Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Ferinject 50mg Iron/ml Solution for Injection/Infusion

DCP no: UK/H/0894/001/DC
UK licence no: PL 15240/0002

Applicant: Vifor France SA

Medicines and Healthcare products Regulatory Agency

Ferinject 50mg Iron/ml Solution for Injection/Infusion
PL 15240/0002; UK/H/0894/001/DC

LAY SUMMARY

Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden and the United Kingdom approved Vifor France SA a Marketing Authorisation (licence) for the medicinal product Ferinject 50mg Iron/ml Solution for Injection/Infusion (PL 15240/0002). This application was by decentralised procedure, was ended successfully on 19th June 2007. There was a subsequent national phase and the licence was granted in the UK on 19th July 2007. These are prescription-only medicines (POM) for the treatment of iron deficiency when oral iron preparations are ineffective or cannot be used.

Ferinject 50mg Iron/ml Solution for Injection/Infusion contains ferric carboxymaltose, a new iron(III)-hydroxide carbohydrate complex (termed VIT-45). It is an iron complex enabling slow, controlled, systemic release of bioavailable iron to iron-binding proteins, with little risk of release of free iron.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Ferinject 50mg Iron/ml Solution for Injection/Infusion outweighed the risks, hence a Marketing Authorisation has been approved.

TABLE OF CONTENTS

Module 1

Product Name	Ferinject 50mg Iron/ml Solution for Injection/Infusion
Type of Application	New Active Substance Initial application Full Dossier (Article 8.3) Chemical substance Prescription only
Active Substance	Ferric carboxymaltose
Form	Solution for Injection/Infusion
Strength	50mg Iron/ml
MA Holder	Vifor France SA 123, rue Jules Guesde F-92300 Levallois-Perret France
RMS	United Kingdom
CMS	Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden
Procedure Number	UK/H/894/001/DC
Timetable	Day 210: 19/06/2007

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FERINJECT 50 mg iron/ml solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One milliliter of solution contains 50 mg of iron as ferric carboxymaltose.

Each 2 ml vial contains 100 mg of iron as ferric carboxymaltose.
Each 10 ml vial contains 500 mg of iron as ferric carboxymaltose.

Ferinject contains sodium hydroxide. One milliliter of solution contains up to 0.24 mmol (5.5 mg) sodium, see section 4.2.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion. Dark brown, non-transparent, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of 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/dl]** x 2.4*** +
iron storage depot [mg]****

* *Target Hb for body weight below 35 kg = 13 g/dl respectively 8.1 mmol/l.*
Target Hb for body weight 35 kg and above = 15 g/dl respectively 9.3 mmol/l.

** *To convert Hb [mM] to Hb [g/dl]: multiply Hb [mM] by the factor 1.61145.*

*** *Factor 2.4 = 0.0034 x 0.07 x 10000;*
0.0034: iron content of haemoglobin ≙0.34%;
0.07: blood volume ≙7% of body weight;
10000: conversion factor 1 g/dl =10000 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 (1000 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 (1000 mg of iron) as an infusion more than once a week.

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

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			Maximum amount of sterile 0.9% sodium chloride solution	Minimum administration time
2	to	< 4 ml	100	to	< 200 mg	50 ml	-
4	to	< 10 ml	200	to	< 500 mg	100 ml	6 minutes
10	to	20 ml	500	to	1000 mg	250 ml	15 minutes

Note: For stability reasons, dilutions to concentrations less than 2 mg iron/ml are not permissible.

FERINJECT must not to be administered by the intramuscular route.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Parenterally administered iron preparations can cause hypersensitivity reactions (see section 5.3). Therefore, facilities for cardio-pulmonary resuscitation must be available.

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). Careful monitoring of iron status is recommended to avoid iron overload.

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.

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.

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

The use of FERINJECT has not been studied in children.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Clinical data on pregnant women are not available. A careful risk/benefit evaluation is required before use during pregnancy.

Animal data suggest that iron released from FERINJECT can cross the placental barrier and that its use during pregnancy may influence skeletal development in the fetus.

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

4.7 Effects on ability to drive and use machines

FERINJECT is unlikely to impair the ability to drive or operate machines.

4.8 Undesirable effects

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

Nervous system disorders
Common (>1/100, <1/10): Headache, dizziness
Uncommon (>1/1,000, <1/100): Paraesthesia

Vascular disorders
Uncommon (>1/1,000, <1/100): Hypotension, flushing

Gastrointestinal disorders
Common (>1/100, <1/10): Nausea, abdominal pain, constipation, diarrhoea
Uncommon (>1/1,000, <1/100): Dysgeusia, vomiting, dyspepsia, flatulence

Skin and subcutaneous tissue disorders
Common (>1/100, <1/10): Rash
Uncommon (>1/1,000, <1/100): Pruritus, urticaria

Musculoskeletal and connective tissue disorders
Uncommon (>1/1,000, <1/100): Myalgia, back pain, arthralgia

General disorders and administration site conditions
Common (>1/100, <1/10): Injection Site Reactions
Uncommon (>1/1,000, <1/100): Pyrexia, fatigue, chest pain, rigors, malaise, oedema peripheral

Investigations
Common (>1/100, <1/10): Transient blood phosphorus decreased, alanine aminotransferase increased
Uncommon (>1/1,000, <1/100): Aspartate aminostransferase increased, gamma-glutamyltransferase increased, blood lactate dehydrogenase increased

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Iron trivalent, parenteral preparation

ATC Code: B03A C01

Ferinject solution for injection/infusion contains iron in a stable ferric state as a complex with a carbohydrate polymer designed to release utilisable iron to the iron transport and storage proteins in the body (ferritin and transferrin). 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.

Using positron emission tomography (PET) it was demonstrated that red cell utilisation of 59Fe and 52Fe from FERINJECT ranged from 61% to 99%. Patients with iron deficiency showed utilisation of radio-labelled iron of 91% to 99% after 24 days, and patients with renal anaemia showed utilisation of radiolabelled iron of 61% to 84% after 24 days.

One millilitre of undiluted Ferinject contains less than 75 µg aluminium. This should be considered in the treatment of patients undergoing dialysis.

5.2 Pharmacokinetic properties

Using positron emission tomography (PET) it was demonstrated that 59Fe and 52Fe from FERINJECT was rapidly eliminated from the blood, transferred to the bone marrow, and deposited in the liver and spleen.

After administration of a single dose of FERINJECT of 100 to 1000 mg of iron in iron deficient patients, maximum iron levels of 37 µg/ml up to 333 µg/ml after 15 minutes to 1.21 hours respectively are obtained. The volume of the central compartment corresponds well to the volume of the plasma (approximately 3 litres).

The iron injected or infused was rapidly cleared from the plasma, the terminal halflife ranged from 7 to 12 hours, the mean residence time (MRT) from 11 to 18 hours. Renal elimination of iron was negligible.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products than those mentioned in section 6.6.

The compatibility with containers other than polyethylene and glass is not known.

6.3 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% sodium chloride solution:
From a microbiological point of view, preparations for parenteral administration should be used immediately after dilution with sterile 0.9% sodium chloride solution.

6.4 Special precautions for storage
Store in the original package. Do not store above 30 °C. Do not refrigerate or freeze.

6.5 Nature and contents of container
2 ml of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 5.

10 ml of solution in a vial (type I glass) with bromobutyl rubber stopper and aluminium cap in pack sizes of 5.

6.6 Instructions for use, handling and disposal
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% 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 section 4.2.

7. MARKETING AUTHORISATION HOLDER
Vifor France SA
123, rue Jules Guesde
92300 Levallois-Perret
France

8. MARKETING AUTHORISATION NUMBER
PL 15240/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/07/2007

10. DATE OF REVISION OF THE TEXT
19/07/2007

Module 3
Product Information Leaflet & Technical Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

FERINJECT® 50 mg iron/ml solution for injection/infusion.
Ferric carboxymaltose

Read all of this leaflet carefully.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet

1. WHAT FERINJECT IS AND WHAT IT IS USED FOR

FERINJECT is an antianaemic preparation, a medicine that is used to treat anaemia. It contains iron in the form of an iron carbohydrate. Iron is an essential element required for the oxygen-carrying capacity of haemoglobin in red blood cells and of myoglobin in muscle tissue. Moreover, iron is involved in many other functions necessary for maintenance of life in the human body.
FERINJECT is used for the treatment of patients with iron deficiency, when oral iron preparations are ineffective or cannot be used. The aim of the therapy is to replenish body iron stores and to remedy anaemia, a lack of red blood cells due to iron deficiency.

Before administration, your doctor will perform a blood test to calculate the dose of FERINJECT you require.

2. BEFORE YOU RECEIVE FERINJECT

You must not receive FERINJECT
- if you are hypersensitive (allergic) to ferric carboxymaltose or any of the other ingredients of FERINJECT,
- if you have anaemia <u>not</u> caused by iron deficiency,
- if you have iron overload (too much iron in your body) or disturbances in utilisation of iron,
- during the first three months of pregnancy.

Take special care with FERINJECT
- Tell your doctor if you have an infection, asthma, eczemas, allergies or liver disorders.
- FERINJECT should not be given to children under 14 years.

Taking other medicines
If FERINJECT is given together with oral iron preparations, then these oral preparations could be less efficient.
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without prescription.

Pregnancy
Tell your doctor if you are pregnant and ask him/her for advice before you are given any medicine.

Breast feeding
Ask your doctor for advice before you are given FERINJECT. It is unlikely that FERINJECT represents a risk to the nursing child.

Driving and using machines
FERINJECT is unlikely to impair the ability to drive or operate machines.

Important information about some of the ingredients of FERINJECT
This medicinal product contains 0.24 mmol (or 5.5 mg) sodium per millilitre of undiluted solution and is to be taken into consideration by patients on a controlled sodium diet.

3. HOW FERINJECT IS ADMINISTERED

Your doctor can administer FERINJECT by three possible routes: undiluted by injection, during dialysis, or diluted by drip infusion.
- By injection, you may receive up to 4 ml of FERINJECT, corresponding to 200 mg of iron, per day directly into the vein. You may receive this dose once to three times a week.
- If you are on dialysis, you may receive FERINJECT during a haemodialysis session via the dialyser.
- By drip infusion, you may receive up to 20 ml of FERINJECT, corresponding to 1000 mg of iron, once a week directly into the vein. Because FERINJECT is diluted with sodium chloride solution for the drip infusion, it may have a volume of up to 250 ml and appear as a brown solution.

Your doctor will take responsibility for calculating the appropriate dose and choosing the route, frequency and duration of your treatment.
Overdose can cause accumulation of iron in storage sites. Your doctor will monitor iron parameters such as serum ferritin and transferrin to avoid iron accumulation.

4. POSSIBLE SIDE EFFECTS

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

Reported side effects are either common (occurring in less than 1 in 10 and more than 1 in 100 patients) or uncommon (occurring in less than 1 in 100 and more than 1 in 1000 patients).

The following symptoms were common: headache, dizziness, nausea, abdominal pain, constipation, diarrhoea, rash, injection site reactions.

The following symptoms were uncommon: paraesthesia, hypotension, flushing, taste disturbance, vomiting, dyspepsia, flatulence, itchiness, hives (urticaria), muscle pain, back pain, joint pain, fever, fatigue, chest pain, rigors, malaise, oedema peripheral.

Some blood parameters may change temporarily, which could be detected in laboratory tests.
The following changes in blood parameters are common: transient decrease in blood phosphorus and increase of a certain liver enzyme called alanine aminotransferase.
The following changes in blood parameters are uncommon: increase in certain liver enzymes called aspartate aminotransferase and gamma-glutamyltransferase and increase in an enzyme called lactate dehydrogenase.
Ask your doctor for more information.

If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

5. HOW TO STORE FERINJECT

Keep FERINJECT out of the reach and sight of children.

Do not use FERINJECT after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

Once the FERINJECT vials have been opened, they should be used immediately. After dilution with sodium chloride solution, the diluted solution should be used immediately.

FERINJECT will normally be stored for you by your doctor or the hospital.

6. FURTHER INFORMATION

What FERINJECT contains
The active substance is iron (as ferric carboxymaltose, an iron carbohydrate compound). The concentration of iron present in the product is 50 mg per milliliter. The other ingredients are sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment), and water for injection.

What FERINJECT looks like and contents of the pack
FERINJECT, solution for injection/infusion is a dark brown, non-transparent solution.

FERINJECT is supplied in glass vials of 2 ml solution, corresponding to 100 mg iron, and in glass vials of 10 ml solution, corresponding to 500 mg iron.

FERINJECT is available as 2 ml and as 10 ml vials in pack sizes of 5.

The Marketing Authorisation Holder and Manufacturer
The Marketing Authorisation Holder is:
Vifor France SA
123, rue Jules Guesde
92300 Levallois-Perret
France

Manufacturer:
Alloga France
534, rue Jean Bertin
45770 Saran
France

This medical product is authorised in the Member states of the EEA under the following names:
Austria, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Ireland, Lithuania, Luxembourg, Latvia, Netherlands, Poland, Portugal, Slovak Republic, United Kingdom: Ferinject®
Sweden: Ferijet™

This leaflet was approved in 07/2007.

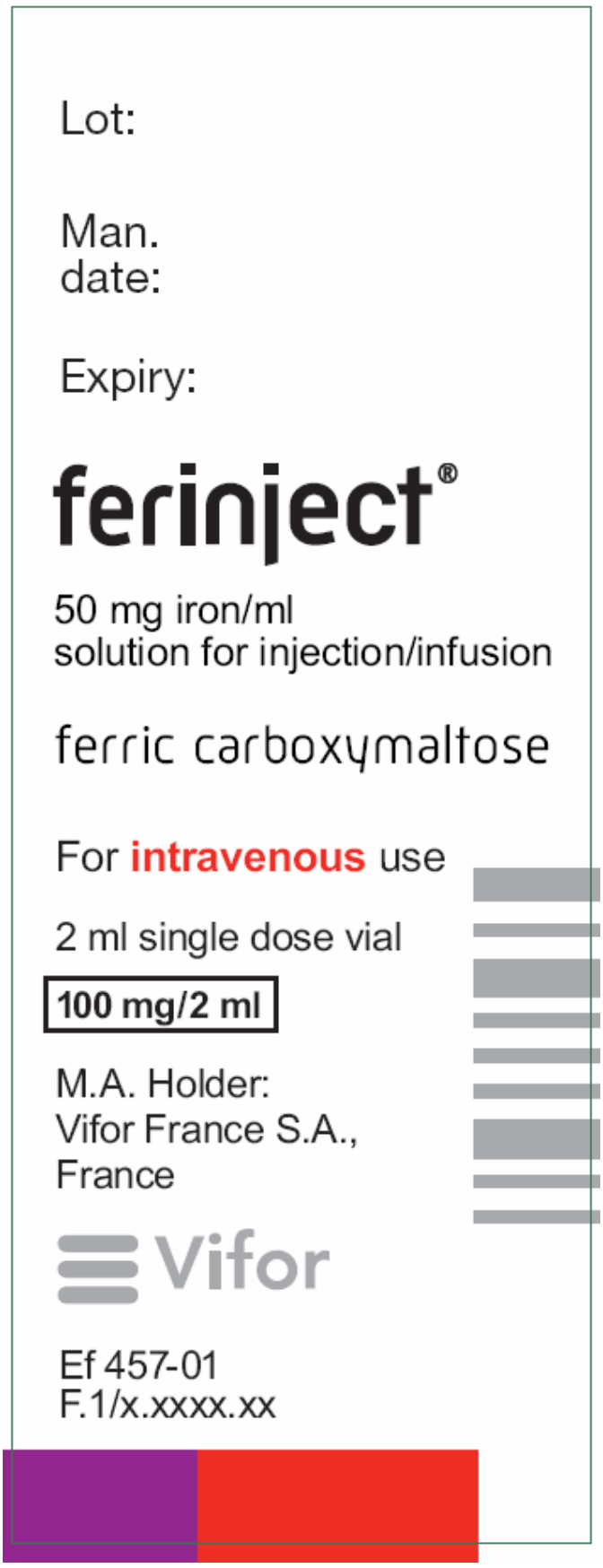
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

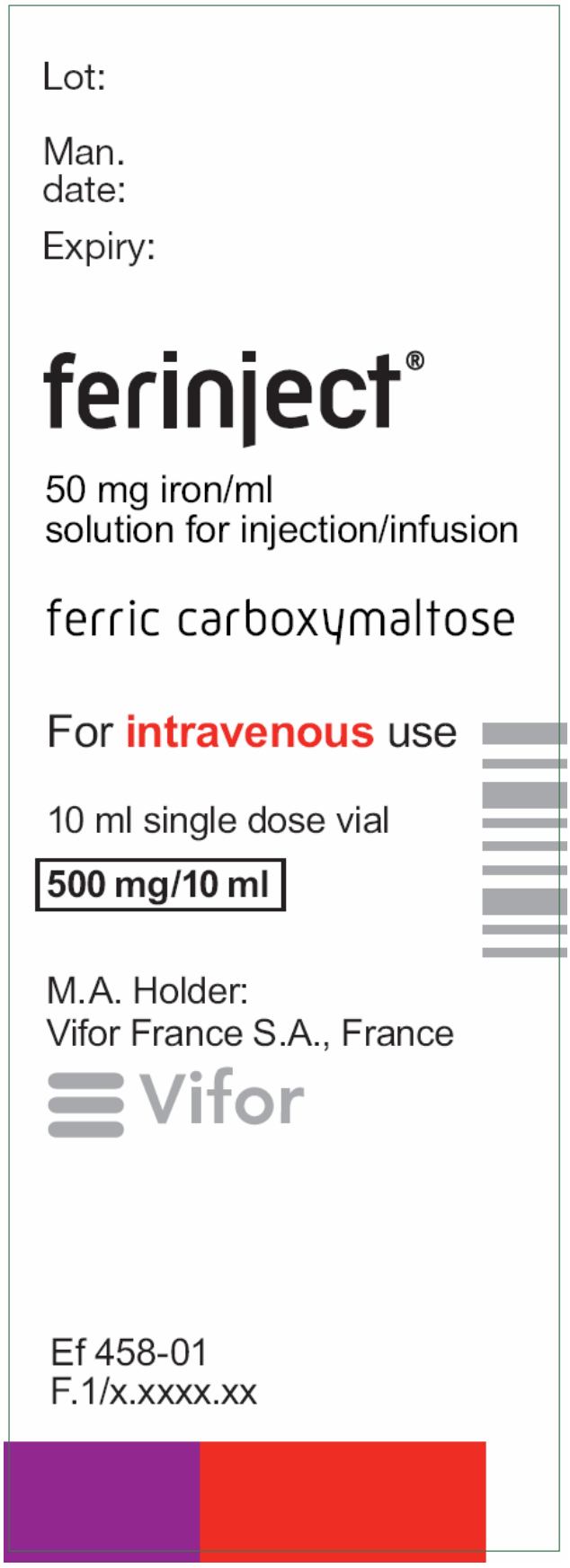
United Kingdom
Vifor France SA
123, rue Jules Guesde
92300 Levallois-Perret
France
Tel.: 33(0)1 41 06 58 90
contact@vifor-france.fr

Ireland
Vifor France SA
123, rue Jules Guesde
92300 Levallois-Perret
France
Tel.: 33(0)1 41 06 58 90
contact@vifor-france.fr

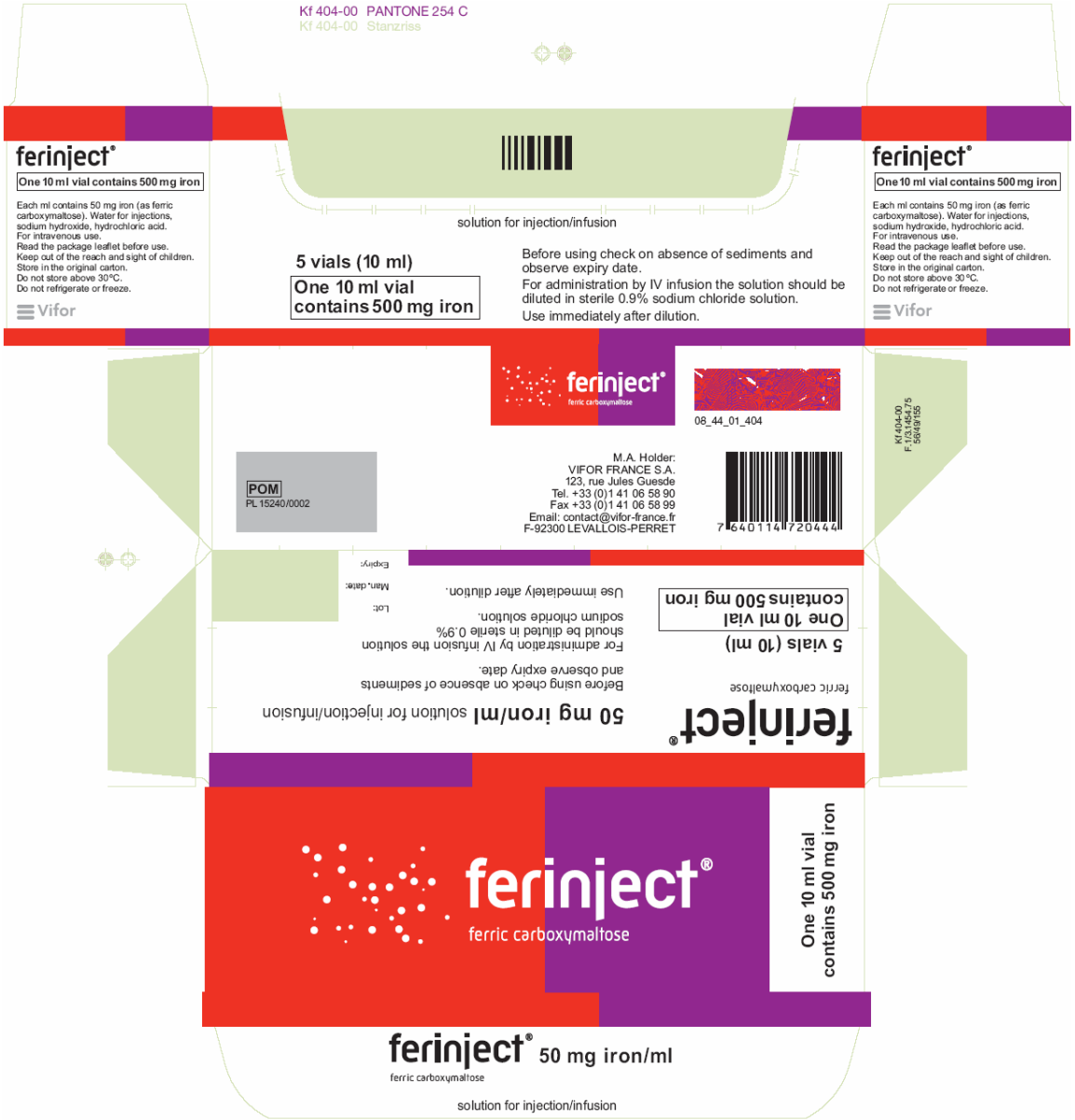
F.1/x.xxxx.xx Pf 323-00

Module 4
Labelling






Kf 403-00 Schwarz
Kf 403-00 PANTONE 485 C
Kf 403-00 PANTONE 254 C
Kf 403-00 Stanzriss
ferinject®
One 2 ml vial contains 100 mg iron
Each ml contains 50 mg iron (as ferric carboxymaltose). Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original carton.
Do not store above 30 °C.
Do not refrigerate or freeze.
Vifor
solution for injection/infusion
5 vials (2 ml)
One 2 ml vial contains 100 mg iron
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
ferinject®
ferric carboxymaltose
08_44_01_403
POM
PL 15240/0002
M.A. Holder:
VIFOR FRANCE S.A.
123, rue Jules Guesde
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
Email: contact@vifor-france.fr
F-92300 LEVALLOIS-PERRET
7 640114 720444
Kf 403-00
F1/3.1454.66
44/40/114
50 mg iron/ml solution for injection/infusion
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
Lot:
Man. date:
Expiry:
One 2 ml vial contains 100 mg iron
5 vials (2 ml)
ferric carboxymaltose
ferinject®
ferinject®
ferric carboxymaltose
One 2 ml vial contains 100 mg iron
ferinject® 50 mg iron/ml
ferric carboxymaltose
solution for injection/infusion


Kf 404-00 PANTONE 254 C
Kf 404-00 Stanzriss
ferinject®
One 10 ml vial contains 500 mg iron
Each ml contains 50 mg iron (as ferric carboxymaltose). Water for injections, sodium hydroxide, hydrochloric acid.
For intravenous use.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Store in the original carton.
Do not store above 30°C.
Do not refrigerate or freeze.
Vifor
solution for injection/infusion
5 vials (10 ml)
One 10 ml vial contains 500 mg iron
Before using check on absence of sediments and observe expiry date.
For administration by IV infusion the solution should be diluted in sterile 0.9% sodium chloride solution.
Use immediately after dilution.
ferinject®
ferric carboxymaltose
08_44_01_404
POM
PL 15240/0002
M.A. Holder:
VIFOR FRANCE S.A.
123, rue Jules Guesde
Tel. +33 (0)1 41 06 58 90
Fax +33 (0)1 41 06 58 99
Email: contact@vifor-france.fr
F-92300 LEVALLOIS-PERRET
7 640114 720444
Kf 404-00
F 103 1464 75
5949/155
Lot:
Man. date:
Expiry:
50 mg iron/ml solution for injection/infusion
ferinject®
ferric carboxymaltose
One 10 ml vial contains 500 mg iron
ferinject® 50 mg iron/ml
ferric carboxymaltose
solution for injection/infusion

Module 5
Scientific discussion during initial procedure

1. INTRODUCTION

Background

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

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

Marketing Authorisations were approved in Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Slovak Republic, Spain and Sweden.

Overall Benefit/Risk Assessment

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

Clinical studies on Ferinject 50mg Iron/ml Solution for Injection/Infusion were carried out in accordance with Good Clinical Practice (GCP). The clinical programme showed that Ferinject 50mg Iron/ml Solution for Injection/Infusion provides satisfactory clinical benefits.

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

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

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

2. QUALITY ASPECTS

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

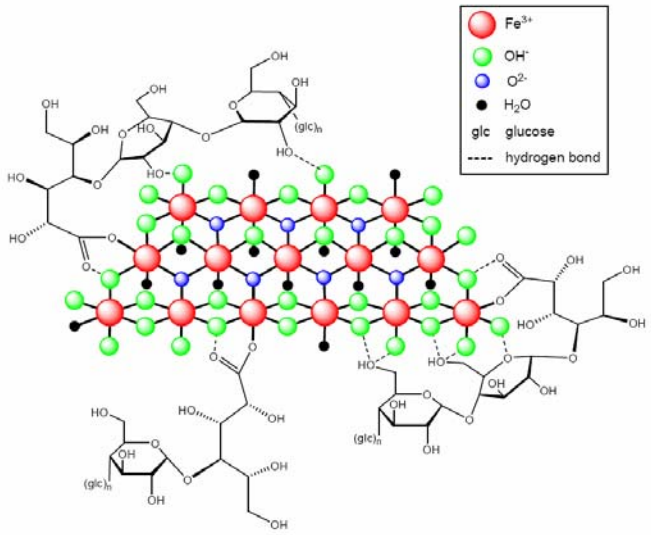
INN: Ferric carboxymaltose

Other names: Iron Carboxymaltose, Eisencarboxymaltose, Iron Polymaltose, VIT-45

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

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

Structure:



Appearance: Brown amorphous powder

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

3.2.S.2 Manufacture

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

3.2.S.3 Characterisation

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

3.2.S.4 Control of Drug Substance

A suitable drug substance specification has been provided. Details of all analytical methods used have been provided and these have been appropriately validated. Batch

analysis data have been provided showing compliance with the active substance specification.

3.2.S.5 Reference Standards or Materials

Suitable certificates of analysis are provided for all reference standards used.

3.2.S.6 Container Closure System

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

3.2.S.7 Stability

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

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

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

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

3.2.P.2 Pharmaceutical Development

Suitable pharmaceutical development data have been provided.

3.2.P.3 Manufacture

A description and flow-chart of the manufacturing method has been provided.

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

3.2.P.4 Control of Excipients

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

3.2.P.5 Control of Drug Product

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification.

3.2.P.6 Reference Standards or Materials

Certificate of analysis have been provided for all working standards used.

3.2.P.7 Container Closure System

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

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

3.2.P.8 Stability

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

SPC, LABELS AND PACKAGE LEAFLET

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

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

PHARMACEUTICAL CONCLUSIONS

The grant of a product licence is recommended.

3. NON-CLINICAL ASPECTS

PHARMACOLOGY

Primary pharmacodynamics

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

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

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

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

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

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

*calculated from estimated tissue weights

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

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

NA = not available

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

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

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

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

The intravenous dosing data from Study B suggest a possible sex difference in the use of iron with 91% (males) and 67% (females) of administered iron reaching the blood cells, with the balance being in the liver and spleen in both sexes. The applicant suggests that female rats may have a higher storage capacity for iron, coupled with an increased retention period for iron stores in order to support the increased requirement of blood (and iron) during pregnancy. Of relevance to this is the finding that, prior to dosing, male rats reached the target haemoglobin concentration range for anaemic status (60-100g/l blood) after approximately 3 weeks on an iron deficient diet while haemoglobin concentrations declined more slowly in females and the target concentration range was eventually amended to <130g/l. It is possible, therefore, that the less severe anaemic status of the females and/or their greater age (resulting from several additional weeks on an iron deficient diet prior to dosing in order to establish anaemic status) may be responsible for the sex differences noted in the use of iron following VIT-45 administration.

Secondary pharmacodynamics

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

Safety pharmacology

GLP compliant *in vivo* safety pharmacology studies have been performed to examine the potential for VIT-45 associated cardiovascular (in dogs), CNS, respiratory and renal (all in

rats) effects. In all studies VIT-45 was administered as a single intravenous dose at 30 and 90mg Fe/kg. Control animals were dosed with 0.9% NaCl.

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

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

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

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

Pharmacodynamic drug interactions

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

Assessor's overall conclusions on pharmacology

The desired pharmacodynamic effect of proposed product is delivery of utilisable iron to the iron storage and transport proteins in the body (ferritin and transferrin) for the correction of iron deficiency (i.e. incorporation into red blood cells and haemoglobin). Primary pharmacodynamic investigations in rats fed iron deficient diets have demonstrated that following intravenous administration of ^{59}Fe VIT-45, iron levels in serum decrease steadily with the bulk of the ^{59}Fe being distributed to red blood cells, liver and spleen. After an initial peak, radioactivity levels in liver and spleen decrease as levels in red blood cells steadily increase over a 4-week period. By 28 days after administration, approximately 91 and 67% of administered radioactivity was found in whole blood in male and female rats, respectively.

Examination of total iron concentrations in liver and spleen demonstrated that, compared to iron concentrations in non-anaemic controls, single iv administration of VIT-45 (5mg Fe)

resulted in a correction of the dietary induced iron depletion in liver and spleen of both males and females.

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

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

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

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

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

PHARMACOKINETICS

Absorption

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

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

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

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

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

Distribution

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

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

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

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

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

Placental transfer of ^{59}Fe was assessed in rats following intravenous administration of ^{59}Fe-VIT-45 (at a dose equivalent to 5mg Fe/rat) on day 12 of gestation. Seven days after drug administration 3.1% of the dose was present in placenta and 9.2% in fetuses. Placental transfer was also assessed using an in vitro human placental perfusion model (Malek, 2005).

In this study the concentration of ^{59}Fe-VIT-45 in the maternal circuit was seen to decrease by 10% but no transferred radioactivity was detected in the fetal circuit.

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

Metabolism

In vitro studies have been performed to examine the carbohydrate breakdown products of VIT-45. Incubation with α-amylase for 60 minutes led to approximately 70% degradation of VIT-45, with the production of maltotriose, maltose and glucose. Incubation with rat liver S9 fraction at 37ºC produced maltotetraose as well as the products seen following incubation with amylase – VIT-45 was approximately 47% degraded after 15 hours incubation.

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

Excretion

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

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

Pharmacokinetic drug interactions

No pharmacokinetic drug interactions are expected.

Assessor's overall conclusions on pharmacokinetics

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

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

Following intravenous administration of ^{59}Fe-VIT-45 to pregnant rats, radioactivity was detected in fetuses – 7 days after drug administration 9.2% and 3.1% of the administered dose

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

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

TOXICOLOGY

Single-dose toxicity

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

Table 6. Summary of acute toxicity studies

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

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

Repeat-dose toxicity

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

Table 7. Outline of repeat dose studies

Study details	Reported NOAEL (mg Fe/kg/week)	Relative amount of iron in liver at NOAEL
13 week study in rats. Animals dosed once weekly with 1 hour iv infusions of 9, 30 or 90mg Fe/kg	9	-
13 week study in rats. Animals administered iv bolus doses of 1, 3, 10 or 30mg Fe/kg 3 times per week (ie weekly doses of 3, 9, 30 or 90mg Fe/kg)	9	4.5 times control value
26 week study in rats with 6 week recovery period Animals administered iv bolus doses of 1, 3 or 10mg Fe/kg 3 times per week (ie weekly doses of 3, 9 or 30mg Fe/kg)	3	≥ 2.2 times control value
13 week study in dogs Animals administered once weekly 1 hour iv infusions at doses of 9, 30 and 90mg/kg/week	9	-
26 week study in dogs with a 6 week recover period Animals administered iv bolus doses of 1, 3 or 10mg Fe/kg 3 times per week (ie 3, 9 or 30mg Fe/kg/week). All studies included control animals dosed with 0.9% NaCl	9	≥ 12.4 times control value

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

- Dose-related increases in serum iron and decreases in total iron binding capacity (TIBC)
- Reduced weight gain and food intake
- Elevated transaminase (ALT and AST) and alkaline phosphatase levels, particularly in the 90mg Fe/kg/week groups
- Elevated beta globulin levels and blood urea nitrogen at 90mg Fe/kg/week
- Increased liver and spleen weights across the groups, most pronounced at high doses
- Modest increases in kidney and lung weights, particularly at the highest doses
- Histology revealed widespread iron deposition in a number of tissues, particularly liver, spleen, kidneys and lymph nodes. In the majority of tissues the iron was present within macrophages and sometimes vascular endothelium with no histopathological changes in other cells. A dose relationship was seen in incidence and degree of these findings. In liver, kidneys, adrenals and spleen iron was also present in parenchymal cells (in a dose related manner)
- In dogs, toxic changes in the liver were seen (perivascular fibrosis and one animal with hepatocyte necrosis at 90mg Fe/kg/week) in the 13 week study
- At 90mg Fe/kg/week levels of iron in the liver were up to 60 times those seen in controls
- Dose-related reductions in red cell parameters
- Increased severity of extramedullary haemotopoiesis in liver in 30mg Fe/kg/week group (in dog studies). This was considered an adaptive response to reduced red blood cell parameters
- Increased plasma cholesterol in 90mg and sometimes 30mg Fe/kg group
- Increased urine volume and decreased specific gravity, particularly in 90mg Fe/kg group
- High platelet and white cell counts and reduced APTT
- Clinical signs of toxicity were rare although in the 13 week dog study yellow discolouration of eyes and gums was noted in the 90mg Fe/kg/week group, as well as dose related increase in incidence of liquid faeces

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

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

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

Genotoxicity

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

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

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

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

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

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

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

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

Other toxicity studies

Antigenicity

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

Studies on impurities

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

Ecotoxicity/environmental risk assessment

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

Assessor's overall conclusions on toxicology

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

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

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

In all but one of the repeat intravenous dose studies, the NOAEL was considered to be 9mg Fe/kg/week, and in the remaining study (26-week rat study) the NOAEL was considered to be 3mg Fe/kg/week. These values are below the maximum recommended human dose of 15mg Fe/kg/week. However, the applicant points out that iron replete animals were used in the toxicity studies and these animals would be expected to readily show signs of iron overload. Consequently the toxicity studies do not provide a parallel to the clinical situation, in which patients will be iron deficient and the dose of VIT-45 will be calculated for each patient based

on their haemoglobin and total body iron store deficit. This should minimise the risk of iron overload occurring. It may be concluded, therefore, that the safety margins derived from the animal toxicity studies are not relevant to the patient population.

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

While the non-clinical overview reports that the proposed product may be used chronically/intermittently (in combination with erythropoietin) in patients with chronic renal disease, the applicant has not performed a chronic non-rodent study or carcinogenicity studies. The applicant argues that this is justified as the product is a replacement therapy and these may be exempt from these requirements. Additionally, the breakdown products are simple glucose oligomers, the product did not show signs of genotoxic potential, and preneoplastic signs were not seen in the repeat-dose studies. It is noteworthy that there have been a number of reports of animal studies in which iron dextran-induced sarcoma following repeat high intramuscular or subcutaneous doses, and two cases of sarcoma after intramuscular injection of iron dextran were reported in humans. The applicant argues that in the animal studies the large doses would have behaved as slowly dissociating depots of iron and this would have allowed considerable local tissue damage, leading to sarcoma formation.

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

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

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

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

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

4. CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacology study programme

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

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

Summary of clinical pharmacology studies

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

Physicochemical and pharmacodynamic properties of VIT-45

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

Mechanism of action

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

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

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

Clinically, the main pharmacodynamic effects of VIT-45 will result in transient elevations of serum iron levels, transferring saturation (TfS) and serum ferritin. The increase in serum ferritin levels illustrates the replenishment of the depleted iron stores, which is a

well-identified and desired effect of iron therapy. In addition, transiently elevated TfS indicate that iron-binding capacity is almost fully utilised following parenteral iron administration.

Pharmacokinetic properties of VIT-45

Ferrokinetics

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

Distribution

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

Metabolism

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

Elimination

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

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

Drug interactions

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

Pharmacokinetics

Study VIT-IV-CL-001

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

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

During the study, the patients received a single i.v. injection of 100 mg iron as $^{52}Fe/^{59}Fe$-labelled VIT-45 corresponding to a radiodose of 20MBq. For pharmacokinetic determination of isotope uptake and distribution characteristics, PET scans were performed from zero to 8 hours post-administration in liver, spleen, bone marrow and heart ventricle (for blood activity). For determination of pharmacodynamic properties, incorporation of radio- labelled iron into RBCs was determined in blood samples during a follow-on period of 24 days. Together with the determination of further parameters on iron status such as Hb, serum iron, total iron-binding capacity (TIBC) and serum ferritin, the results of this study also provided first data for the efficacy of VIT-45 in humans. In addition, a preliminary safety evaluation was performed. Descriptive statistical analysis was performed, including median, mean, and standard deviation for pre- and post-treatment values as well as changes from pre- to post-treatment.

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

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

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

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

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

The pharmacokinetic endpoints were:

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

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

In addition, safety parameters were assessed.

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

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

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

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

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

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

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

In the first dose group, patients received a dose of 100mg iron as VIT-45 undiluted within 1 minute as bolus injection. At the three higher dose levels, the injection bolus was diluted to

achieve a volume of 250 mL infusion solution using physiological saline. The administered dose was infused at a variable i.v. dose rate, but at constant infusion time and infusion volume, in a superficial vein via an infusion pump. Infusion was stopped at 15 minutes post dose.

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

Inductively coupled plasma (ICP) Optical Emission Spectrometry applying validated methods was used for the determination of total iron in serum and urine samples. Serum ferritin was assessed by a validated enzyme-immunoassay on an Abbott Axsym instrument using Abbott assay kits. Transferrin was assayed by a validated immuno-turbimetric assay method on a Roche Hitachi Modular instrument using Roche Hitachi assay kits. UIBC in serum was determined according to a validated analytical method. TfS in serum was calculated from serum iron and transferrin concentrations before dose administration and from UIBC and transferrin concentrations after administration.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pharmacokinetic parameters of total serum iron are summarised below.

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

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

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

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

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

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

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

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

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

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

ANOVA for the assessment of dose linearity of VIT-45

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

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

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

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

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

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

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

C_{max} and AUC of iron serum exposure increased with ascending doses in a non-proportional manner, in particular regarding AUC. Based on non-compartmental analysis, MRT was less than 24 hours on average and study drug was cleared from serum with a $t_{1/2}$ of 10-18 hours.

Total body clearance was between 2.6 to 3.4 mL/min. The volumes of distribution at steady state and during elimination were similar (2.4-5.2 L).

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

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

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

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

The main endpoints of the study were:

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

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

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

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

completed the study. In Cohort 2, a total of 26 patients were enrolled and 19 patients completed the study.

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

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

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

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

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

Haemoglobin levels at baseline and over time

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

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

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

Serum ferritin levels at baseline and over time

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

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

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

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

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

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

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

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

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

Serum ferritin and TfS values showed that iron stores were successfully filled up during study participation. Mean serum ferritin levels of the treated patients were above normal range

during the study participation and in the target range (100-500 µg/L) at all time points, except the 4-week follow-up visit.

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

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

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

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

CLINICAL EFFICACY

Overview of Efficacy

Introduction

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

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

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

[a] 'Evaluable population' in study 1VIT03001

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

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

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

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

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

Study Design
Selection of patients:
Patients could be included for participitation in the studies if the degree of iron deficiency required replacement treatment with parenteral iron.

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

Inclusion criteria for haemoglobin, transferrin saturation and serum ferritin

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

Iron deficit at baseline

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

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

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

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

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

Mean treatment period

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

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

Choice of endpoints:
In all clinical studies the change of the haemoglobin level was evaluated as the primary efficacy endpoint. In Study 53214, treatment responders were defined by an increase of haemoglobin >10g/L from baseline at any point during the study. In Study VIT-IV-CL-015, the percentage of patients reaching an increase in haemoglobin of ≥10 g/L at 4 weeks was defined as the primary efficacy endpoint. In Study VIT-IV-CL-008 and Study VIT-IV-CL-009, the change from baseline levels of haemoglobin to Week 12 was defined as the primary efficacy endpoint, whereas in Study 1VIT03001 the primary endpoint was ‘success’ defined as number of subjects with an increase in haemoglobin levels of ≥20 g/L anytime between baseline and Week 6 (end of study).

Secondary efficacy endpoints were the serum values of the proteins of iron storage and transport. Levels of serum ferritin and TfS were determined at the scheduled study visits and change from baseline was calculated. Moreover, the haemoglobin values during the course of the study were defined as an additional secondary endpoint.

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

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

Endpoints in clinical studies

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

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

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

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

The null hypothesis and the alternative hypothesis assessed were:

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

Where μv and $\mu 0$ denoting the mean change in haemoglobin from baseline after administration of VIT-45 and oral ferrous sulphate, respectively. The analysis was performed by calculating the two-sided 95% confidence interval (CI) for the difference "VIT-45 minus oral ferrous sulphate" in haemoglobin change, and non-inferiority of VIT-45 compared to oral ferrous sulphate was concluded if the lower limit of the CI was equal to or greater than -5 g/L.

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

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

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

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

According to the Note for Guidance on "The choice of control groups in clinical trials" (CPMP/ICH/364/96) in a trial that is intended to demonstrate efficacy by showing a test treatment to be non-inferior to an active control, an efficacy endpoint with evidence of sensitivity to drug effects should be chosen. An acceptable non-inferiority margin should be defined taking into account historical data and relevant clinical and statistical considerations. Furthermore, in a non-inferiority trial the active control treatment needs to be of established

efficacy at the dose used under the conditions of the study. In general, this means it should be a drug acceptable in the region to which the studies will be submitted for the same indication at the dose being studied. All these criteria described in the guideline have been considered in the design of Studies VIT-IV-CL-008, -009, and 1VIT03001.

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

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

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

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

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

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

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

Secondary efficacy endpoints:
In studies VIT-IV-CL-015, -008, and -009, maximum increase and change from baseline were determined for haemoglobin, serum ferritin and TfS. In Study 53214, these parameters were also evaluated, but maximum increase was not evaluated. Moreover, in Studies VIT-IV-CL-

015, -008, and -009, treatment responders with regard to the achievement of target values of haemoglobin, serum ferritin and TfS were defined.

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

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

Haemoglobin: Mean change from baseline (ITT set)

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

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

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

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

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

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

The efficacy of treatment with VIT-45 with regard to an increase in haemoglobin values is reflected by the secondary response rates. In study VIT-IV-CL-015 the proportion of patients who achieved haemoglobin target levels (≥110 g/L in patients with a baseline haemoglobin ≤100 g/L or ≥120 g/L in patients with a baseline haemoglobin >100 g/L to ≤115 g/L) 4 weeks after the final dose of study medication was 30.9% in patients treated with VIT-45 and 23.3% in patients treated with Venofer®.

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

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

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

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

Serum ferritin: Mean change from baseline (ITT set)

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

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

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

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

The definition with regard to the response rate for serum ferritin was different in the individual studies. In Study VIT-IV-CL-015 in dialysis patients, target ranges (200-800 µg/L)

higher than the normal range were defined in order to allow for optimal haematopoiesis with the given EPO levels. In Study VIT-IV-CL-008 in IBD patients, the target ranges were set at 100-800 µg/L, whereas in study VIT-IV-CL-009 in patients with post-partum anaemia the target ranges were 50-800 µg/L. In Study 1VIT03001, no definition with regard to the response rate for serum ferritin was determined.

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

Serum ferritin treatment responders (ITT set)

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

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

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

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

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

Transferrin saturation: Mean change from baseline (ITT set)

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

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

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

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

Transferrin saturation treatment responders (ITT set)

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

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

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

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

Haemoglobin levels increased significantly to expected and clinically acceptable levels.

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

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

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

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

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

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

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

CLINICAL SAFETY

Overview of Safety

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

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

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

Relevant Animal Toxicology

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

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

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

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

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

Patient Populations and Extent of Exposure

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

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

to VIT-45. Safety data are available from single-dose studies (VIT-IV-CL-001: three patients with IDA and three patients with renal anaemia; and VIT-IV-CL-02: 24 patients with mild IDA), and one multiple-dose study (VIT-IV-CL-03; 46 patients with IDA secondary to a gastrointestinal disorder).

Patients exposed in clinical pharmacology studies (Safety set)

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

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

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

Patients exposed in efficacy and safety studies (Safety set)

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

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

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

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

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

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

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

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

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

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

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

Age of patients treated with comparator (Safety set)

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

Common Adverse Events

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

Number (percentage) of patients with at least one TEAE

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

FS: Ferrous sulphate

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

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

There were no TEAEs of severe intensity.

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

There were no TEAEs of severe intensity.

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

There were no TEAEs of severe intensity.

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

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

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

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

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

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

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

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

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

Study 1VIT03001 [5.3.5.1.4]
The most commonly (≥5%) experienced TEAEs by highest level term were: headaches (39 patients [22.4%] in the VIT-45 group and 32 patients [18.0%] in the ferrous sulphate group), infections with unspecified pathogen class (19 patients [10.9%] in the VIT-45 group and 20 patients [11.2%] in the ferrous sulphate group), gastrointestinal signs and symptoms (15 patients [8.6%] in the VIT-45 group and 27 patients [15.2%] in the ferrous sulphate group), gastrointestinal motility and defaecation conditions (10 patients [5.7%] in the VIT-45 group and 32 patients [18.0%] in the ferrous sulphate group), epidermal and dermal conditions (13 patients [7.5%] in the VIT-45 group and four patients [2.2%] in the ferrous

sulphate group), neurological disorders (not elsewhere classified, 10 patients [5.7%] in the VIT-45 group and seven patients [3.9%] in the ferrous sulphate group).

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

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

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

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

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

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

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

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

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

Relationship to Study Medication

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

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

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

FS Ferrous sulphate

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Serious Adverse Events, Withdrawals, and Deaths

Serious Adverse Events

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

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

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

FS Ferrous sulphate

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

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

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

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

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

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

In the subanalysis, four breast-fed infants (1.7%) in the VIT-45 group and one (0.9%) in the ferrous sulphate group experienced eight serious TEAEs (six VIT-45 and two ferrous

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

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

Serious adverse events by body system

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

In summary, serious adverse events were reported for many different body systems and no accumulation in one or more body systems became obvious. As none of the serious adverse events was considered to be related to study medication, it can be assumed that treatment with VIT-45 is not causally related with the occurrence of serious adverse events.

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

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

Study discontinuation due to TEAS

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

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

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

Listing of deaths

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

FS Ferrous sulphate

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

Study VIT-IV-CL-015 [5.3.5.1.1]:
One patient (0.8%) in the VIT-45 group died. This patient had acute anterior myocardial infarction, which was serious, severe in intensity and unlikely to be related to study

medication. The patient died more than a week after study medication was withdrawn due to another, non-serious TEAE.

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

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

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

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

Similarities and Differences in Results Among Studies
In Studies VIT-IV-CL-008 and 1VIT03001, a higher rate of pruritus, rash and urticaria was reported in patients treated with VIT-45 if compared to patients treated with oral ferrous sulphate.
A comparison between the number and percentage of patients experiencing these adverse events during the clinical development of VIT-45 is presented below. In the single-dose pharmacology studies, VIT-IV-CL-001, –02, and VIRD-VIT-45-IM, no such adverse events were reported, thus these studies were not included in the table.

Comparison of adverse events

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

[1] including "pruritus generalised"

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

As can be seen, individual reports of pruritus, rash and urticaria were received in every study. These events occurred in patients treated with VIT-45 and in patients treated with the comparator Venofer® or oral ferrous sulphate.
In Study VIT-IV-CL-008, three patients experienced four events of urticaria. The intensity of urticaria was assessed as mild in three cases and moderate in one case (a second event experienced by one patient, which was unrelated to study drug) by the investigator. All

three patients were re-challenged with a second dose of VIT-45 and the events did not recur. It can be concluded that the events were not due to immunological reactions after receiving study medication.

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

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

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

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

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

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

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

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

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

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

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

Specific drug interactions for VIT-45 are not known.

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

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

Haemoglobin levels were raised to expected and clinically meaningful levels.

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

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

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

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

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

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

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

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

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

5. OVERALL CONCLUSION

QUALITY

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

NON-CLINICAL

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

EFFICACY

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

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

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

RISK BENEFIT ASSESSMENT

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

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

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