compared with ferrous sulfate tablets orally (n=103). Patients receiving ferric carboxymaltose achieved significantly better Hb response (percentage of patients with increase in Hb ≥ 10 g/L) than those receiving ferrous sulfate. The Hb response was 60.4% for ferric carboxymaltose and 34.7% for ferrous sulfate, 95% CI of difference [13.0%, 38.5%], p<0.001. The percentage of patients with Hb change ≥ 10 g/L and serum ferritin change ≥ 160 µg/L was also significantly better for ferric carboxymaltose than ferrous sulfate – 60.4 % versus 0%, 95% CI of difference [48.2%, 72.6%], p<0.001.

The uncontrolled extension study 1VIT05005 of 1VIT04004 supported the efficacy of ferric carboxymaltose in long-term treatment up to 44 weeks. Clinical success, defined as Hb ≥ 110 g/L, serum ferritin 100-800 µg/L and TSAT 30-50% on the same day, occurred in 51.4% of patients. However, clinical success was sustained (occurred in > 50% of assessments) in only 10% of patients.

In trial VIT-IV-CL-008, a randomised 2:1, open-label trial in patients with anaemia secondary to chronic inflammatory bowel disease, ferric carboxymaltose IV (n=136) was compared with ferrous sulfate capsules orally (n=60). Ferric carboxymaltose was non-inferior to ferrous sulfate in the increase in patient's Hb from baseline to Week 12 (mean 36.0 g/L for ferric carboxymaltose versus 32.9 g/L for ferrous sulfate, lower limit of 95% CI of difference -4.4 in the intent-to-treat population). The non-inferiority criterion was lower limit of 95% CI of difference ferric carboxymaltose minus ferrous sulfate ≥-5.0 g/L. The non-inferiority criterion was also met in the per protocol population. The Hb response was faster in patients treated with ferric carboxymaltose. The mean increase in serum ferritin from baseline to Week 12 was 67.3 µg/L for patients treated with ferric carboxymaltose and 18.3 µg/L for patients treated with ferrous sulfate.

In trial 1VIT04002/3, a randomised, open-label trial in patients with anaemia secondary to heavy uterine bleeding (HUB), ferric carboxymaltose IV (n=246) was compared with ferrous sulfate tablets orally (n=231). Patients receiving ferric carboxymaltose achieved significantly better Hb response (percentage of patients with increase in Hb ≥ 20 g/L within 6 weeks) than those receiving ferrous sulfate – 82.0% versus 61.8%, 95% CI of difference [12.2%, 28.3%], p<0.001. Mean increases in serum ferritin were also

significantly greater in patients treated with ferric carboxymaltose than in those treated with ferrous sulfate.

In trial VIT-IV-CL-009, a randomised 2:1, open-label trial in patients with post-partum anaemia, ferric carboxymaltose IV (n=227) was compared with ferrous sulfate capsules orally (n=117). Ferric carboxymaltose was non-inferior to ferrous sulfate in the increase in patient's Hb from baseline to Week 12 (mean 33.4 g/L for ferric carboxymaltose versus 31.8 g/L for ferrous sulfate, lower limit of 95% CI of difference -1.5 in the intent-to-treat population). The non-inferiority criterion was lower limit of 95% CI of difference ferric carboxymaltose minus ferrous sulfate ≥ -5.0 g/L. The non-inferiority criterion was also met in the per protocol population. The mean increase in serum ferritin from baseline to Week 12 was 115.1 µg/L for patients treated with ferric carboxymaltose and 8.1 µg/L for patients treated with ferrous sulfate. There was support from two similar trials 1VIT03001 and 1VIT06011.

Trial FER-CARS-01 was a pilot study of ferric carboxymaltose IV (n=30) versus Venofer (n=27) and placebo (n=15) in patients with iron deficiency anaemia associated with chronic heart failure and renal deficiency. The trial was supportive of improvements in patient global assessment and New York Heart Association status in patients treated with ferric carboxymaltose and Venofer; however, it was not powered to show superiority over placebo.

Safety

The safety of ferric carboxymaltose was assessed in 15 trials (n=2,080). Half the subjects had received a maximum single dose of 1,000 mg. Common adverse reactions were headache, dizziness, nausea, abdominal pain, diarrhoea, constipation, rash and injection-site reactions. Common laboratory abnormalities were decreased serum phosphorus and increased serum AST and ALT. Decreased serum phosphorus was transient and not associated with reports of adverse events. Hypersensitivity reactions were uncommon (3 in 2,080).

More deaths occurred with ferric carboxymaltose (10) than controls (1) in the clinical trials; however, exposure was twice as great with ferric carboxymaltose compared to controls. In the controlled post-partum/HUB trials, deaths per 100 patient-years were 0.87 for ferric carboxymaltose and 0 for controls. In the other controlled trials, deaths per 100 patient-years were 5.28 for ferric carboxymaltose and 1.96 for controls and, in the uncontrolled trials, 4.20 for ferric carboxymaltose. The intrinsic risk of death varied significantly across the trial populations. The deaths were assessed by independent experts as unrelated to ferric carboxymaltose. The control death was with Venofer in trial FER-CARS-01 and was due to heart failure. It was assessed as unrelated to the drug.

The incidence of serious adverse events was similar for ferric carboxymaltose and controls. No serious adverse events were considered related to ferric carboxymaltose.

Post-market safety experience for ferric carboxymaltose was provided from the time of EU approval (June 2007) to December 2008. Exposure was 40,000 patient-years. There were no new signals.

The evaluator recommended approval.

Risk Management Plan

The proposed risk management plan was generally acceptable. The justification for not requiring a test dose of ferric carboxymaltose prior to first therapeutic use was based on nonclinical data. Comment was sought from the nonclinical section. Based on the nonclinical advice and the lack of clinical experience, the Delegate recommended a test

dose be required if the product is to be registered. Registration, if granted, will also be conditional on implementation of the final Risk Management Plan agreed with the TGA Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

An intravenous dose of ferric carboxymaltose is cleared from the circulation and distributed to bone marrow, liver and spleen within 8 hours. In pharmacodynamic studies, the drug was effective in increasing Hb and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The target serum ferritin concentration 100-500 µg/L was reached within 4 days.

Ferric carboxymaltose produced consistent and clinically relevant Hb and serum ferritin responses under various clinical conditions including chronic renal disease, inflammatory bowel disease, heavy uterine bleeding and post-partum anaemia in 10 randomised controlled trials. The ferric carboxymaltose dose was individualised based on calculated iron deficit according to Ganzoni in the majority of trials. The maximum bolus dose was 200 mg per day not more than three times per week and the maximum infused dose 1,000 mg or 15 mg/kg weekly. For doses of 200-400 mg, the drug was infused in 100 mL of normal saline over 6 min and for doses of 500-1,000 mg, 250 mL of normal saline over 15 min. This is consistent with the proposed dose recommendations.

Ferric carboxymaltose at single doses up to 1,000 mg was generally well tolerated in a diverse group of patients. Deaths were higher with ferric carboxymaltose than controls after allowing for differing exposure, although no deaths were assessed as being due to the drug. The underlying risk differed significantly across studies. The FDA requested further studies to confirm the mortality risk. The Delegate requested that the sponsor provide an update of these studies and discussions with the FDA in their Pre-Advisory Committee on Prescription Medicines (ACPM) Response.

Ferinject has the advantage that large doses can be infused rapidly compared with the registered iron products. Intravenous iron infusions are under-utilised in Australia for iron deficiency anaemia compared with blood transfusions because of restrictions with the available iron products, yet iron infusions have a lower risk of anaphylaxis and fluid overload than blood transfusions.

There were significant chemistry and quality control issues; in particular, it could not be guaranteed that the manufacture and stability of the final product would be consistent. This may lead to increased adverse reactions. Manufacturing standards for this class of products are not well developed. Tonicity for bolus injection could also not be guaranteed with risk of haemolysis or red cell damage. The sponsor was invited to summarise for the ACPM and the Delegate how they will ensure consistent manufacture, tonicity and stability in their Pre-ACPM Response.

Given possible increased mortality compared with controls and the pharmaceutical chemistry issues, the benefit-risk balance was against approval.

The Delegate proposed to reject the application to register Ferinject on the grounds that the safety of the product has not been satisfactorily established.

Response from Sponsor

The sponsor noted that to date, Ferinject is approved in 33 countries, of which 28 are in Europe. In the EU, the UK acted as Reference Member State. Some of the key conclusions described in the UK Public Assessment Report (UK PAR), were that no new or unexpected

safety concerns arose from this application and that the benefits outweighed the risks.[11] Also the UK PAR states that the important quality characteristics are well-defined and controlled, the specifications and batch analytical results indicate consistency from batch to batch and that there are no outstanding quality issues that would have a negative impact on the benefit/risk balance. All approvals have been granted independent of the FDA decision and their request of further safety studies.

The exclusion of a test dose has been accepted in all approved countries and the FDA has never required a test dose in the clinical trials of FCM being undertaken for the US NDA.

The safety of ferric carboxymaltose (FCM) has been assessed to date in 26 clinical trials with over 6,400 patients exposed to FCM. The number of Ferinject ampoules sold since the international birth date of 18 June 2007 to 31 October 2010, corresponds to 202,727 patient years*. Post-marketing surveillance has not indicated any unexpected safety issues with Ferinject or any indication that a test dose is required. As concluded in each of the five available PSURs, the overall safety evaluation of Ferinject indicates that the positive benefit/risk ratio remains unchanged, with no new safety issue.

The key issues raised in the Delegate's summary are addressed in more detail below.

Clinical Safety at Time of Submission

In the 15 clinical studies submitted in this application, 6 death cases occurred in controlled clinical studies (5 in the FCM treated group versus 1 in the comparator), where frequently a 2:1 randomisation scheme was used. Five further deaths were reported in uncontrolled trials (that is, no comparator). Unbiased comparison of treatment groups for deaths must account for treatment group differences in numbers of subjects and length of observation, as well as treatment group differences in the baseline mortality risk.

The fatal cases were reported in patients with underlying diseases most of which have a high background mortality rate: non-dialysis dependent chronic kidney disease (4 cases), haemodialysis-dependent chronic kidney disease (3 cases), post-partum condition (1 case), inflammatory bowel disease (1 case) or undefined underlying medical condition (1 case). The bulk of the deaths (7 out of 10) cases occurred in patients with chronic kidney disease (CKD), an underlying medical condition associated with a high background mortality rate.

Also, the sponsor considered it important to note that there was no unifying pattern or dose-response relationship for mortality. The observed deaths did not share any significant features except for a high comorbid disease burden. Additionally all deaths were judged by the investigators to be unrelated to the study drug.

It was also relevant to highlight that in the recent study in patients with heart failure and iron deficiency, published in the New England Journal of Medicine, FCM (compared with placebo) showed a statistically significant benefit in relation to investigator reported cardiac disorder adverse events.[12] The deaths were 3.4/100 patient years at risk for FCM versus 5.5/100 patient years for placebo despite higher background mortality risk (in a meta-analysis of patients with chronic heart failure (n=153,180), 46.8 % of anaemic patients with heart failure died compared to 29.5 % of non anaemic patients).

In view of the safety concerns raised by the Delegate, Vifor Pharma sought and received a review of the risk/benefit assessment for Ferinject by a recognised Australian expert. The

[11] Medicines and Healthcare products Regulatory Agency. Public Assessment Report Decentralised Procedure: Ferinject. Available from: http://www.mhra.gov.uk/home/groups/l-unit1/documents/websiteresources/con014025.pdf

[12] Anker SD, Colet JC, Filippatos G et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009; 361: 2436-2448.

review clearly summarises the significant benefits offered by Ferinject over available intravenous iron products and confirms that these benefits can be achieved without increased treatment risk.

Further, as indicated in the section below, important safety data has been collected in 11 additional clinical trials completed since the submission of the original clinical data to the TGA. These trials include 2 large safety studies conducted by the sponsor's licensing partner for the submission to the FDA. The safety data from all of these trials and of the post-marketing data obtained up to now further support the excellent safety profile of Ferinject.

In conclusion, there is no basis for the association of a higher mortality risk with treatment with ferric carboxymaltose and the imbalance noted in the Australian submission is most likely due to the play of chance and the frequent use of a 2:1 randomisation scheme.

Update on further studies requested by FDA and complete clinical trial safety summary

In conjunction with the FDA, the sponsor's licensing partner for the US have designed 2 safety studies in CKD and iron deficiency anaemia (IDA), respectively, which are both ongoing:

1. 1VIT09030: "Randomised Evaluation of Efficacy and Safety of Ferric Carboxymaltose in Patients with Iron Deficiency Anemia and Impaired Renal Function (REPAIR-IDA)." The trial will include 2,500 patients in total and is ongoing in the US. 2,170 patients were randomized as of December 23, 2010 and the trial is on target to close enrolment in February 2011.
2. 1VIT09031: "A Multi-Center, Randomised, Active Controlled Study to Investigate the Efficacy and Safety of Intravenous Ferric Carboxymaltoes (FCM) in Patients with Iron Deficiency Anemia (IDA)." Enrolment for this trial ended in November 2010 with over 1,000 patients enrolled.

The purpose of 1VIT09030, a cardiovascular outcomes trial in patients with non-dialysis dependent chronic kidney disease, was to directly compare the safety and efficacy of FCM to that of an approved treatment for this indication in patients at high risk for cardiovascular events.

The main objective of 1VIT09031 was to demonstrate the efficacy and safety of FCM compared to oral iron in subjects who have IDA and have been shown to have an unsatisfactory response to oral iron.

Both 1VIT09030 and 1VIT09031 include a composite cardiovascular safety endpoint and both are being regularly monitored by an independent Data Safety Monitoring Board (DSMB). At the 26 October 2010 DSMB meeting, it was concluded that there were no differences in the safety profile of treatment with FCM or comparator/control for these studies. This report was consistent with minutes of previous DSMB meetings which concluded that there is no safety difference between FCM and non-FCM treatment.

There have been also 11 additional clinical trials conducted either by Vifor Pharma or by its US partner. These studies provide corroborative safety data for FCM in patients with IDA with a variety of aetiologies. These trial data in addition to previously provided data constitute a total of approximately 4,400 patients which were exposed to FCM. Thus, including the patient exposure in the original Australian submission, the total patient exposure in the clinical program is now over 8,700.

With the studies 1VIT09030 and 1VIT09031 ongoing, the current ratio of deaths in the overall clinical trial program supports the safety of FCM.

The imbalance perceived at the time of the initial submission to the US FDA as well as with the submission in Australia was probably due to the play of chance and the frequent use of a 2:1 randomisation scheme, as the numbers of deaths in the FCM and comparator arms are presently nearly equal.

In summary, the totality of the clinical data with FCM indicates that FCM is safe in treating iron deficiency in a variety of indications and that there is no imbalance of deaths seen with use of FCM.

Risk Management Plan: Test dose

The requirement for a test dose was discussed in the majority of other world wide applications for Ferinject but not requested after assessment of the existing data. Thus, a test dose is not included in any of the Ferinject labels worldwide.

Historically, the concept for the use of a test dose was based on the fact that IgE-mediated anaphylactic reactions have been reported with iron dextran products due to anti-dextran antibodies induced by previous applications. This reaction is induced specifically by dextran.

Cross-reactivity of these antibodies with other non-dextran containing intravenous iron preparations such as Venofer and sodium ferric gluconate (Ferrlecit) has not been reported. The carbohydrate ligand of Ferinject is based on maltose (carboxymaltose), which does not contain dextran. Unlike dextran, carboxymaltose is not associated with anaphylactic reactions.

As the first generation intravenous iron products contained dextran, a test dose was required and justified. As a consequence, the first clinical trials of the second generation non-dextran containing intravenous iron products such as Venofer were required to be conducted with a test dose. To reflect the administration procedure applied in the clinical registration trials, the requirement that a test dose had to be introduced was present in the Summary of Product Characteristics of Venofer. However, for example in the US, clinical trials with Venofer were performed without a test dose and thus, the FDA-approved US Package Insert of Venofer does not request a test dose. This is also the case in New Zealand. As the next generation of intravenous iron products such as Ferinject do not contain dextran, and as a consequence of the clinical and post-marketing experience of the approved non-dextran containing products, all clinical trials with FCM were conducted without a test dose.

In conclusion, the worldwide clinical experience collected during the last decades with nondextran containing intravenous iron preparations such as Venofer and Ferrlecit, and the extensive clinical and post-marketing safety data with Ferinject, justifies the omission of a test dose for FCM. This conclusion is reflected in all FCM clinical trials (to date with an FCM exposure of over 6,400 patients in 26 trials), which were all conducted without a test dose and no confirmed IgE mediated anaphylactic reactions have been reported.

Chemistry & Quality Control

Product characterization

The Drug Substance (DS) FCM is made of a polynuclear iron(III)-oxyhydroxide core stabilized by carbohydrate units (carboxymaltose). As such, it is a polymeric compound which is very different from conventional small molecule active pharmaceutical ingredients (APIs). Characterization of polymeric compounds requires a set of analytical methods different from those used for conventional APIs.

A polymer is composed of a large number of molecules of different molecular weights and the structure depends on the mechanism, kinetics, and conditions of polymerization and is

characterized by its distinct molecular weight distribution. To fully characterize a polymer, it is important to determine not only the molecular weight but also the molecular weight distribution. Regrettably, the term molecular weight distribution is often abbreviated with molecular weight, as is the case for our application documents.

To determine the molecular weight distribution, the weight average (Mw) and the number average (Mn) are calculated. The value of Mw is sensitive to high-molecular-weight components, whereas that of Mn is sensitive to low-molecular-weight material. The width of the distribution, called polydispersity (P), is calculated from the ratio Mw/Mn. The polydispersity is indicative of the homogeneity of the polymer, that is, it is sensitive to the distribution of molecular masses of individual components. Thus, the molecular weight distribution comprises three different parameters that are characteristic for a specific polymeric compound.

Size exclusion chromatography is the most appropriate method for determining the average molecular weight and the molecular weight distribution. This technique was used to characterize FCM and all three parameters are included in the specification and are stability indicating parameters.

Stability

The sponsor was of the opinion that stability studies have been performed adequately. Both for the drug substance and the drug product (DP), ICH stability studies on three full-scale batches have been performed up to 36 months. Stress testing of FCM revealed that Mw, Mn, and P are sensitive stability-indicating parameters and the first to change significantly resulting in bimodal distributions or even in totally deformed peaks.

In addition, the amount of iron(II) (a degradation product of FCM generated over the shelf-life of the DP) is a quality and stability indicating measure for the DS. The total amount of iron(II) was shown to increase in the stress testing investigations, implying that iron(II) is also an adequate quality and stability indicating parameter. The quantity of iron(II) detected at release is very low. Hence, to date, iron(II) has only been included as a shelf-life test and specification. If deemed necessary, this parameter could also be added to the release specification.

In conclusion, chemical changes in the complex upon storage would lead to a notable increase of the amount of iron(II) and to a significant change in the three parameters defining the molecular weight distribution (Mw, Mn, and P). All these parameters have been thoroughly investigated throughout the development process and have been shown to be stability indicating. As demonstrated from all the submitted stability data, no significant changes were observed for these parameters during accelerated or long-term testing.

Control of tonicity for the use of the product as bolus injection

The applicant has determined osmolarity values for 70 lots of the DP manufactured between 1998 and 2010: results were in the range of 286–380 mOsm/L (the physiological osmolality is about 300 mOsm/L). These values correlate with the sodium chloride content of the solution.

The upper limit of sodium chloride of 1.4% m/V, set in the specification of the DP, corresponds to an osmolarity of 480 mOsm/L. However, the routine results measured for sodium chloride were all significantly lower, that is, in the range 0.83 –1.05% m/V, which corresponds to 285–360 mOsm/L.

The osmolarity of parenteral solutions is usually only relevant when large volumes are infused and is less problematic for small volume injections. Three clinical studies have

been completed, in which bolus injections of undiluted doses up to 1000 mg iron have been administered in over 1,300 patients (1VIT06011, 1VIT07017 and 1VIT07018). The number of adverse events was similar to that observed in the studies submitted to the TGA. Although two of these studies were not included in the original submitted application (1VIT07017 and 1VIT07018), they are relevant to demonstrate that the safety profile of FCM is unchanged. In addition, the Vifor Pharma global drug safety database was searched for FCM bolus injection cases. This search returned one non-serious injection site reaction case (no outcome was provided by the reporter).

In conclusion, the sponsor was of the opinion that the data provided sufficiently justify not including a test and limit for osmolarity in the Drug Product specification. However, should this control be deemed necessary by the TGA, the sponsor was willing to include a test and limit.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

The ACPM advised that there was a lack of safety data on the incidence of anaphylaxis. It was noted with some concern that it has become more common for infusions to be administered in non-hospital settings such as at pathology collection centres and at home. The reporting of adverse events may thus not always reflect actual incidence. It is usual for a test dose to be administered initially for such IV products and hypersensitivity reactions to be monitored; this practice should be encouraged in the PI.

The ACPM further advised that the stated osmolarity of the product was likely to cause local toxicity issues in peripheral veins and may also cause pain.

The ACPM noted that there were no data provided for treatment in children and would encourage the sponsor to submit this.

It was recommended that the specific conditions of registration should include:

- Addressing the concerns of the PSC in regards to long term stability, particle size and quality control issues.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include:

- Amendments to the *Dosage and Administration* section to recommend administration of a test dose with subsequent monitoring for hypersensitivity reactions.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Ferinject containing ferric carboxymaltose, indicated for:

Treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. The diagnosis must be based on laboratory tests.

The sponsor provided a further response to the ACPM requirement for a test dose. The Delegate decided not to require a test dose because the evidence for it is lacking. As a specific condition of registration, the Risk Management Plan, dated 8 February 2011, and any subsequent revisions, as agreed with the TGA Office of Product Review must be

implemented. The draft protocols for the planned studies FER-CARS-04 and 05 must be provided to the TGA Office of Product Review for review when they become available.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

FERINJECT®

NAME OF THE MEDICINE

FERINJECT
Ferric carboxymaltose

Chemical structure
The active substance of FERINJECT is a complex of polynuclear iron(III)-hydroxide with 4(R)-(poly-(1→4)-*O*-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate. The relative molecular weight is approximately 150,000 Da, corresponding to the empirical formula:

$[FeO_x(OH)_y(H_2O)_z]_n$ $[\{(C_6H_{10}O_5)_m$ $(C_6H_{12}O_7)\}_l]_k$, where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$.

CAS-Number
9007-72-1

DESCRIPTION

Solution for intravenous use. FERINJECT is a dark brown, non-transparent, colloidal solution.

Excipients
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

PHARMACOLOGY

Pharmacodynamic properties
FERINJECT solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to provide iron for the iron transport and storage proteins in the body (transferrin and ferritin). Ferric carboxymaltose was effective in increasing Hb and serum ferritin concentrations in patients with mild to moderate iron-deficiency anaemia. The intravenous (IV) iron dose was 500 mg weekly for up to 4 weeks (n=20) or 1,000 mg weekly for up to 2 weeks (n=26). With the 500 mg iron dose, 37% of patients achieved normal Hb levels within 8 weeks and 75% achieved a ≥20 g/L increase in Hb on at least one occasion. With 1,000 mg iron, 48% of patients achieved normal Hb levels within 6 weeks and 73% achieved a≥ 20 g/L increase in Hb on at least one occasion. The target serum ferritin concentration 100-500 µg/L was reached with both doses and remained within the target range at 2 weeks follow-up (at 6 and 4 weeks respectively for the two dose groups)-data were only available for about half the 500 mg iron dose group.

Pharmacokinetic properties

After a single 100 mg IV iron dose of ferric carboxymaltose (n=6) injected over 1 min, serum iron concentration peaked at a mean of 15 min. After 500, 800 or 1,000 mg iron in 250 mL normal saline infused over 15 min (n=6 for each dose), serum iron concentration peaked at means of 20 min, 1 h and 1.2 h, respectively. The mean volume of distribution was approximately 3 L, corresponding to the plasma volume. Mean plasma clearance ranged from 2.6-4.4 mL/min and terminal half life from 7-12 h. Renal elimination was negligible.

Within 8 h of a single radiolabelled 100 mg IV iron dose of ferric carboxymaltose to patients with iron deficiency or renal anaemia, most of the radiolabelled iron had cleared the circulation and distributed to the bone marrow, liver and spleen. Within 6-9 days, the radiolabelled iron was incorporated into the red blood cells. After 24 days, iron utilisation was 91-99% in iron deficiency anaemia and 61-84% in renal anaemia.

CLINICAL TRIALS

Clinical studies showed that the haematological response and the filling of the iron stores was faster after intravenous administration of FERINJECT than with orally administered comparators.

The phase I II studies undertaken with FERINJECT included patients with iron deficiency anaemia (IDA) of different aetiologies, i.e. IDA associated with non-dialysis and dialysis dependent chronic kidney disease, IDA secondary to inflammatory bowel disease or heavy uterine bleeding, post-partum IDA, and IDA in patients with chronic heart failure and iron deficiency.

IDA associated with haemodialysis-dependent chronic kidney disease. The efficacy and safety of FERINJECT compared to Venofer® (iron sucrose, intravenous) for the treatment of IDA secondary to chronic renal failure was assessed in a multi-centre, open-label, randomised, parallel-group, Phase III study in 237 patients on haemodialysis or haemodiafiltration. IDA was defined as Hb ≤115 g/L in addition to TSAT <20% and/or serum ferritin <200 µg/L. Patients received 200 mg iron 2 or 3 times weekly (depending on the timing of dialysis sessions) until their individual calculated cumulative dose had been reached. The mean duration of treatment was 15.8 days (range 1 to 27) and 16.2 days (range 1 to 43 days) for the FERINJECT and Venofer® groups, respectively.

Patients treated with erythropoietin (EPO) should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. The primary efficacy endpoint was defined as the percentage of patients reaching an increase in Hb of≥10 g/L at 4 weeks. The percentage of responders was 44.1% (52/118) in the FERINJECT group and 35.3% (41/116) in the Venofer® group; the difference between groups was not statistically significant (chi^2 = 0.2254). At follow-up 4 weeks after the final dose of medication, secondary efficacy parameters (Hb ≥110-120 g/L, serum ferritin 200-800 µg/L, TSAT 20-50%) demonstrated successful increase in iron stores for both treatment groups.

IDA associated with non-dialysis-dependent chronic kidney disease. A multi-centre, randomised, open-label, controlled, 8-week, Phase III study in 255 patients was conducted to compare the safety and efficacy of intravenous infusions of FERINJECT with oral administration of ferrous sulphate, independent of Hb response to EPO, in

treating IDA in non-dialysis-dependent chronic kidney disease (ND-CKD). IDA was defined as Hb ≤110 g/L, TSAT ≤25%, and serum ferritin ≤300 µg/L. Patients treated with EPO should have had received this treatment for at least 8 weeks prior to inclusion in the study and increases in the dose of EPO were not permitted. Patients randomised to FERINJECT treatment received 1 to 3 doses of FERINJECT intravenously at 2-4 week intervals: 15 mg iron/kg for weight ≤66 kg to a maximum of 1,000 mg iron for the initial dose and a maximum of 500 mg iron for subsequent doses. Patients randomised to oral iron treatment received ferrous sulphate tablets (65 mg iron) 3 times daily for 8 weeks.
In a modified intent-to-treat analysis which excluded 8 FERINJECT patients and 2 ferrous sulfate patients, the primary efficacy endpoint, defined as the percentage of patients with an increase in Hb ≥10 g/L at any time between baseline and end of study, or time of intervention, was reached by 60.4% (87/144) of FERINJECT-treated patients compared to 34.7% (35/101) of oral iron-treated patients (p<0.001; 95% confidence interval (CI) 13.0, 38.5). The modified intent-to-treat population comprised patients with at least one dose of study medication, stable erythropoietin dose, at least one post-baseline Hb assessment and GFR ≥ 45 mL/min/1.73 m^2. FERINJECT was also demonstrated to be superior to oral iron across all secondary ranked efficacy endpoints: Hb change ≥10 g/L and a serum ferritin change ≥160 µg/L at any time during the study (60.4% versus 0.0%, respectively; p<0.001; 95% CI 48.2, 72.6) or a Hb change ≥10 g/L before Day 42 (54.2% versus 28.7%, respectively; p<0.001; 95% CI 12.8, 38.1).
In a 44-week extension to this study, the efficacy of FERINJECT in the long-term maintenance treatment of anaemia in ND-CKD was evaluated in 140 patients. Clinical success (Hb ≥110 g/L, serum ferritin 100-800 µg/L, TSAT 30-50%) was achieved in 51.4% (72/140) of patients, with 10% (14/140) exhibiting sustained clinical success at 50% or more of the assessments.

IDA secondary to inflammatory bowel disease. The efficacy of infusions of FERINJECT compared to oral administration of ferrous sulphate in the treatment of IDA secondary to chronic inflammatory bowel disease was examined in a multi-centre, open-label, randomised, 12-week, Phase III study in 200 patients. 4 patients did not receive study drug and were excluded from the analysis. IDA was defined as Hb ≤110 g/L in combination with TSAT <20% and/or serum ferritin <100 µg/L. Patients were randomised in a 2:1 (FERINJECT: ferrous sulphate) ratio to receive 1 of 2 treatments: FERINJECT intravenous on Day 1 with subsequent doses at 1-week intervals until the patient's calculated cumulative dose had been reached (a maximum dose of 1,000 mg iron per infusion) or oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks. Based on the primary response parameter of change in mean Hb from baseline to Week 12 (36.0 g/L FERINJECT group, 32.9 g/L oral iron group), the results of this study demonstrated that FERINJECT was non-inferior to ferrous sulphate. The non-inferiority criterion was lower limit of 95% CI of difference ferric carboxymaltose minus ferrous sulphate ≥ -5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations. Furthermore, the mean Week-12 values of serum ferritin (80.2 µg/L FERINJECT group, 38.6 µg/L oral iron group) and TSAT (23.1% FERINJECT group, 29.2% oral iron group) demonstrated a successful repletion of the iron stores in patients treated with FERINJECT.

IDA secondary to heavy uterine bleeding. The safety and efficacy of intravenous infusions of FERINJECT, compared to oral administration of ferrous sulphate, in improvement of Hb levels in females with IDA secondary to heavy uterine bleeding was assessed in a multi-centre, randomised, open-label, 6-week, Phase III study. At enrolment, patients had a baseline Hb ≤114 g/L, TSAT ≤25%, and serum

ferritin ≤100 µg/L. Patients were randomised to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly FERINJECT infusions (a maximum dose of 1,000 mg iron per infusion) until the patient's calculated cumulative dose had been reached, to a maximum of 2,500 mg iron. In a modified intent-to-treat analysis which excluded 18 FERINJECT patients and 6 ferrous sulphate patients, FERINJECT was shown to be superior to oral iron in achieving an increase from baseline in Hb ≥20 g/L at any time during the study: 82.0% (187/228) in the FERINJECT group versus 61.8% (139/225) in the oral iron group (p<0.001; 95% CI 12.2, 28.3). The modified intent-to-treat population comprised patients with at least one dose of study medication, baseline Hb ≤ 110 g/L, TSAT ≤ 25%, serum ferritin ≤100 µg/L, at least one post-baseline Hb assessment and confirmed diagnosis of heavy uterine bleeding.

Post partum IDA. The safety and efficacy of FERINJECT compared to oral ferrous sulphate as treatment for post partum IDA (Hb ≤100 g/L or ≤105 g/L) was assessed in 3 randomised, open-label, multi-centre trials. In 2 of the studies, patients were randomised 1:1 to receive either oral ferrous sulphate tablets (65 mg iron) 3 times daily for 6 weeks or weekly intravenous FERINJECT at dosages based on the calculated iron deficit. A maximum of 1,000 mg of iron (15 mg iron/kg for pre-pregnancy weight ≤66 kg), as intravenous FERINJECT, was given at weekly intervals until the individual's calculated cumulative dose had been reached or a maximum total dose of 2,500 mg had been administered. In the third study, patients were randomised 2:1 to receive either oral ferrous sulphate capsules (100 mg iron) twice daily for 12 weeks or weekly intravenous FERINJECT at dosages based on the calculated iron deficit (to a maximum of 3 infusions and not exceeding a weekly dose of 1,000 mg iron).
In all 3 studies, FERINJECT was shown to be efficacious for the treatment of IDA in post partum subjects. In the first study, the superiority of FERINJECT was demonstrated according to the primary efficacy endpoint (defined as Hb >120 g/L), with a greater proportion of patients in the FERINJECT group (91.4%, 127/139) versus the oral iron group (66.7%, 98/147) achieving success at any time during the study (p<0.0001; 95% CI 15.20, 34.20). This was based on a modified intent-to-treat population which excluded 4 ferric carboxymaltose patients and one ferrous sulfate patient.
In the second study, FERINJECT was demonstrated to be non-inferior to oral iron among subjects who achieved an increase in Hb ≥20 g/L: 96.4% (162/168) of the FERINJECT group versus 94.1% (159/169) of the oral iron group (95% CI -2.19, 6.88). The analysis was in a modified intent-to-treat population (6 ferric carboxymaltose patients and 9 ferrous sulphate patients excluded) and the non-inferiority margin was 15% based on a 1-sided 97.5% CI of the treatment difference.
Statistically significantly greater increases from baseline to highest Hb, TSAT, and serum ferritin values were also observed in the FERINJECT groups compared with the oral iron groups.
In the third study, FERINJECT was shown to be non-inferior to ferrous sulphate for the mean change in Hb from baseline to Week 12 (33.4 g/L in the FERINJECT group (n=227) versus 31.8 g/L in the oral iron group (n=117).
The non-inferiority criterion was lower limit of 95% CI of difference ferric carboxymaltose minus ferrous sulfate ≥ - 5.0 g/L. The non-inferiority criterion was met in both the intent-to-treat and per protocol populations.

IDA associated with chronic heart failure and renal deficiency. A pilot study of IV ferric carboxymaltose (n=30) versus Venofer® (n=27) and placebo (n=15) in patients with iron deficiency anaemia associated with chronic heart failure and renal deficiency

was supportive of improvements in patient global assessment and New York Heart Association (NYHA) status in patients treated with ferric carboxymaltose and Venofer®. The study was not powered to show superiority over placebo.

There are no data available regarding the long term use of FERINJECT.

INDICATIONS

FERINJECT is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.
The diagnosis must be based on laboratory tests.

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

PRECAUTIONS

Body iron excretion is limited and excess tissue iron can be hazardous. Patients receiving FERINJECT require regular monitoring of red cell indices and serum ferritin to detect iron overload. If there is evidence of iron overload, iron therapy should be withheld.

In patients with liver dysfunction, parenteral iron should only be administered after careful risk/benefit assessment. Parenteral iron administration should be avoided in patients with hepatic dysfunction where iron overload is a precipitating factor, in particular Porphyria Cutanea Tarda (PCT).

Parenteral iron must be used with caution in case of acute or chronic infection, asthma, eczema or atopic allergies. It is recommended that the administration of FERINJECT is stopped in patients with ongoing bacteraemia.
In patients with chronic infection a risk/benefit evaluation has to be performed, taking into account the suppression of erythropoiesis.

One millilitre of undiluted FERINJECT contains up to 5.5 mg (0.24 mmol) of sodium. This has to be taken into account in patients on a sodium-controlled diet.

Hypersensitivity Reactions
Parenterally administered iron preparations can cause hypersensitivity reactions including anaphylactoid reactions, which may be potentially fatal. Therefore, facilities for cardio-pulmonary resuscitation must be available.

Paravenous Leakage
Caution should be exercised to avoid paravenous leakage when administering FERINJECT. Paravenous leakage of FERINJECT at the injection site may lead to

brown discolouration and irritation of the skin. In case of paravenous leakage, the administration of FERINJECT must be stopped immediately.

Effects on fertility

Reduced weights of reproductive organs (prostate, seminal vesicle, epididymides, testis or uterus) were seen in rats and dogs at maternally toxic doses following repeated IV dosing with ferric carboxymaltose. There were no effects of ferric carboxymaltose on the fertility or reproductive performance of rats given thrice weekly IV doses of up to 30 mg/kg (roughly equal to the maximum weekly clinical dose, based on BSA).

Use in pregnancy (Category B3)

Studies in rats have shown that iron released from ferric carboxymaltose can cross the placental barrier.

In pregnant rabbits and rats, embryotoxicity (decreased placental or litter weights and increased resorptions) and increases in fetal skeletal abnormalities (thickened/kinked ribs in rats and cranial, forepaw and/or limb abnormalities in rabbits) were observed at maternally toxic IV iron doses from 9 or 30 mg/kg/day, respectively given during organogenesis (1.4-2.5 times the maximum weekly clinical dose, based on BSA). No effects were observed at IV iron doses up to 4.5 or 9 mg/kg/day, respectively (0.7 times the maximum weekly clinical dose, based on BSA).

There are no adequate and well-controlled studies in pregnant woman. Because animal reproductive studies are not always predictive of human response, FERINJECT should be used during pregnancy only if clearly needed, and should not be used in the first trimester (see Contraindications).

Use in lactation

Clinical studies showed that transfer of iron from FERINJECT to human milk was negligible (≤ 1%).

Evidence of delayed postnatal growth and development has been observed in rats exposed to ferric carboxymaltose. Milk transfer of administered iron from ferric carboxymaltose was demonstrated in lactating rats. Caution should be exercised when FERINJECT is used in lactating woman.

Paediatric use

The use of FERINJECT has not been studied in children and therefore is not recommended in children under 14 years.

Carcinogenicity

The carcinogenic potential of FERINJECT has not been studied in animals.

Genotoxicity

Ferric carboxymaltose was not genotoxic in assays for gene mutation (in vitro bacterial and mouse lymphoma cell assays) and chromosomal damage (human lymphocytes in vitro and mouse micronucleus test in vivo).

Interaction with other medicines

As with all parenteral iron preparations the absorption of oral iron is reduced when administered concomitantly.

ADVERSE EFFECTS

Clinical studies experience

The most commonly reported ADR is headache, occurring in 3.3% of the patients.

Very common (>1/10)
Common (>1/100, <1/10)
Uncommon (>1/1,000, <1/100)
Rare (>1/10,000, <1/1,000)
Very rare (<1/10,000), including isolated reports

Immune System Disorders
Uncommon: Hypersensitivity including anaphylactoid reactions

Nervous system disorders
Common: Headache, dizziness
Uncommon: Paraesthesia

Vascular disorders
Uncommon: Hypotension, flushing

Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, abdominal pain, constipation, diarrhoea
Uncommon: Dysgeusia, vomiting, dyspepsia, flatulence

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Pruritus, urticaria

Musculoskeletal and connective tissue disorders
Uncommon: Myalgia, back pain, arthralgia

General disorders and administration site conditions
Common: Injection site reactions
Uncommon: Pyrexia, fatigue, chest pain, rigors, malaise, oedema peripheral

Investigations
Common: Transient blood phosphorus decreased, alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon: Gamma-glutamyltransferase increased, blood lactate dehydrogenase increased

Post marketing experience

As part of the continuing post-marketing surveillance of FERINJECT, the following serious adverse reactions have been observed:

Psychiatric disorders
Anxiety

Nervous system disorders
Loss of consciousness and vertigo

Cardiac disorders
Tachycardia

Vascular disorders
Hypertension and syncope

Respiratory, thoracic and mediastinal disorders
Bronchospasm

Skin and subcutaneous tissue disorders
Angioedema, dermatitis, erythema, pallor and face oedema

General disorders and administration site conditions
Chills

DOSAGE AND ADMINISTRATION

Calculation of the cumulative dose
The adequate cumulative dose of FERINJECT must be calculated for each patient individually and must not be exceeded. For overweight patients, a normal body weight/blood volume relation should be assumed when determining the iron requirement. The dose of FERINJECT is expressed in mg of elemental iron.

The cumulative dose required for Hb restoration and repletion of iron stores is calculated by the following Ganzoni formula:

Cumulative iron deficit [mg] =
body weight [kg] x (target Hb* - actual Hb) [g/L] x 0.24 +**
iron storage depot [mg]***

* *Target Hb for body weight below 35 kg = 130 g/L.*
Target Hb for body weight 35 kg and above = 150 g/L .
** *Factor 0.24 = 0.0034 x 0.07 x 1,000;*
0.0034: iron content of haemoglobin ≙ 0.34%;
0.07: blood volume ≙ 7% of body weight;
1,000: conversion factor 1 g/L =1,000 mg/l.
*** *Depot iron for body weight below 35 kg = 15 mg/kg body weight.*
Depot iron for body weight 35 kg and above = 500 mg.

For patients ≤ 66 kg: the calculated cumulative dose is to be rounded down to the nearest 100 mg.
For patients > 66 kg: the calculated cumulative dose is to be rounded up to the nearest 100 mg.

Patients may continue to require therapy with FERINJECT at the lowest dose necessary to maintain target levels of haemoglobin, and other laboratory values of iron storage parameters within acceptable limits.

Maximum tolerated single dose
The adequate cumulative dose of FERINJECT must be calculated for each patient individually and must not be exceeded.

Intravenous bolus injection:
FERINJECT may be administered by intravenous injection up to a maximum single dose of 4 ml (200 mg of iron) per day but not more than three times a week.

Intravenous drip infusion:
FERINJECT may be administered by intravenous infusion up to a maximum single dose of 20 ml of FERINJECT (1,000 mg of iron) but not exceeding 0.3 ml of FERINJECT (15 mg of iron) per kg body weight or the calculated cumulative dose. Do not administer 20 ml (1,000 mg of iron) as an infusion more than once a week.

Method of administration
FERINJECT must be administered only by the intravenous route: by bolus injection, during a haemodialysis session undiluted directly into the venous limb of the dialyser, or by drip infusion. In case of drip infusion FERINJECT must be diluted only in sterile 0.9% sodium chloride solution as follows:

Dilution plan of FERINJECT for intravenous drip infusion

FERINJECT	Iron	Amount of sterile 0.9% m/V sodium chloride solution	Minimum administration time
2 to 4 ml	100 to 200 mg	50 ml	3 minutes
> 4 to 10 ml	>200 to 500 mg	100 ml	6 minutes
>10 to 20 ml	>500 to 1,000 mg	250 ml	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/ml are not permissible.
FERINJECT must not be administered by the intramuscular route.

Inspect vials visually for sediment and damage before use. Use only those containing sediment-free, homogeneous solution.

Each vial of FERINJECT is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

FERINJECT must only be mixed with sterile 0.9% m/V sodium chloride solution. No other intravenous dilution solutions and therapeutic agents should be used, as there is the potential for precipitation and/or interaction. For dilution instructions, see above.

This medicinal product must not be mixed with other medicinal products than those mentioned above. The compatibility with containers other than polyethylene and glass is not known.

OVERDOSAGE

Administration of FERINJECT in quantities exceeding the amount needed to correct iron deficit at the time of administration may lead to accumulation of iron in storage sites eventually leading to haemosiderosis. Monitoring of iron parameters such as serum ferritin and transferrin saturation may assist in recognising iron accumulation.

PRESENTATION AND STORAGE CONDITIONS

Presentations
2 ml of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials. Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.

10 ml of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 1 and 5 vials. Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.

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

Shelf-life
Shelf-life of the product as packaged for sale:
3 years.

Shelf-life after first opening of the container:
From a microbiological point of view, preparations for parenteral administration should be used immediately.
Shelf-life after dilution with sterile 0.9% m/V sodium chloride solution:
To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 12 hours.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE
S4

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Therapeutic Goods Administration

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Reference/Publication #