# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 203565Orig1s000

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# Clinical Pharmacology

| | |
|---|---|
| **NDA** | 203-565 |
| **Submission Date:** | 30 September 2011; 21 June 2012 |
| **Brand Name:** | INJECTAFER® |
| **Generic Name:** | Ferric carboxymaltose |
| **Formulation:** | solution for injection |
| **OCP Reviewers:** | Bahru A Habtemariam, Pharm.D. |
| **OCP Acting Team Leader:** | Bahru A Habtemariam, Pharm.D. |
| **OCP Division:** | Division of Clinical Pharmacology V |
| **ORM Division:** | Division of Drug Hematology Products |
| **Sponsor:** | Luitpold |
| **Submission Type; Code:** | NDA, Original |
| **Dosing regimen:** | 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron 750 mg |
| **Indications** | Iron Deficiency Anemia (IDA) |

NDA 203-565 for Injectafer (Ferric carboxymaltose (FCM)) is a new application for a previous NDA (#22-054) that received a complete response on July 9, 2007 due to safety issues. NDA 22-054 was submitted on June 15, 2006 but was not approved because 10 deaths were reported among subjects exposed to FCM while no deaths were reported among subjects exposed to comparator iron replacement products.

The clinical pharmacology aspects of FCM were reviewed previously and are available in DARRTS (C John, 5/30/2007). The clinical pharmacology aspects of the NDA were found to be acceptable during the original NDA 22-054 submission and no specific clinical pharmacology studies were requested.

In the current NDA submission, the sponsor conducted two phase three clinical studies to address the safety issues outlined in the complete response letter for NDA 22-054. No PK data were submitted with the new NDA (NDA 203-565) submission. However, it was brought to the attention of our division that previously submitted (06/15/2006) breast milk PK data collected among nursing mothers who took part in study VIT-IV-CL-009 were not reviewed. On the other hand, the findings of the breast milk PK study were described in section 8.3 of the proposed labeling. Electronic copy of study VIT-IV-CL-009 report was submitted on 6/21/2012 for review by the agency.

This review summarizes results of the breast milk PK sub-study that was conducted as part of study VIT-IV-CL-009. Study VIT-IV-CL-009 was a multi-centre, controlled, phase 3 clinical trial that compared the safety and efficacy of intravenous infusions of FCM (n=227) and ferrous sulfate (n=117) in women with post-partum anemia (N= 344). Patients received three doses of either up to 1000 mg of FCM, given via IV infusion, or 200 mg of iron sulfate. See **Appendix 1** for details of the study design. As part of study VIT-IV-CL-009, the sponsor conducted a breast milk PK sub-study where iron levels

were measured in breast milk following treatment with either FCM or ferrous sulfate (n=25).

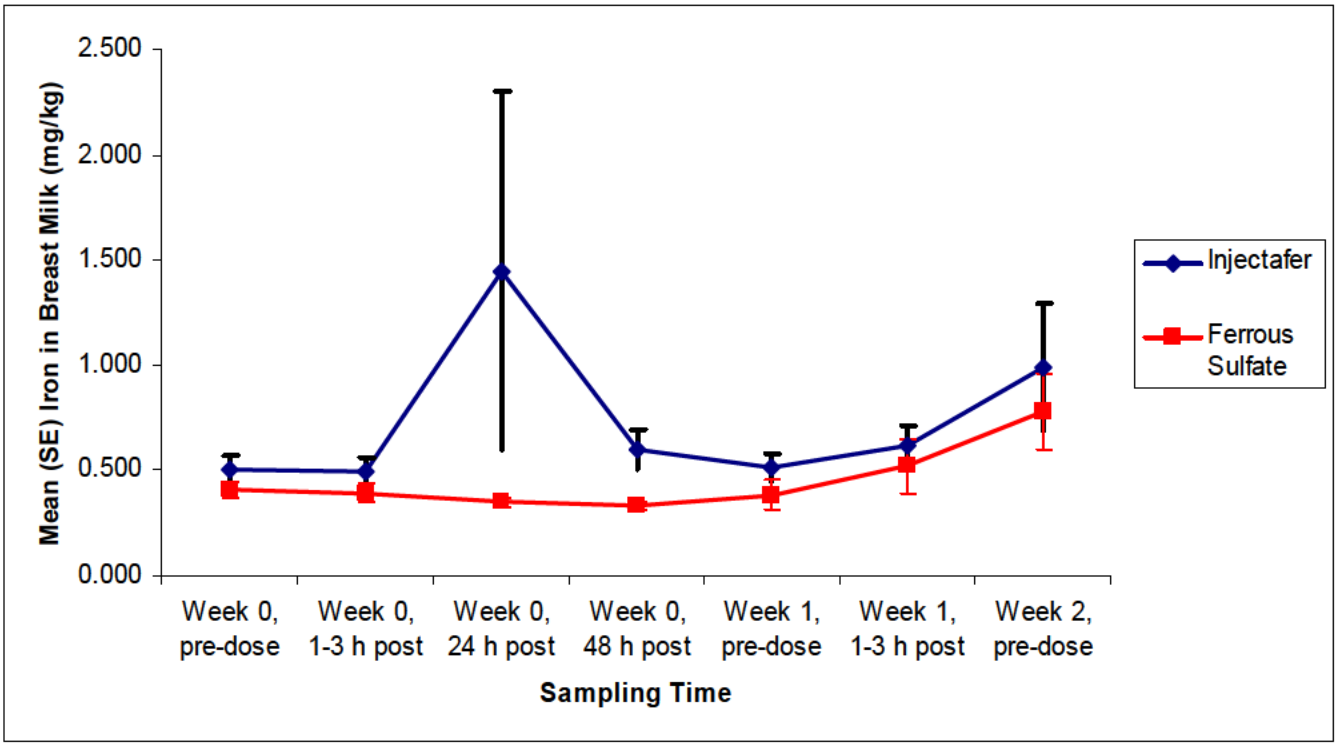
Breast milk sample collection was performed manually during a two week treatment period. Approximately 2-4 mL (minimum 2 mL) of breast milk was collected from patients in both treatment groups at each of the following time-points:

- Week 0: Pre-dose, 1 to 3 hours, 24±3 hours and 48±3 hours post-dose
- Week 1: Pre-dose and 1 to 3 hours post-dose
- Week 2: Pre-dose

At each of these time-points, patients participating in this sub-study were asked to breast-feed their children, or use a breast pump to empty their breast, prior to infusion of VIT-45 or ingestion of oral ferrous sulfate. All post-dose breast milk samples were collected at the start of a feeding period, if possible.

Results:
Breast milk iron level data were available from 25 subjects; 11 following FCM treatment and 15 following iron sulfate treatment. Mean, standard deviation, and range of iron level values were calculated for each PK sampling time described above (**Appendix 2**). Following treatment with either FCM or iron sulfate, mean iron levels post baseline were higher compared to mean baseline (week 0, predose) iron levels. It appears that breast milk iron levels were higher in women treated with FCM than those treated with iron sulfate (**Figure 1**). In the breast milk sub-study, the maximum iron level observed was 9.96 mg/kg, which was observed in a patient who received FCM.

**Figure 1**. Mean (SE) breast milk iron levels in mothers treated with either FCM (injectafer) or ferrous sulfate.



Based on the above data, the sponsor made the following conclusion:

*Assuming an infant weighs 4 kg and consumes breastmilk at about 1/6 of his b.w. [27], an infant receiving breastmilk with 1.44 mg iron per kg breastmilk (average value in the substudy) may have ingested up to 0.96 mg iron/day (0.24 mg/kg b.w./day). An infant receiving breastmilk with 9.96 mg iron per kg breastmilk (highest value measured in a single sample in the substudy) may have ingested up to 6.64 mg iron/day (1.66 mg/kg b.w./day) for 1 day due to parenteral iron treatment of the mother (assuming a specific weight of mature breastmilk of 1.031 lg/L). Recommendations for iron intake are 1 mg/kg/day for full-term infants and 2-4 mg/kg/day for low birth-weight infants, starting no later than 4 months of age in full term infants [28]. The US recommended dietary allowance (RDA) of iron in children from 0-3 years of age is 6-10 mg/day [29]. The US RDA maximum iron intake for infants from birth to age 6 months is 40 mg iron/day [30]. The highest concentration of breastmilk iron measured in the study would therefore result in iron intake well below the recommended maximum US RDA iron intake.*

The reviewer agrees with the sponsor that the highest iron level measured in the breast milk sub-study was well below 40 mg. However, we defer to clinical reviewers regarding the appropriate threshold of iron levels in breast milk.

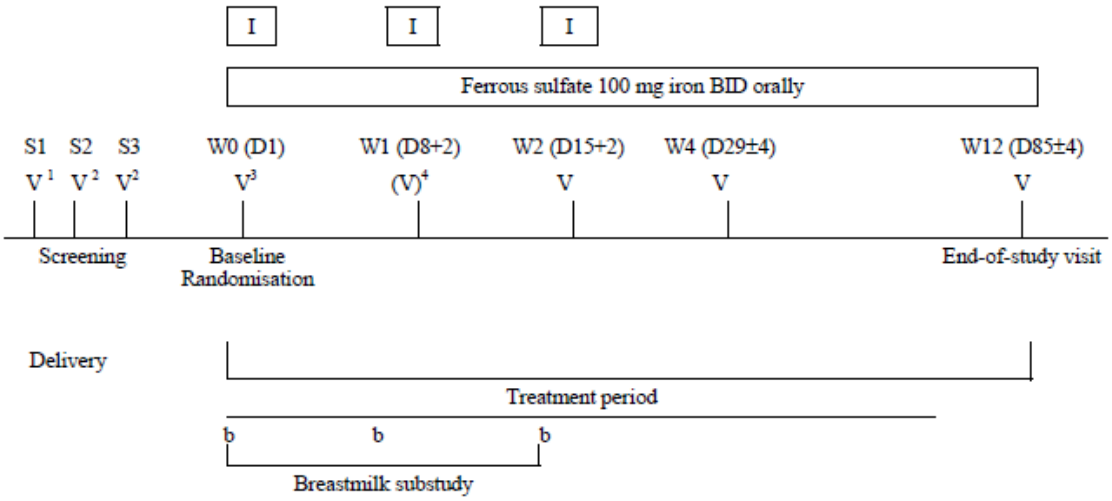
Reviewer's Note:
The breast milk PK data were not submitted by the time this review was completed. The review was completed using sponsor's PK analysis as described in the clinical study report for study VIT-IV-CL-009. The sponsor will submit breast milk PK data at a later date and an addendum will be made to this review. From reviewer's perspective, the submitted clinical study report provides sufficient information to complete the labeling for injectafer.

| | |
|---|---|
| Reviewer: Bahru A Habtemariam, Pharm.D.<br>Division of Clinical Pharmacology 5 | Acting Team Leader:<br>Bahru A Habtemariam, Pharm.D.<br>Division of Clinical Pharmacology 5 |

Cc: DDOP: CSO - **A Baird;** MTL - **K Robie Suh**; MO - **M Lu**
DCP-5: Reviewers - **B Habtemariam**, TL - **J Bullock**, DDD - **B Booth,**
DD - **A Rahman**

**Appendix 1**: Study Design

**Figure 1: Schematic of Study Design**




Abbreviations: D: day, S: screening visit, V: scheduled visit, W: week, b: breastmilk sampling (breastmilk substudy only, sampling times detailed in Section 9.5.1.6), BID: twice daily

I Up to 1000 mg iron as VIT-45 i.v. administered at a maximum rate of 16.7 mL per minute. Infused at weekly intervals until the calculated cumulative dose has been reached (maximum of three infusions).

[1] Screening 1 was within 14 days before the estimated date of delivery (maximum of 5 weeks before delivery).

[2] Screening 2 and 3 (for measurement of post-partum Hb only) were 48-72 and <96 hours post-partum, respectively.

[3] Baseline could be on the same day as Screening 3 and was a maximum of 7 days post-partum and 6 weeks after Screening 1.

[4] Only patients scheduled to receive VIT-45.

**Appendix 2**: Breast milk Iron levels in breast feeding mothers.

**Table 11-16: Measured Values of Iron in Breastmilk: PP Set (N=25)**

| mg/kg | | Values by Visit | | Change from Baseline | | p-values for change from baseline* |
|---|---|---|---|---|---|---|
| | | VIT-45 | Ferrous Sulfate | VIT-45 | Ferrous Sulfate | |
| **Baseline, pre-dose** | N | 11 | 14 | - | - | |
| | Mean (SD) | 0.500 (0.248) | 0.407 (0.151) | - | - | |
| | Range (min, max) | 0.24, 1.12 | 0.25, 0.83 | - | - | |
| **Baseline, 1-3 h post** | N | 11 | 14 | 11 | 14 | 0.5171 |
| | Mean (SD) | 0.496 (0.224) | 0.394 (0.163) | -0.004 (0.116) | -0.014 (0.046) | |
| | Range (min, max) | 0.28, 0.93 | 0.22, 0.83 | -0.20, 0.15 | -0.10, 0.09 | |
| **Baseline, 24 h post** | N | 11 | 14 | 11 | 14 | 0.2293 |
| | Mean (SD) | 1.447 (2.827) | 0.347 (0.099) | 0.947 (2.766) | -0.060 (0.103) | |
| | Range (min, max) | 0.44, 9.96 | 0.20, 0.56 | -0.35, 9.27 | -0.27, 0.12 | |
| **Baseline, 48 h post** | N | 11 | 14 | 11 | 14 | 0.0052** |
| | Mean (SD) | 0.601 (0.310) | 0.332 (0.081) | 0.101 (0.301) | -0.075 (0.177) | |
| | Range (min, max) | 0.26, 1.23 | 0.24, 0.48 | -0.59, 0.59 | -0.49, 0.18 | |
| **Week 1, pre-dose** | N | 11 | 9 | 11 | 9 | 0.2159 |
| | Mean (SD) | 0.513 (0.229) | 0.382 (0.268) | 0.013 (0.364) | -0.082 (0.311) | |
| | Range (min, max) | 0.23, 0.86 | 0.20, 1.07 | -0.74, 0.49 | -0.44, 0.63 | |
| **Week 1, 1-3 h post** | N | 11 | 10 | 11 | 10 | 0.4143 |
| | Mean (SD) | 0.615 (0.322) | 0.519 (0.470) | 0.115 (0.460) | 0.071 (0.537) | |
| | Range (min, max) | 0.25, 1.11 | 0.22, 1.62 | -0.74, 0.76 | -0.44, 1.32 | |
| **Week 2, pre-dose** | N | 11 | 11 | 11 | 11 | 0.4675 |
| | Mean (SD) | 0.991 (1.007) | 0.779 (0.663) | 0.491 (1.069) | 0.352 (0.656) | |
| | Range (min, max) | 0.29, 3.15 | 0.20, 2.06 | -0.70, 2.82 | -0.23, 1.52 | |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BAHRU A HABTEMARIAM
06/21/2012

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

NDA 203-565 for Injectafer (Ferric carboxymaltose (FCM)) is a new application for a previous NDA (#22-054) that received a complete response on July 9, 2007, due to safety issues. NDA 22-054 was submitted on June 15, 2006 but was not approved because 10 deaths were reported among subjects exposed to FCM while no deaths were reported among subjects exposed to comparator iron replacement products.

The clinical pharmacology aspects of FCM were reviewed previously and are available in DARRTS (C John, 5/30/2007). The clinical pharmacology aspects of the NDA were found to be acceptable during the original NDA 22-054 submission and no specific clinical pharmacology studies were requested.

In the current NDA submission, the sponsor conducted two phase three clinical studies to address the safety issues outlined in the complete response letter for NDA 22-054. No PK data were collected in these two studies.

| | **Information** | | **Information** |
|---|---|---|---|
| **NDA/BLA Number** | 203,565 | **Brand Name** | Injectafer |
| **OCP Division (I, II, III, IV, V)** | 5 | **Generic Name** | Ferric carboxymaltose (FCM) |
| **Medical Division** | Oncology | **Drug Class** | Hematology |
| **OCP Reviewer** | Bahru A Habtemariam, Pharm.D | **Indication(s)** | Injectafer is indicated for the treatment of iron deficiency anemia |
| **OCP Team Leader** | Julie Bullock, Pharm.D | **Dosage Form** | solution |
| **Pharmacometrics Reviewer** | NA | **Dosing Regimen** | 15 mg/kg up to a maximum single dose of 750 mg of iron on two occasions separated by at least 7 days up to a cumulative dose of 1500 mg of iron. |
| **Date of Submission** | September 30, 2011 | **Route of Administration** | Intravenous |
| **Estimated Due Date of OCP Review** | May 29, 2011 | **Sponsor** | Luitpold |
| **Medical Division Due Date** | June 29, 2011 | **Priority Classification** | Standard |
| PDUFA Due Date | August 3, 2012 | | |

***Clin. Pharm. and Biopharm. Information***

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | X | 2 | 2 | |
| **Tabular Listing of All Human Studies** | X | 2 | 2 | |
| **HPK Summary** | | | | |
| **Labeling** | X | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|---|---|---|---|
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | This is a very small study (n=7) of which 6 and 1 patients had Child Pugh classification classes B and C, respectively |
| **PD -** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | X | 127 | - | |
| **Total Number of Studies** | 2 | 2 | 2 | |
| | | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | | | X | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | | X | |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | | | X | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | | X | |
| 5 | Has a rationale for dose selection been submitted? | | | X | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | | | X | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | | | X | There are no PK data |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | x | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | X | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | X | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | | | X | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | | X | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | X | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | X | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | X | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | | X | |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | | | | |

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|---|---|---|---|---|---|
| | | | | X | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | | | X | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | | X | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**
**Yes**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Bahru A. Habtemariam, Pharm.D. December 1, 2011
Reviewing Clinical Pharmacologist Date

Julie Bullock, Pharm.D. December 1, 2011
Team Leader/Supervisor Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BAHRU A HABTEMARIAM
12/14/2011

JULIE M BULLOCK
12/19/2011

| | | | |
|---|---|---|---|
| *NDA* | 22054 | *Submission Date(s)* | June 16, 2006; February 16, 2007 |
| *Brand Name* | | Ferinject | |
| *Generic Name* | | N/A | |
| *Reviewer* | | Christy S. John, Ph.D | |
| *Team Leader* | | Young Moon Choi, Ph.D. | |
| *OCP Division* | | V | |
| *ORM Division* | | Division of Medical Imaging and Hematology Drug Products | |
| *Sponsor* | | Luitpold Pharmaceuticals, Inc | |
| *Relevant IND(s)* | | 63,243 | |
| *Submission Type; Code* | | S | 1 |
| *Formulation; Strength(s)* | | Intravenous infusion, 15 mg/kg body weight IV infusion, not exceeding 1000 mg Fe/week or 200 mg iron given as bolus injection up to 3 times a weeks | |
| *Indication* | | For the treatment of iron deficiency anemia (IDA) secondary to pregnancy/childbirth (postpartum anemia), heavy uterine bleeding (HUB), and inflammatory bowel disease (IBD) and hemodialysis. | |
| | | | |

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# 1 Executive Summary

VIT-45 (Ferinject also known as iron carboxymaltose) is a complex of polynuclear iron(III)-hydroxide with 4®-(poly-(1-4)O-α-D- glucopyranosyl)-oxy-2®,3(S),5®,6-tetrahydroxy-hexanoate, having a relative molecular weight of approximately 150,000 Dalton. Ferinject is indicated for the treatment of iron deficiency anemia (IDA) secondary to pregnancy/childbirth (postpartum anemia), heavy uterine bleeding (HUB), and inflammatory bowel disease (IBD) and hemodialysis.

Four clinical pharmacology studies were conducted. An imaging study (VIT-IV-CL-001) used Fe-52 with positron imaging tomography (PET) and Fe-59 to assess the pharmacokinetics of VIT-45. The study showed that from 0 to 8 hours post-injection most of the VIT is found in the liver, spleen, and a much higher amount in bone marrow. Fe-59 was used to show the radio-iron utilization by the red blood cells (RBC). Incorporation of radioiron in RBC increased rapidly during first 6-9 days indicated the potential use of VIT-45 as iron supplement. A dose escalation PK Study (VIT-IV-CL-02) in patients with mild iron deficiency anemia was performed to study safety and tolerability of the drug. The study included single IV doses of 100, 500, 800, and 1000 mg via a bolus IV injection or IV infusion. The increase in geometric mean Cmax for total serum iron concentration did not increase linearly with dose (particularly in 800 mg dose group). The average terminal half-life ($t_{1/2}$) of VIT-45 (injected or infused) ranged from 10.3 h to 17.7 hours.

The pharmacodynamic variables evaluated included total serum iron concentration, ferritin and transferrin concentrations, transferrin receptor concentrations, reticulocyte count and hemoglobin concentrations. No single pharmacodynamic variable was established as the primary pharmacodynamic factor. The percent increase in transferrin saturation for 500, 800, 1000 mg was 76, 63, 71%, respectively at 24-36 hrs post-dose. Iron binding capacity was fully utilized (as shown by 90% transferrin saturation) after doses of 500, 800 and 1000 mg. Mean hemoglobin concentrations 8 days post dosing for different treatment arms and placebo were not significantly different. Thus, optimal dosing was not fully explored by the sponsor based on pharmacodynamic variables or clinical endpoint (hemoglobin level). The highest dose level 1000 mg was selected for weekly injection and its use was not justified.

The drug-related treatment-emergent adverse events reported by at least 2% of VIT-45 subjects in the first-dose 1,000 mg studies were headache (3.9%) and blood phosphate decrease (3.4%) as compared to zero for oral iron. A total of 9 subjects died during VIT-45 clinical development program. According to the sponsor no death in Ferinject trials was consistent with hypophosphatemia.

### 1.1.1 Recommendations:

The NDA 22-054, Ferinject for intravenous use is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective. However, the relationship between dose and various pharmacodynamic variables indicate that Ferinject dose has not been optimized. Therefore, the following comment should be sent to the applicant:

Based upon the pharmacodynamic variables, such as, unsaturated iron binding capacity and mean changes in transferrin saturation from baseline at 24-36 hours data, it appears that a lower dose such as 500 mg and 800 mg may be equally efficacious clinically. It is noted that higher serum ferritin concentrations have been linked to increased risk of cardiovascular disease and oxidative stress (G. Aronoff. J. Am. Soc. Neph. 15, 99-106, 2004; Lim, PS. et. al. Nephrol. Dial. Transplant. 14, 2680-2687, 1999; Drueke T. et. al. Circulation 106, 2212-2217, 2002). Therefore, the applicant should conduct a pharmacokinetic-pharmacodynamic study to explore the effectiveness and safety of lower doses of Ferinject.

## 1.2 Phase IV Commitments

Not applicable

## 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

VIT-45 (Ferinject also known as iron carboxymaltose) is a complex of polynuclear iron(III)-hydroxide. Ferinject is indicated for the treatment of iron deficiency anemia (IDA) secondary to pregnancy/ childbirth (postpartum anemia), heavy uterine bleeding (HUB), and inflammatory bowel disease (IBD) and hemodialysis. Four clinical pharmacology studies were conducted (Table I) in support of this NDA.

Table I. Summary of Clinical Pharmacology Studies Performed

| Study Number | Number of Subjects | Objectives | Type of Study |
|---|---|---|---|
| VIT-IV-CL-001 | 6 | To prove the safety and efficacy of iron(III)-hydroxide dextrin complex by measuring the distribution of Fe-52 by PET imaging and the incorporation of Fe-59 in RBCs in subjects with iron-deficiency anemia or renal anemia | PET Imaging study of ferrokinetics and RBC iron utilization |
| VIT-IV-CL-02 | 32 | To obtain PK/PD and safety information on ascending single doses of VIT-45 in subjects with mild iron-deficiency anemia. | Dose-Finding, placebo-controlled, blinded |
| VIT-IV-03 | 46 | To obtain PK/PD and safety information after multiple doses of VIT-45 in subjects with moderate iron-deficiency anemia | Dose-finding, non-controlled |
| 1VIT05006 | 10 | To obtain PK and safety information after a single dose of VIT-45 in postpartum subjects with iron-deficiency anemia | Sub-study; non-controlled |

A dose escalation PK Study (VIT-IV-CL-02) in patients with mild iron deficiency anemia was performed to study safety and tolerability of the drug. The study included single IV doses of 100, 500, 800, and 1000 mg via a bolus IV injection or IV infusion. The increase in geometric mean Cmax for total serum iron concentration did not increase linearly with dose (particularly in 800 mg dose group). The average terminal half-life ($t_{1/2}$) of VIT-45 (injected or infused) ranged from 10.3 h to 17.7 hours.

The intravenously injected iron complex VIT-45 100 mg led to a maximum total serum iron of 37 µg/mL (geometric mean Cmax). A short infusion of VIT-45 at doses of 500, 800, 1000 mg led to mean maximum total serum iron concentrations of 156, 319 and 331 µg/mL, respectively. Particularly, the 800 mg dose deviated from the dose-linear increase, while the maximum levels after 1000 mg VIT-45 were approximately doubled when compared to the 500-mg dose. Similarly, average AUC was 426 µg-h/mL for 100 mg VIT-45. The increase in AUC values with incremental dose of VIT-45 was higher than expected for dose-proportional increases; the geometric means for 500, 800 and 1000 mg doses were 2443, 5218, 6311 µg-h/mL, respectively. The Tmax was about 30 minutes for the lower doses (100 and 500 mg). However, increasing VIT-45 doses led to a shift of Tmax that was about 1 h or longer at 800 to 1000 mg VIT. The average terminal half-life (t1/2) of the injected or infused iron complex solution was calculated to be in the range of 10.3 h (1000 mg) to 17.7 h (100 mg VIT-45). The geometric mean residence time (MRT) was less than a day (16.9 h to 23.6 h). The total body clearance, CL, was low and averaged at approximately 3.4 mL/min for the 100- and 500-mg doses and at approximately 2.6 mL/min for the two higher doses. The majority of administered iron complex was utilized or excreted within 24 h after a low dose of 100 mg and within 72 h after higher doses of 500-1000 mg.

The pharmacodynamic variables included the measurement of serum iron concentrations, serum ferritin and transferrin concentrations, transferrin receptor concentrations, iron binding capacity and transferrin saturation (TfS). In addition, the hemoglobin levels and reticulocyte counts were also measured. The sponsor has not established a primary pharmacodynamic variable. There is no correlation defined between pharmacokinetic profile and a primary pharmacodynamic variable. For example, iron binding capacity (TSAT >95%) was almost fully utilized after the doses of 500 mg, 800 mg and 1000 mg iron and lasted for 2 to 3 days. A dose optimization and justification of dose based on pharmacodynamic variables has not been provided by the sponsor.

Based upon the pharmacodynamic variables, such as, unsaturated iron binding capacity and mean changes in transferrin saturation from baseline at 24-36 hours data, it appears that a lower dose such as 500 mg and 800 mg may be equally efficacious clinically. Based upon applicant's data, the maximum serum ferritin concentration after administration of VIT-45 increased significantly for 500, 800 and 1000 mg dose groups to 423, 488, 652 ng/mL, respectively. Higher serum ferritin concentrations have been linked to increased risk of cardiovascular disease and oxidative stress (G. Aronoff. J. Am.

Soc. Neph. 15, 99-106, 2004; Lim, PS. Et al. Nephrol. Dial. Transplant. 14, 2680-2687, 1999; Drueke T. et. al. Circulation 106, 2212-2217, 2002). The applicant should conduct a pharmacokinetic-pharmacodynamic study to explore the effectiveness and safety of lower doses of Ferinject.

The clinical efficacy of VIT-45 was demonstrated in treatment of IDA in a variety of patient populations. In the clinical program, the effectiveness of VIT-45 was evaluated in 7 studies; a) Patients with postpartum IDA (2 Studies) b) Anemic patients undergoing regular hemodialysis (2 Studies); c) Patients with IDA secondary to GI disorders (2 Studies); d) Patients with IDA secondary to heavy uterine bleeding. Four of the seven studies provide the primary evidence of effectiveness of VIT-45 for the treatment of IDA. Responder analyses were based on an increase from baseline in hemoglobin of >2.0 g/dL, an increase from baseline in hemoglobin >3.0 g/dL, and hemoglobin level >12 g/dL on or before Week 4. These criteria represent increasing magnitude of hemoglobin response, and hemoglobin levels >12 g/dL indicate that subjects have achieved hemoglobin levels within or approaching normal range. Among subjects in the Modified Intent-to-Treat Population in the pivotal studies (1VIT03001, VIT-IV-CL-009, VIT-IV-CL-008, and 1VIT04002/1VIT04003) combined, a statistically significant greater proportion of VIT-45 subjects (485/748; 64.8%) achieved a >12 g/dL hemoglobin up to Week 4 compared to oral iron subjects (266/563; 47.2%).

The drug-related treatment-emergent adverse events reported by at least 2% of VIT-45 subjects in the calculated dose/first-dose 1,000 mg studies were headache (3.9%) and blood phosphate decrease (3.4%) as compared to zero for oral iron. A total of 9 subjects died during VIT-45 clinical development program.

# 2 Question-Based Review

## 2.1 General Attributes of the drug

VIT-45 is a complex of polynuclear iron(III)-hydroxide with 4®-(poly-(1-4)-O-αD-glucopyranosyl)-oxy-2®, 3(S),5®,6-tetrahydroxy-hexanoate, having a relative molecular weight of approximately 150,000 Da corresponding to the empirical formula: $[FeOx(OH)y(H_2O)z]n[\{C_6H_{10}O_7\}l]k$, where n=103, m = 8, l=11 and k=4 (where l is the branching degree of the ligand).

VIT-45 active pharmaceutical ingredient contains [redacted] (b) (4) The final product is an isotonic sterile solution of VIT-45 in water for injection at a concentration of [redacted] (b) (4) The product has also been called Iron-dextrinate or Iron-polycaboxymaltose.

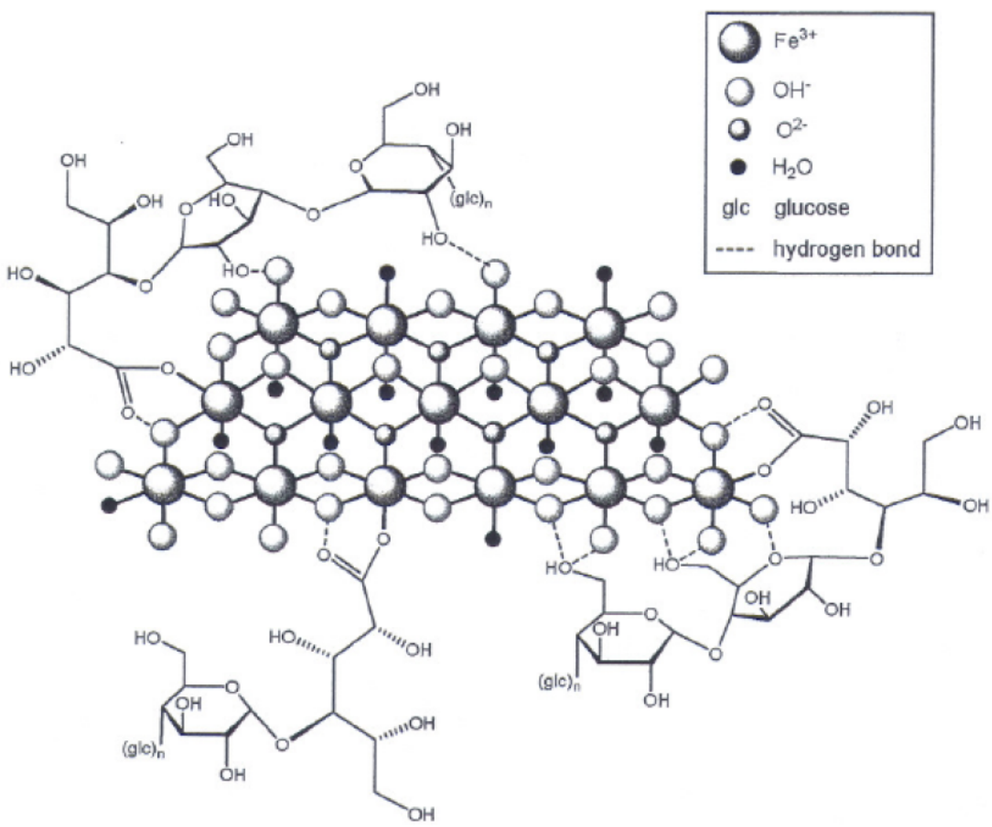



Figure 1. Chemical Structure of VIT-45 or Ferinject or Iron Carboxymaltose

### 2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

A search of DFS reviews for the IND 63,243 (associated with Ferinject development program) showed that there are no reviews done by clinical pharmacology team during the drug development. Therefore, there is no regulatory history from clinical pharmacology perspective.

### 2.1.2 What are the advantages of Ferinject over other approved iron products?

According to the sponsor VIT-45 is an optimal complex for parenteral administration, due to its degradation rate and physico-chemical characteristics providing a very efficient means of delivering iron to the body stores and transport proteins in the body (transferring and ferritin). It is much more efficient and less toxic than lower molecular weight complexes such as iron sorbitol/citrate complex, and does not have the same limitations of high pH and osmolarity that leads to dosage limitations in case of iron sucrose and iron gluconate. Other iron therapy agents like iron sucrose need an infusion over a period of up to 3.5 hours on each occasion due to limitations imposed by the pH and osmolarity of the preparation. With respect to efficiency of delivery of iron and stability of the complex, VIT-45 is comparable to iron dextran with a much reduced risk of antibody formation or hypersensitivity occurring in clinical and ambulatory use.

### 2.1.3 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

VIT-45 active pharmaceutical ingredient (API) contains (b) (4) [redacted]. The drug product is a dark brown, non transparent, aqueous solution. It is provided in (b) (4) [redacted] Each mL of drug solution contains 50 mg Fe(III).

### 2.1.4 What are the proposed mechanism(s) of action and therapeutic indication(s)?

VIT-45 is a specialized pharmaceutical product intended for iron-replacement therapy. It possesses no pharmacological activity other than its ability to deliver utilizable iron to the iron storage and transport proteins in the body (ferritin and transferrin) for the correction of iron deficiency (i.e., incorporation of iron into red blood cells and hemoglobin, respectively).

IDA (Iron deficient anemia) is defined as a hemoglobin level <115 g/L and at least one of the following: a) transferrin saturation (TfS) <20% b) serum ferritin <100 µg/L.

### 2.1.5 What are the proposed dosage(s) and route(s) of administration?

The maximum recommended human dose by intravenous route is 15 mg/kg body weight, not exceeding 1000 mg Fe/week (as an intravenous infusion) or 200 mg iron given as a bolus injection up to 3 times per week. For most patients, the total dose of iron administered during the course of VIT-45 therapy is not likely to exceed 2500 mg Fe.

## 2.2 General Clinical Pharmacology

There were four pharmacokinetics studies performed by the sponsor during the development of VIT-45. A) Study VIT-IV-CL-001 (n=6) was a PET study on ferrokinetics and RBC iron utilization. The primary objective of the study was to prove the safety and efficacy of iron(III)-hydroxide dextrin complex (iron dextrinate) by measuring the distribution of Fe-52 by PET and the incorporation of Fe-59 into the red blood cells in subjects with iron deficiency anemia or renal anemia. B) A dose finding, placebo controlled, blinded Study VIT-IV-CL-02 (n=32) was conducted to obtain pharmacokinetic (PK) and pharmacodynamic (PD) information on single doses escalation of VIT-45 in subjects with mild-iron deficiency anemia; C) A dose finding, non-controlled Study VIT-IV-CL-03 (n=46) was conducted to obtain PK/PD and safety information after multiple dose administration of VIT-45 in subjects with moderate iron-deficiency anemia. D) A non-controlled Study VIT-05006 was conducted to obtain PK and safety information after a single dose of VIT-45 in postpartum subjects with iron-deficiency anemia.

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

During the clinical pharmacology study VIT-IV-Cl-02, five escalating doses (100 mg to 1000 mg) of VIT-45 were evaluated and various pharmacodynamic variables such as serum ferritin concentration, transferrin saturation, transferring receptor concentration and hemoglobin levels. However, no attempt was made to correlate PK parameters to pharmacodynamic variables. The highest dose of 1000 mg was chosen for the clinical trials. It appeared that lower doses could be equally effective based on transferrin saturation.

A dose escalation PK study (VIT-IV-CL-02) in patient with mild iron deficiency anemia was performed to study safety and tolerability of the drug. The study included single IV doses of 100, 500, 800 and 1000 mg via a bolus IV injection of via IV infusion. The intravenously injected iron complex VIT-45 100 mg led to a maximum total serum iron of 37 µg/mL (geometric mean Cmax). A short infusion of VIT-45 at doses of 500, 800, 1000 mg led to mean maximum total serum iron concentrations of 156, 319 and 331 µg/mL, respectively. Particularly, the 800 mg dose deviated from the dose-linear increase, while the maximum level after 1000 mg VIT-45 were approximately doubled when compared to the 500-mg dose. Similarly, average AUC was 426 µg-h/mL for 100 mg VIT-45. The increase in AUC values with incremental dose of VIT-45 was higher than expected for dose-proportional increases; the geometric means were 2443, 5218, 6311 µg-h/mL. The Tmax was about 30 minutes for the lower doses (100 and 500 mg). However, increasing VIT-45 doses led to a shift of Tmax that was about 1 h or longer at 800 to 1000 mg VIT. The average terminal half-life ($t_{1/2}$) of the injected or infused iron complex solution was calculated to be in the range of 10.3 h (1000 mg) to 17.7 h (100 mg VIT-45). The geometric mean residence time (MRT) was less than a day (16.9 h to 23.6 h). The total body clearance, CL, was low and averaged at approximately 3.4 mL/min for the 100- and 500-mg doses and at approximately 2.6 mL/min for the two higher doses.

The majority of administered iron complex was utilized or excreted within 24 h after a low dose of 100 mg and within 72 h after higher doses of 500-1000 mg.

The mean transferrin receptor concentrations before dosing were 2.43±0.78 to 2.72±1.66 mg/L for the 100- to 1000- mg treatment groups, while a somewhat lower value was obtained in the placebo group: 1.91±0.49 mg/L. The variability was higher in the 500- and 800 mg groups with an approximately 4- to 6-fold range of individual data vs an approximately 2-fold range in the other groups. After administration of VIT-45, the mean transferrin receptor concentration showed minor fluctuations across all dose groups during observation period (Figure 2), with the most pronounced changes occurring in the 1000 mg dose group. On Day 4, the serum concentrations were similar in all active treatment groups, while these more decisively varied at the post-study visit on Day 8.

Unsaturated iron binding capacity (UIBC) is reciprocally linked with the post-dose transferrin saturation. As expected, no major change was observed following placebo administration. In contrast, the i.v. administration of VIT-45 led to steep decline in UIBC, particularly in 500- 800- and 1000 mg VIT-45 dose groups. However, no major notable differences were seen in different higher dose groups (500, 800, and 1000 mg) (Figure 3).

The results of these two important pharmacodynamic variables showed that lower doses could have been used by the sponsor for clinical trials.

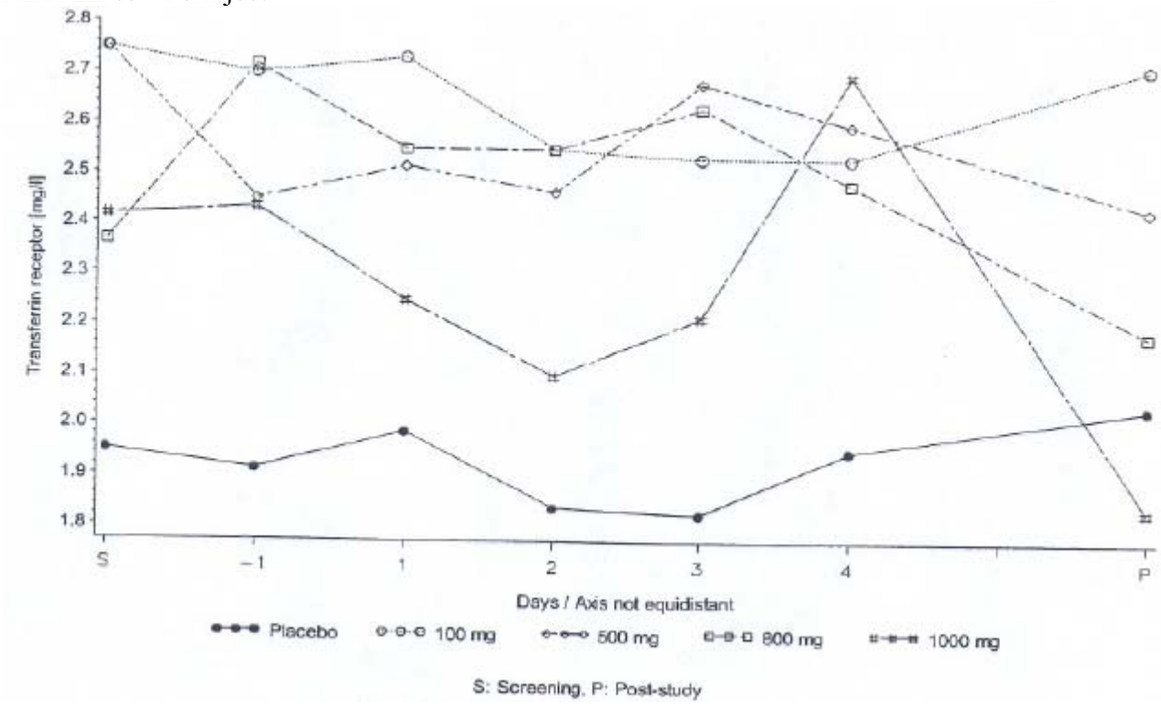



Figure 2. Mean Transferrin Receptor Concentration [mg/L] by Treatment

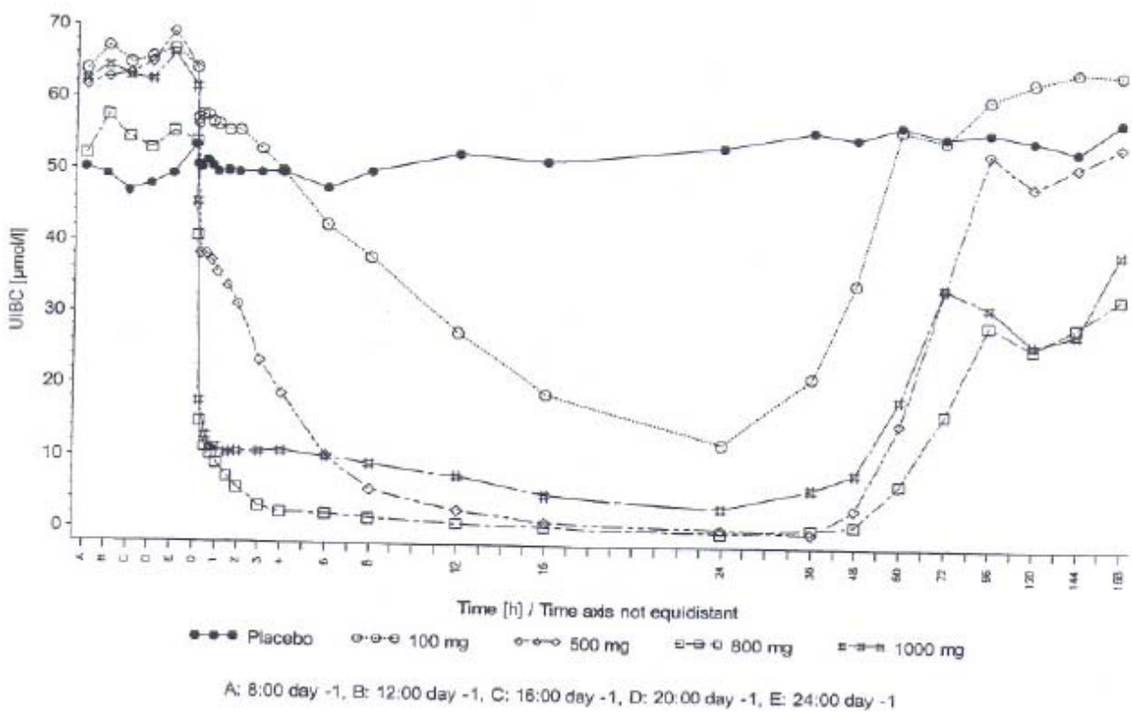



Figure 3. Mean UIBC [µmol/L] by Treatment

Furthermore, the results from Study VIT-45-CL-03 showed that using 1000 mg weekly or 500 mg once a week gave essentially overlapping serum hemoglobin levels. There was no change in serum hemoglobin levels up to Day 28 post VIT-45 administration (Figure 8; p. 33).

### 2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The basis for selecting the response endpoints or clinical endpoint was the basic iron storage and transport proteins as they will be directly affected by an injection of any iron delivery drug. Total serum iron, serum ferritin and transferrin concentrations, transferrin saturation and UIBC in serum were assessed as pharmacodynamic variables. However, the most important clinically relevant factor is hemoglobin level. An increase of 2.0 g/dL in hemoglobin level up to 4 Weeks was considered as clinical endpoint. A hemoglobin level achievement in patients >12 g/dL up to 4 Weeks was also considered a clinical endpoint.

### 2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

There are no active moieties in plasma or urine. Iron (III) polycarboxymaltose or VIT-45 decomposes in iron hydroxide and sugars glucose and polysaccharides such as glucose dimer (maltose), and as oligomers maltotriose and maltotetraose.

### 2.2.4 Exposure-Response Evaluation

It appeared from the data that there is no linear correlation between the higher doses (500, 800 or 1000 mg) and the pharmacodynamic variables such as serum ferritin. Serum ferritin concentrations for 500, 800 and 1000 mg doses were found to be 423, 488 and 652 ng/mL, respectively. Similarly, maximum mean changes in % in transferrin saturation from baseline at 24-36 h post VIT administration were 76±8%, 63±5%, 71±6% for 500, 800 and 1000 mg dose groups, respectively. These results imply that a lower dose may be clinically useful.

#### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

The pharmacodynamic variables included the measurement of serum iron concentrations, serum ferritin and transferrin concentrations, transferrin receptor concentrations, iron binding capacity and transferrin saturation (TfS). In addition the hemoglobin levels and reticulocyte counts were also measured. The sponsor has not established a primary pharmacodynamic variable. There is no correlation defined between pharmacokinetic profile and a primary pharmacodynamic variable. For example, iron binding capacity (TSAT >95%) was almost fully utilized after the doses of 500 mg, 800 mg and 1000 mg iron and lasted for 2 to 3 days (Figure 3). A dose optimization and justification of dose based on phramacodynamic variables has not been provided by the sponsor.

#### 2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Since the sponsor has not optimized dose, and not correlated exposure to pharmacodynamic parameter(s), it is difficult to say if the deaths observed or hypo-phosphatemia observed as an adverse event during the development program of VIT-45 could be attributed to iron exposure.

#### 2.2.4.3 Does this drug prolong the QT or QTc interval?

The sponsor has not conducted thorough relevant QT or QTc interval prolongation studies. However, ECG of subjects were monitored. The analysis is being done by medical team.

#### 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose selected by the sponsor for the treatment of IDA may not be an optimal. A lower dose 500 mg or 800 mg would probably have given same clinical results as judged by pharmacodynamic variables.

### 2.2.5 Pharmacokinetic Characteristics

#### 2.2.5.1 What are the PK characteristics of the drug and its major metabolite?

The breakdown products of the VIT-45 complex are iron(III)hydroxide, maltose, maltriose, maltotetraose and glucose. These products are either endogenous or have been extensively used in other parenteral pharmaceutical formulations, such as iron sucrose or iron gluconate in sucrose. The breakdown products of the complex are mainly “generally regarded as safe (GRAS) sugars”. There are no “formal” metabolism studies conducted in humans.

## 2.3 Intrinsic Factors

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

There were no PK studies conducted evaluating the effect of VIT-45 on age, gender, race, weight and organ dysfunction.

### 2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The sponsor has not studied the exposure response relationship in special elderly, pediatric, or special population (renal or hepatic impaired) subjects.

## 2.4 Extrinsic Factors

### 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

The effect of VIT dose concentration on pharmacokinetics in persons with alcohol use or smoking was not studied.

### 2.4.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted.

## 2.4 General Biopharmaceutics

Not applicable

# 3 Detailed Labeling Recommendations

The labeling has not been reviewed at this point.

# 4 Appendices

## 4.1 Proposed Package Insert (Original and Annotated)

## 4.2 Individual Study Review:

Here is the summary of four PK studies performed by the sponsor:

**Study VIT-IV-CL-02**

Study VIT-IV-CL-02 was a single-center, randomized, double blind, placebo controlled, single-dose escalation study. The study objectives were to assess the pharmacology, safety, and tolerability following single IV doses of iron as iron carboxymaltose (VIT-45) at doses of 100, 500, 800 and 1,000 mg in volunteers with mild iron-deficiency anemia.
The pharmacokinetic end points were:

1) Total serum iron
2) Total iron in urine
3) Model-independent parameters derived from total iron concentrations in serum and urine (with and without baseline adjustment) e.g., Cmax, Tmax, AUC0-t, AUC0-24, AUC0-72, t1/2, CL, Vd,area, Vd,ss and MRT for total serum iron and for total iron in urine.
4) Model-dependent half-lives derived from total serum iron concentrations.
5) The pharmacodynamic endpoints were serum ferritin and transferrin, latent iron binding capacity (LIBC), % transferrin saturation (post), hemoglobin, reticulocyte count and soluble transferrin receptor in serum.

The study was conducted in 32 subjects, selected from a pool of volunteers. Male and female Caucasians between 18 and 45 years with mild iron-deficiency anemia (hemoglobin ≥90 and <120 g/L for females and ≥90 and <130 g/L for males), serum ferritin <20 µg/L, and transferring saturation (TSAT) <16% were eligible for enrollment.

The 4 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/m2. Most of the subjects were female (N=30; 94%), while only 2 male subjects (6%) participated in the study. Hemoglobin concentrations were between 92 and 119 g/L and serum ferritin was <10 µg/L in most subjects and did not exceed 18.3 µg/L in any of the subjects. Except for two subjects with transferring saturation >16%, all subjects complied with the inclusion criteria for this study.

Treatment:

Subjects were randomized to 4 different dose groups. Six subjects per dose group received VIT-45 and 2 subjects each received placebo. Each subject received a single IV administration of VIT-45 or placebo on the fasted state each morning, starting on Day 1. The doses under investigation were 100, 500, 800 and 1000 mg iron as VIT-45.
The eligibility of subjects for the different dose levels was evaluated according to subjects potential iron requirement as calculated from hemoglobin levels and body weights (Table II). To ensure that subjects were assigned to a VIT-45 dose level that would not exceed the individually required amount of iron to a relevant extent (<10%), subjects were assigned as follows:

Table II. Hemoglobin and iron requirements for different dose groups

| Subjects hemoglobin level | Potential iron requirement | Randomized dose level of iron as VIT-45 |
|---|---|---|
| 90-130 g/L(males)<br>90-120 g/L (females) | 740-1,796 mg | 100 to 800 mg iron or placebo |
| 90-130 g/L(males)<br>90-120 g/L (females) | 980-1,796 mg | 1,000 mg iron or placebo |

**Administration of Dose: BOLUS vs INFUSION**

In the first dose group, subjects received a dose of 100 mg iron as VIT-45 undiluted within 1 minute as bolus injection. At the 3 higher dose levels, the injection bolus was diluted to achieve a volume of 250 mL infusion solution using physiological saline. The administered dose was infused at a variable IV dose rate, but at constant infusion time and infusion volume, in a superficial vein via an infusion pump. Infusion was stopped at 15 minutes post-dose.

**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 transferrin saturation (pre-dose) and unsaturated iron binding capacity (UIBC) (post-dose) were collected at 0800, 1200, 1600, 2000 and 2400 hours in the morning prior to Day 1 within 10 minutes before and at several time points after the dose (28X). The last sample was taken 168 hours after the dose (i.e. on Day 8). Urine samples for the determination of total iron concentrations were obtained 24 hours prior to dosing and at 0-4, 4-8, 8-12, 12-24, 24-48 and 48-72 hour post-dose collection intervals.

ICP (inductively coupled plasma) Optical Emission Spectrometry applying validated method 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 immunoturbimetric assay method on a Roche Hitachi Modular instrument using Roche Hitachi assay kits. UIBC in serum was measured by according to a validated method that was developed by (b) (4) . Transferrin saturation in serum was calculated from serum iron and transferrin concentrations before dose administration and from UIBC and transferring 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 subjects from the different dose levels but not for subjects randomized to placebo. Parameters were derived from individual concentration profiles either with or without correction for different individual baseline levels.

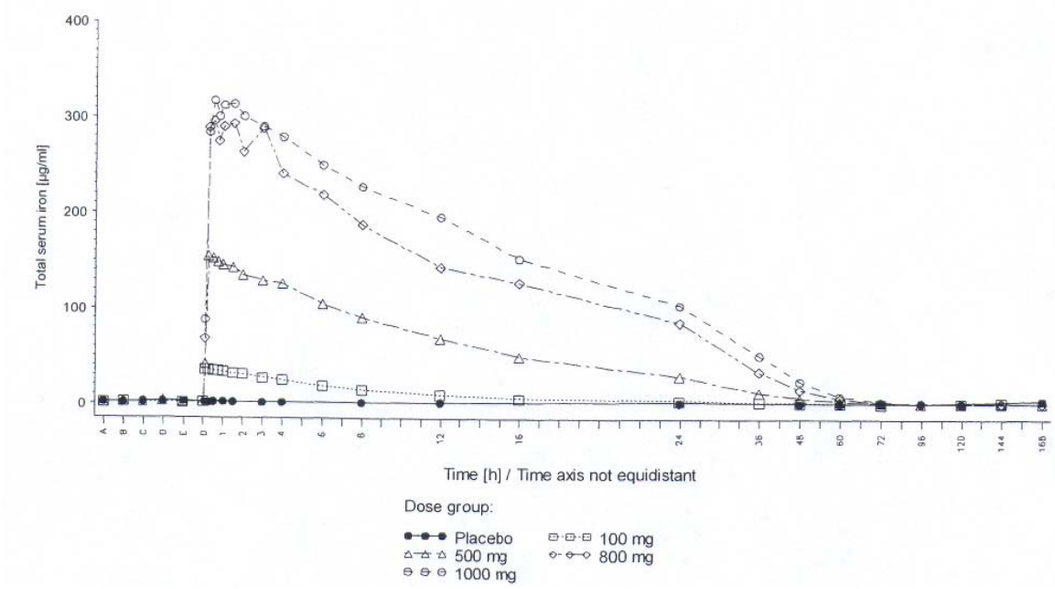
**Pharmacodynamic Variables:**

Serum ferritin and transferrin concentrations, transferrin saturation and UIBC in serum were assessed as pharmacodynamic variables. In addition, hemoglobin level, reticulocyte count and soluble transferring receptor in serum were also considered as pharmacodynamic variables.

**Pharmacokinetic Results:**

All 32 subjects completed the study. In most subjects, total serum iron concentrations were below the quantitation 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 the start of infusion. As expected, no changes were observed in placebo group. Mean maximum concentrations were between (36.9±4.4µg/mL after 100mg and 317.9±42.3µg/mL after 1,000 mg VIT-45. After peak concentrations were reached, the mean concentration-time curves constantly declined (Figure 4).

Figure 4. Mean total serum iron concentration (µg/mL).




A short infusion of VIT-45 at doses of 500, 800 and 1000 mg led to mean maximum total serum iron concentrations of 156, 319 and 331 µg/mL, respectively. Particularly 800 mg dose deviated from a dose-linear increase, while the maximum levels after 1000 mg VIT were approximately doubled when compared to the 500 mg dose (Figure 4).

The median Tmax after the bolus injection of 100 mg VIT-45 was reached at approximately 5 minutes (i.e. at the end of injection). In the groups where patients received an i.v. infusion of 15 minute duration, median Tmax were either reached at the end of infusion i.e. 15 minutes post infusion in the 500 mg dose group, or noticeably later, i.e. approximately 53 minutes (800 mg) and 1 h 16 min (1000 mg).

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 characterized 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,

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 Tmax 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 Cmax and AUC, increased with incremental doses, but did not occur in an exactly dose-proportional manner. The average AUC0-t was 426 µg-h/mL following 100 mg VIT-45. The geometric means were 2443, 5218, 6311 µg-h/mL for the 500, 800 and 100-mg dose groups respectively. 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 3 subjects 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 mean T1/2 in the range from 10 to 18 hours. Mean total body clearance was between 2.6 and 3.4 mL/min and mean 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.
Concentration of total iron in urine were below detection levels for most of the subjects after VIT-45 application, except for 2 subjects in the 800 mg iron group and 4 subjects in the 1,000 mg iron group showing measurable urine concentrations during 0-4 hours sample interval, but not at later time intervals.
The pharmacokinetic parameters of total serum iron using data up to 168 hours post-dose are summarized in Table II and up to 72 hours are shown in Table III.

Table II. Pharmacokinetic parameters of total serum iron (168 hour 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) |

Considering the PK data only until 72 hours post-dose (24 h in the 100- mg dose group), the terminal half lives were in the range of 7.4-12.1 hours (geometric means) and MRT in the range of 11.2-16.6 hours. Also, the volume of distribution at equilibrium, Vd, ss, was calculated to be lower in the 100-mg (2.9 L vs 4.6 L) and 500-mg groups (3.4 L vs 4.1 L), without remarkable differences in the data of the other groups. Vd,area ranged from 2.1 to 3.6 L. This pointed to a volume of distribution that matches the blood serum volume. CL was between 2.6 ml/min and 4.3 ml/min. This practically shows that majority of administered iron complex was utilized or excreted witin 24 h after a low dose of 100 mg and witin 72 h after high doses of 500-1000 mg.

Table III. Pharmacokinetic parameters of total serum iron (72 hour 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) |

This increase in serum concentration was dose dependent but not dose-linear. Maximum serum ferritin concentrations after dosing and the respective pre-dose concentrations are summarized in Table III. The mean seum ferritin concentration on Day -1 (measured at 08:00, 12:00, 16:00, 20:00 and 24:00 hours) were approximately 2 to 6 ng/mL across the different treatment groups. After dosing with placebo, the mean ferritin levels remained unchanged around 5 ng/mL until 168 –hour assessment. In contrast, ferritin levels started to rise approximately 6 to 12 hours after dosing in all actively treated patient groups. The highest serum concentrations were reached between 48 hours (100 mg VIT-45) and 120 hours (800 and 1000 mg VIT-45) after dosing, with a 23- to 210 fold increase above baseline. The increase in serum ferritin concentrations was dose dependent, but not strictly linear. Figure 4 shows mean ferritin concentration ng/mL by treatment.

Table IV. Pre-dose and maximum serum ferritin concentration 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 |

Transferrin levels showed a trend towards lower concentrations after IV administration of different doses of VIT-45 compared to pre-dose levels. These changes were 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. Transferrin receptor concentration (Figure 5) showed minor fluctuations after IV administration of VIT-45 and no clear trend was observed. Administration of VIT-45 led to steep decline in UIBC, particularly after 800 mg 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 groups (Figure 3).

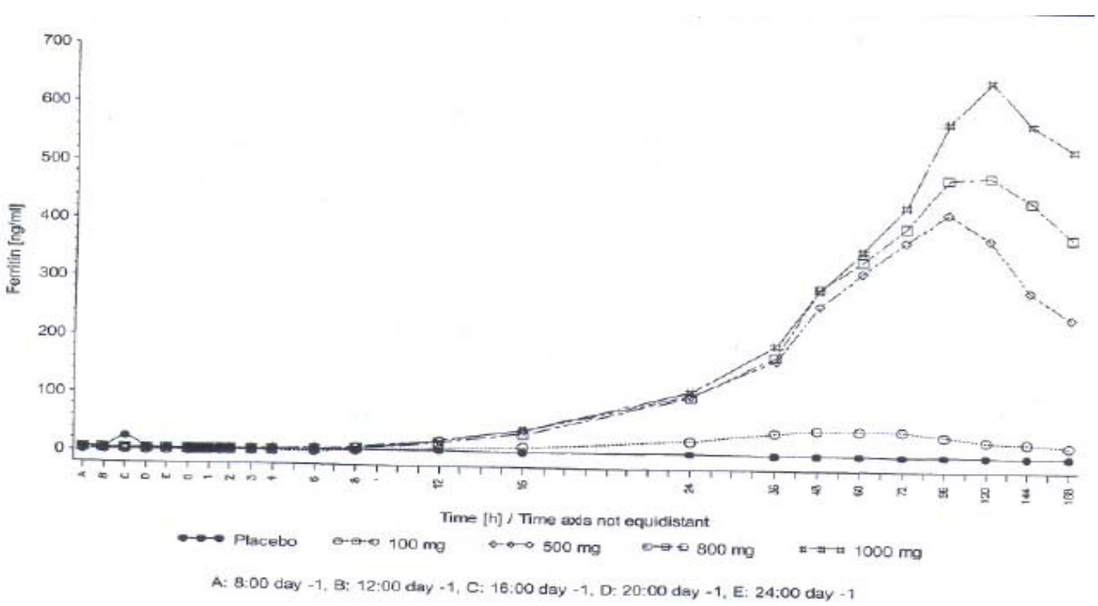



Figure 4. Mean Ferritin Concentration [ng/mL] by Treatment

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

Table V. Maximum mean changes in transferrin saturation from baseline at 24-36 h after VIT-45 administration.

The % of transferrin saturation 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 summarized in Table V.

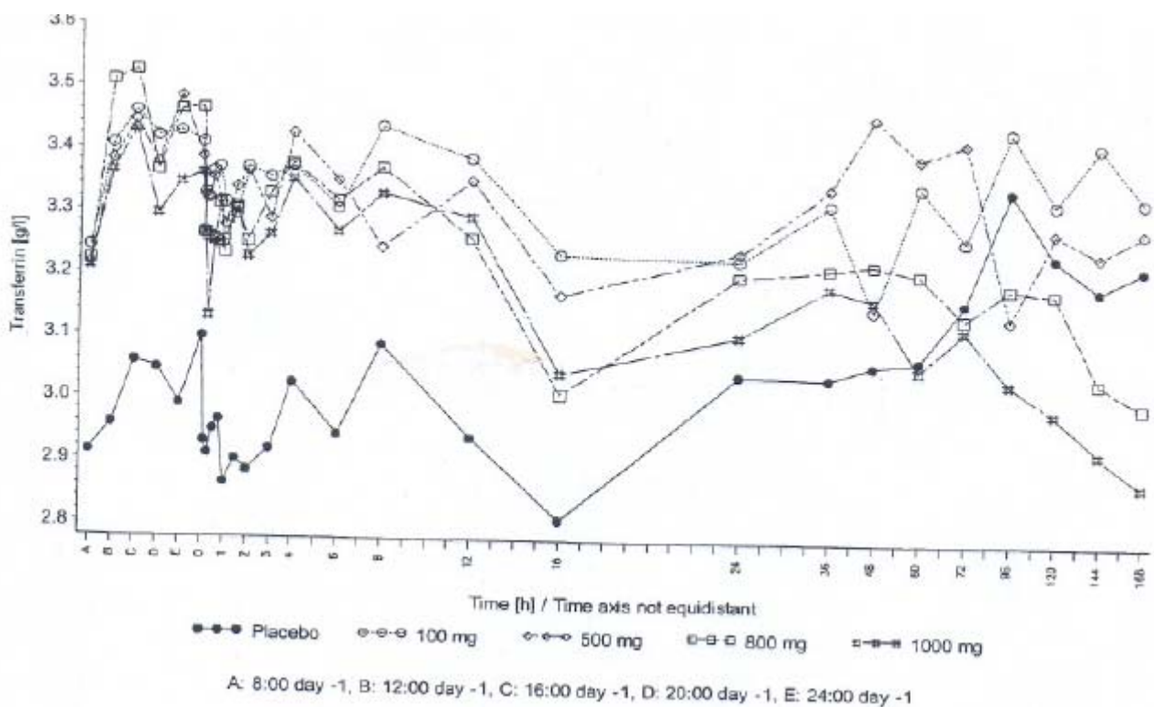



Figure 5. Mean Transferrin Concentration [g/L] by Treatment

The mean transferrin receptor concentrations before dosing were 2.43±0.78 to 2.72±1.66 mg/L for the 100- to 1000- mg treatment groups, while a somewhat lower value was obtained in the placebo group: 1.91±0.49 mg/L. The variability was higher in the 500- and 800 mg groups with an approximately 4- to 6-fold range of individual data vs an approximately 2-fold range in the other groups. After administration of VIT-45, the mean transferrin receptor concentration showed minor fluctuations across all dose groups during observation period (Figure 5), with the most pronounced changes occurring in the 1000 mg dose group. On Day 4, the serum concentrations were similar in all active treatment groups, while these more decisively varied at the post-study visit on Day 8.

**Unsaturated Iron Binding Capacity (UIBC) and Transferrin Saturation (TfS):**
UIBC is reciprocally linked with the post-dose transferrin saturation. As expected, no major change was observed following placebo administration. In contrast, the i.v. administration of VIT-45 led to steep decline in UIBC, particularly in 500- 800- and 1000 mg VIT-45 dose groups (Figure 3). In the 100- mg group, % UIBC was approximately 14% (±23%) corresponding to an UIBC of 12.4±20 µmol/L at 24 h post-dose. % of UIBC reached pre-dose values in the 100-mg dose group only at the end of observation period, and increased in other dose groups as well. Before dosing, the transferrin saturation ranged between 25±8% (VIT-45, 500 mg) and 38±7% (VIT-45, 800 mg). A baseline profile was obtained on Day-1 showed similar values within each dose group. After dosing, there was a clear treatment-related increase in % TfS that was not observed after administration of placebo. The maximum mean (±SD) changes from baseline were +63% (±22%) after 100 mg VIT-45, +76%(±8%) after 500 mg VIT-45, +63%(±5%) after 800 mg VIT-45 and 71% (±6%) following 1000 mg VIT-45 at 24 h to 36 h post-dose.

**Hemoglobin Concentrations:**
Hemoglobin was considered as a pharmacodynamic parameter in this study. The patients had to have a mild iron deficiency anaemia, as expressed by Hb levels of >90% and <120 g/L for women or >90 and <130 g/L for men, which was confirmed for all patients at the screening examination.

Before dosing, the mean hemoglobin concentrations were in the range between 103±7.4 g/L (100 mg VIT-45) and 117±6.9 g/L (800 mg VIT-45). The minimum – maximum concentrations that ranged between 94-125 g/L in the placebo group were similar to those obtained for the pooled VIT-45 group (90-125 g/L). Individual values after dosing were similar to these pre-dosing figures and ranged between 99-130 g/L (placebo) and 88 and 137 g/L for the pooled VIT-45 group (Figure 6).

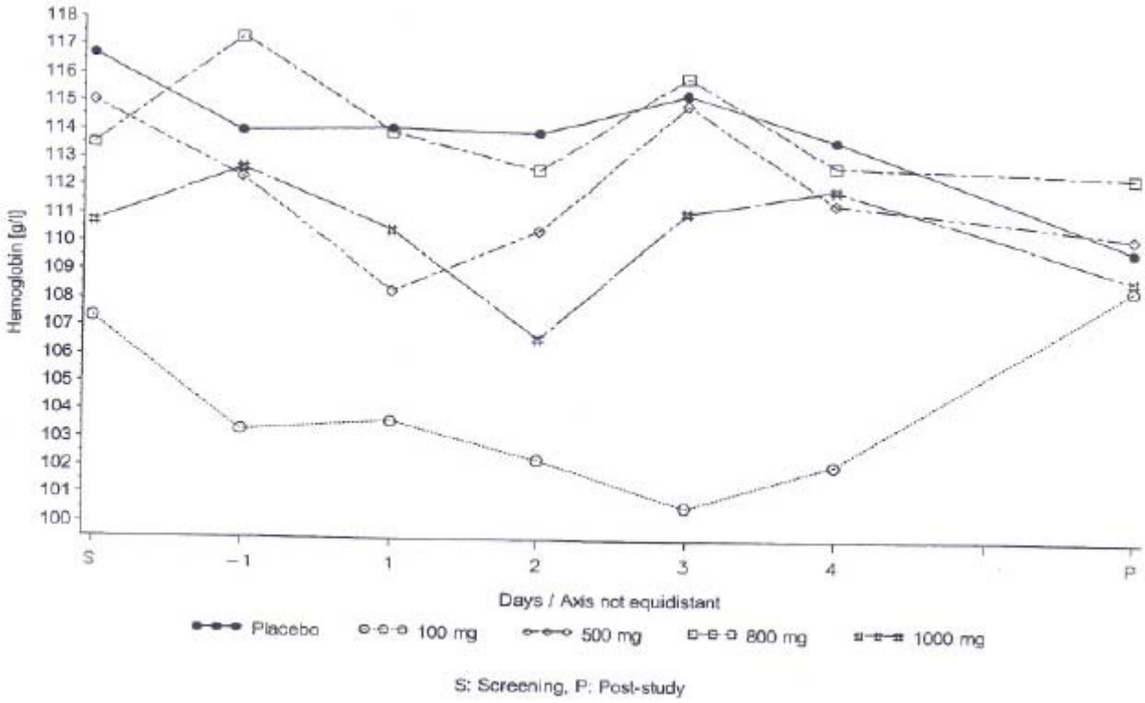



Figure 6. Mean Hemoglobin Concentration [g/L] by Treatment

**Reticulocyte Count:**

Before administration of VIT-45, the mean reticulocyte counts did not largely differ among the different dose groups and ranged between 11 (800 mg VIT-45) and 17 (100 mg VIT-45). Eight day after dosing (i.e. at the post-study visit), the reticulocyte counts showed a clear treatment-related increase in those groups where patients received VIT-45. The highest individual values obtained on Day 8, with increases up to 54% observed in the 500- mg group. The average counts in actively treated patient groups were between 24 and 35% at post study visit as compared to 12 in the placebo group (Figure 7).

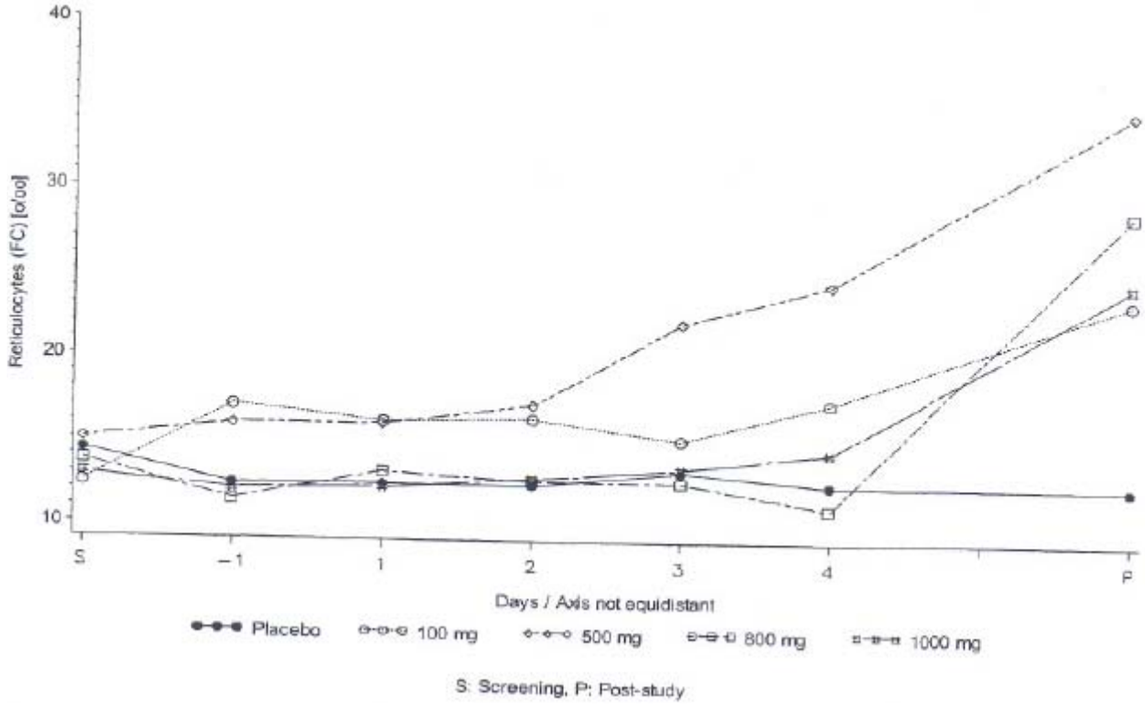



Figure 7. Mean Reticulocyte Count by Treatment

**Pharmacodynamic Conclusions:**

A dose-dependent, but not dose-linear, increase in serum ferritin concentration was observed in the VIT-45 treated subject 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 a significant impact on serum transferring levels or soluble transferring receptor in serum over the observation period. Changes were small and without clear relationship to treatment or dose level. Iron binding capacity was almost fully utilized after doses of 500, 800 and 1,000 mg of VIT-45, as indicated by an unsaturated iron binding capacity (UIBC) <5% or a transferring saturation >95%, respectively. The effect began shortly after infusion of VIT-45 and lasted for 2 to 3 days. Only at 100-mg dose level, the iron binding capacity of the serum was not fully saturated. At the end of 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 protein was still utilized for iron binding, which can be considered a normal finding in a sufficiently treated anemic subject.

Hemoglobin levels did not significantly change during the 8-day observation period.

Reticulocyte counts increased in actively treated subjects 8 days after dosing with VIT-45. This pharmacodynamic effect indicates activation of hematopoietic system in anemic subjects after treatment with VIT-45.

**Pharmacokinetic Conclusions:**

Infusion or injection of VIT-45 led to a rapid increase in (total) serum iron levels in 24 anemic subjects. However, increasing VIT-45 doses led to a shift of Tmax that was approximately 1 hour or longer at doses of 800 to 1000 mg iron as VIT-45. This considerably exceeded the end of the infusion and may be explained by differences of individual re-distribution from initial sites of uptake, such as liver, spleen and bone marrow. Cmax and AUC of iron serum exposure increased with ascending doses in a non-proportional manner, in particular AUC. Based on non-compartmental analysis, mean residence time was less than 24 hours on average and study drug was cleared from serum with a mean T1/2 of 10-18 hours. Mean total body clearance was between 2.6 to 3.4 mL/min. The mean 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 T1/2 (7.4-12.1 hours), MRT (11.2-16.6 hours) were slightly lower as compared to non-truncated data.

## STUDY VIT-IV-CL-03

Study Objectives and Design

Study VIT-IV-CL-03 was a multi-center, open-label, uncontrolled, multiple-dose study. The study objectives were to evaluate safety and tolerability of VIT-45 following IV 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 subjects with moderately stable iron deficiency anemia secondary to gastrointestinal disorders.

The main endpoints of the study were:

A) To evaluate safety and tolerability

B) To provide preliminary information on the therapeutic benefit of VIT-45, based on the time-course and magnitude of changes in hemoglobin and iron storage parameters

C) To provide pharmacokinetic data on iron levels

D) To provide preliminary data on inter-subject variability with regards to the safety, iron status and pharmacokinetic parameters assessed

Study Population and Main Criteria for Inclusion

Recruitment continued until approximately 18 subjects started therapy in order to include 12 subjects in each cohort. Male and female subjects aged between 18 and 60 years with moderate iron-deficiency anemia secondary to a gastrointestinal (GI) disorder and a calculated total iron requirement of at least 1,000 mg were eligible for enrollment. At least 50% of subjects in each cohort were to required ≥1,500 mg total iron. Subjects could be out-patients or in-patients.

Subjects 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 hemoglobin levels returned to normal range. All enrolled subjects to whom at least one dose of study medication was administered were considered for analysis (full analysis set). The safety set included all enrolled subjects.

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

The 2 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 (5 per cohort). All subjects reported a medical history in the abdominal and GI system, as

expected for this subject population. Serum iron, hemoglobin and serum ferritin levels were below the normal range in both cohorts. Transferrin saturation levels were below the normal range and transferrin levels were generally within or above the limits of normal range, as expected for subjects with iron-deficiency anemia.

**Treatment:**

Treatment began with the first dose of VIT-45 (Day 1). In Cohort 1, all subjects received 500 mg iron as VIT-45 IV infusions, once weekly for up to 4 weeks. In Cohort 2, all subjects 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 dose depending on the subjects' total iron requirements. VIT-45 was infused IV 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 (±2days) and 4 weeks (±2days) after the last dose of VIT-45. Bioanalytics of serum for assessment of iron status were performed by (b) (4) . Parameters assessed were serum iron, serum ferritin, transferrin and transferrin saturation. UIBC, representing the amount of unsaturated transferrin in serum, was measured in order to determine transferrin saturation. Hemoglobin was measured as part of the hematology panel. Iron status assessments were performed on a Roche INTEGRA 700, Roche Modular and Abbott Axysm. 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).

**Pharmacokinetics Results and Conclusions:**

At pre-dose on Day 1, mean serum iron levels were 1.03 µg/mL in Cohort 1 and 0.94 µg/mL in Cohort 2. Following IV infusion on Day 1, a rapid increase in serum iron levels was observed at maximum 1 hr after the dose (Cohort 1: 154.1 µg/mL, Cohort 2: 306.4 µg/mL).

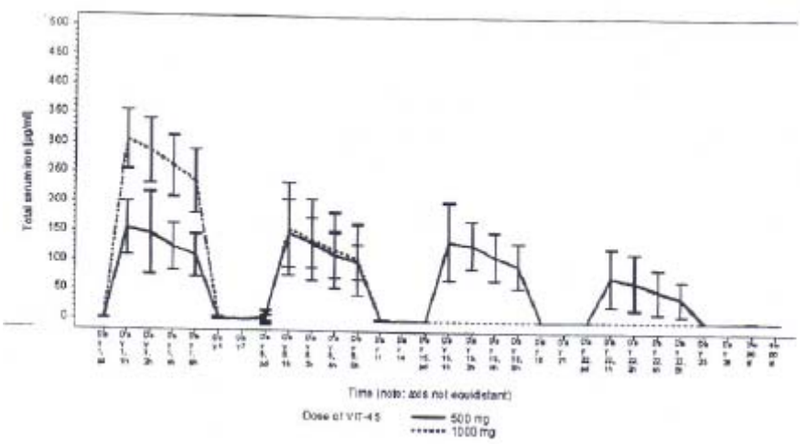



Figure 8. Total serum iron change with multiple administration of VIT-45

Mean serum iron levels in Cohort 2 were almost double compared to those in Cohort 1, reflecting the larger doses given in this group (1000 mg vs 500 mg iron as VIT in Cohort 1). Levels slowly decreased and were back to baseline levels by Day 7 (0.94 µg/mL, both Cohorts) (Figure 8).

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 many subjects received less than 1000 mg doses at this time-point (most subjects had iron deficit <2000 mg). By Day 11, mean 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 14.

On Days 15 and 22, similar patterns and time-courses of total serum iron levels increasing to maximum levels and returning to baseline 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 subjects' requirements. At 2- and 4-week follow-up visits, both cohorts showed total serum iron levels similar to pre-dose values. No accumulation of iron with repeated study drug administration was observed, and a dosing interval of about a week for iron doses of 500-1000 mg is adequate to allow the body to absorb the iron from the bloodstream.

**Pharmacodynamics Results**

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

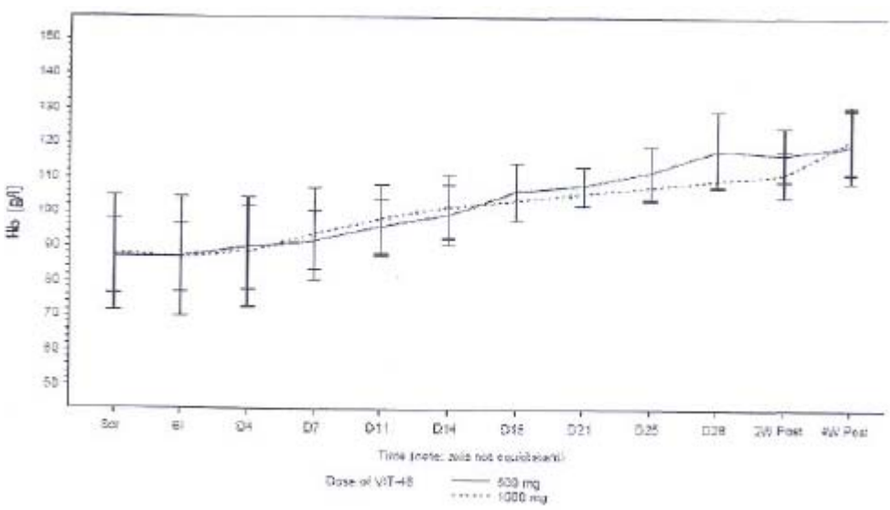



Figure 9. Mean±SD Hemoglobin Concentration Over Time

Giving iron in multiple doses caused a clinically relevant increase in hemoglobin in over 97% of the participating subjects (Table VI). At all time points from day Day 7 on, mean hemoglobin levels were elevated compared to baseline in both cohorts (Figure 9) By Day 14, 27% and 44% of subjects, respectively, in Cohort 1 (500 mg) and 2 (1000 mg) had achieved a 20 g/L increase in hemoglobin on at least 1 occasion. At the 4-week follow-up visit, 37% and 48% of subjects in Cohorts 1 and 2, respectively, had achieved normal hemoglobin levels, and 75% and 73% respectively, had achieved a >20 g/L increase in hemoglobin on at least 1 occasion.

Table VI. Hemoglobin levels at baseline and over time

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

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

Except for 1 subject, serum ferritin levels were below the lower limit of the normal range at baseline. In both cohorts, serum ferritin increased rapidly from baseline and was significantly elevated at all time points from Day 4 onward. Mean serum ferritin (Table VII) values were within the target range of 100-500 µg/L from Day 4 until Day 28 or the two weeks follow-up visit. All subjects responded to treatment in terms of serum ferritin. At the 4-week follow-up visit, mean serum ferritin levels were within the normal range but below the target range.

The subjects in Cohort 2 showed higher values of serum ferritin during the first two weeks of treatment, and many subjects in Cohort 2 had serum ferritin values above the upper limit of the normal range during this time.

Table VII. Serum ferritin levels at baseline and over time

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

Normal Range =20-500 µg/L

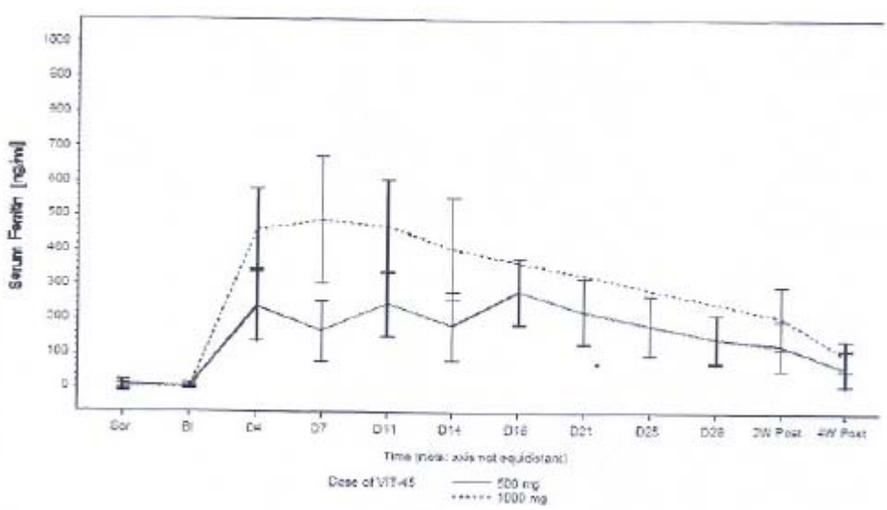



Figure 10. Mean ±SD Serum Ferritin Concentration Over Time

**Serum Transferrin Concentrations:**

In both groups, mean values of serum transferrin were similarly elevated at baseline (3.4 g/L and 3.3 g/L in Cohort 1 and 2, respectively). Mean values gradually decreased over time in both cohorts. On day 14, mean values were 2.8 g/L and 2.5 g/L and at follow-up visit, mean serum transferrin values were 2.5 g/L and 2.3 g/L, respectively (Figure 11).

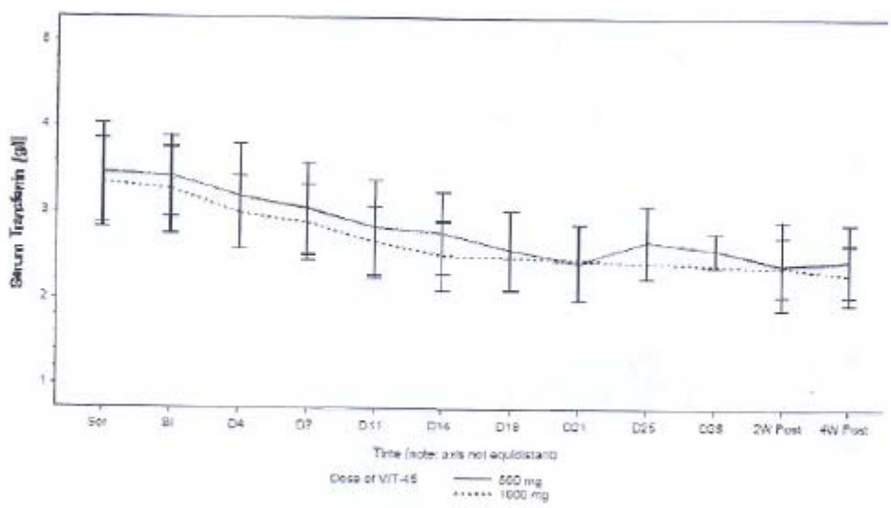



Figure 11. Mean±Serum Transferrin Concentration Over Time

**Pharmacodynamic Conclusions:**

Most pharmacodynamic parameters were below the normal range at baseline, as expected for a subject population experiencing iron-deficiency anemia. Analyzed parameters showed a trend towards normalization during treatment period. Hemoglobin levels continued to improve during the follow-up period, indicating the long term benefit of VIT-45 as iron supplementation. Over 97% subjects showed a meaningful benefit from VIT-45 therapy with respect to hemoglobin levels. Normal hemoglobin levels were achieved at the 4 week follow-up visit in 36% of subjects in Cohort 1 and 48% of subjects in Cohort 2.

Serum ferritin and transferrin saturation values showed that iron stores were repleted during study participation. Mean serum ferritin levels of the treated subjects 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.

Serum Transferrin Saturation
At screening, all but 1 subject had transferrin saturation values <16%. At all time-points after baseline (except Day 25, Cohort 1), serum transferring saturation was significantly increased. In both cohorts, serum transferring saturation increased after each VIT-45 infusion, before decreasing again prior to the next infusion. At the 4-week follow-up visit,

mean serum transferring saturation values were 41.0% and 39.1% in Cohorts 1 and 2, respectively.

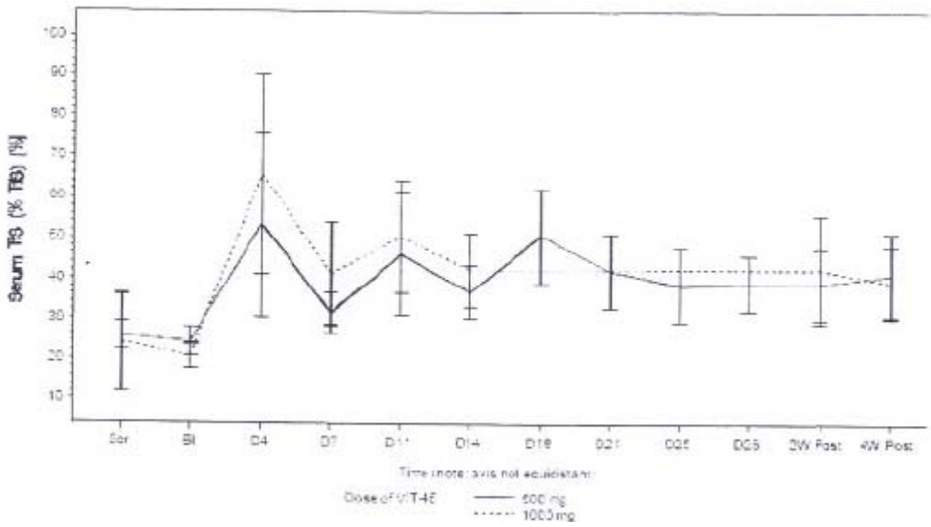



Figure 12. Mean (SD) serum transferrin saturation over time (full analysis set)

**STUDY 1VIT-5006**

Study 1VIT05006 was a multicenter, randomized, blinded, placebo-controlled, crossover study to investigate the safety and tolerability of a single 1000 mg dose of VIT-45 compared to placebo. A pharmacokinetic sub-study in 10 postpartum subjects was performed as part of this study. The study drug, subjects, and all study personnel were not blinded in the pharmacokinetic arm of the study. The subjects who participated in the pharmacokinetic arm of the study were not randomized. One dose of unblinded VIT-45 1,000 mg was administered with subsequent pharmacokinetic analysis over the next 7 days.
The pharmacokinetic variables assessed the total serum iron using Atomic Absorption methodology. The following pharmacokinetic variables were assessed:

A) Total serum iron levels at approximate time of maximum serum iron concentration (Tmax) and at trough time points
B) Maximum serum concentration (Cmax)
C) Time to maximum concentration (Tmax)
D) Area under the serum concentration curve from time zero to the last sampling
E) The extrapolated area under the serum concentration time curve from zero to infinity
F) Half-life ($t_{1/2}$) estimate
G) Apparent serum clearance (Cl)

Postpartum subjects >18 years of age weighing >66 kg, with a hemoglobin ≤12 g/dL, serum transferring saturation ≤25%, and ferritin ≤100 ng/mL, were offered participation in this study.

Twelve subjects entered into the pharmacokinetic arm of the study. Two subjects were excluded from the analysis due to a pre-dose outlier value (>150 times that of other subjects) and missing data at hours 2 and 4, respectively.

Dosing Regimen

Subjects received an unblended dose of 1000 mg of iron as VIT-45 over 15 minutes intravenously in 250 cc normal saline.

Pharmacokinetic Measurements:

Pharmacokinetic parameters calculated from total serum iron concentrations that were determined by a validated Atomic Absorption assay in postpartum subjects following a single 1,000 mg VIT-45 dose over 15 minutes in Study 1VIT05006 were comparable to results obtained following the same dose in subjects with mild iron-deficiency anemia in Study VIT-IV-CL-02. Peak iron concentrations were identified at the first or second sampling period (1 and 2 hours, respectively) after VIT-45 injection. The mean time to maximum concentration, 1.48 hours (minimum 1.25 hours to maximum 2.25 hours), was

similar to the 1.21 hour time to maximum concentration observed in Study VIT-IV-CL-02 conducted in subjects with mild iron-deficiency anemia following a single 1,000 mg infusion over 15 minutes.

The mean pre-dose total serum iron concentration was 46.8 mcd/dL. Mean peak concentrations (Cmax) were approximately 21,987 mcg/dL (219.9 mg/dL) for baseline corrected and 22,034 mcg/dL (220.3 mg/dL) for measured total serum iron and were associated with a coefficient of variation of 18.2% for both baseline corrected and measured serum iron values. The mean peak concentration following the single 1000 mg dose in this study was similar to 333 mcg/dL reported following the 1000 mg dose in Study VIT-IV-CL-02.

The elimination half-life calculated from baseline corrected serum iron was 22.8 (2.7 SD) hours and was longer than 10.5 (2.6 SD) (Table VIII) hours previously reported in Study VIT-IV-CL-02. The difference may be easily explained by the more frequent sampling times between 6 and 168 hours in the confined Phase I study VIT-IV-CL-02.

Serum clearance values showed limited variations ranging from 1.4 to 4.2 dL/h, with a median value of 2.15 dL/h (SD 1.76), which was similar to the 1.61 dL/h (2.68 mL/min) reported in Study VIT-IV-CL-02.

Table VIII. Pharmacokinetic Parameters with Summary Statistics for Total Serum Iron After 1,000 mg VIT-45 Administration

| Parameter (unit) | Summary Statistics | Baseline Corrected[a] | Measured Total Serum Iron |
|---|---|---|---|
| $C_{max}$ (mcg/dL) | Mean (±SD)<br>Median<br>(Min, Max)<br>CV% | 21987.2 (4003.09)<br>21473<br>(15526, 29101)<br>18.2% | 22034.0 (4012.09)<br>21505<br>(15550, 29140)<br>18.2% |
| $AUC_{0-t}$ (mcg*h/dL) | Mean (±SD)<br>Median<br>(Min, Max)<br>CV% | 518159.00 (162201.378)<br>566273.1<br>(236680.1, 710055.6)<br>31.3% | 543889.45 (169067.852)<br>590987.8<br>(246063.0, 740247.2)<br>31.1% |
| $AUC_{0-\infty}$ (mcg*h/dL) | Mean (±SD)<br>Median<br>(Min, Max)<br>CV% | 521555.93 (163572.253)<br>570576.7<br>(238223.0, 711597.9)<br>31.4% | |
| $t_{1/2}$ (h) | Mean (±SD)<br>Median<br>(Min, Max)<br>CV% | 22.784 (2.7212)<br>23.01<br>(18.76, 27.0)<br>11.9% | |
| Cl (dL/h) | Mean (±SD)<br>Median<br>(Min, Max)<br>CV% | 2.154 (0.8810)<br>1.76<br>(1.41, 4.20)<br>40.9% | |

SD=standard deviation; Min=minimum; Max=maximum; CV=coefficient of variation

a Concentrations are corrected for the baseline iron concentration. Parameters are calculated using baseline corrected data.

**STUDY VIT-IV-CL-001:**

Study VIT-IV-CL-001 was an open-label, controlled isotope study performed at the PET center of the [redacted] (b) (4). The study was conducted in compliance with Declaration of Helsinki (1996) and in accordance with ICH Guidelines for Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP). The study was also approved by the Isotopes Committee of the Medical Faculty of Uppsala University, Sweden, the Medical Products Agency, Uppsala, Sweden, and the X-Ray and Radioactive Agents Unit, Swedish Radiation Protection Institute, Stockholm, Sweden.

**Study Objectives and Design**

The study objective was to assess iron pharmaco-kinetics after a single IV dose of VIT-45 labeled with $^{52}Fe/^{59}Fe$ as a tracer in subjects with iron-deficiency anemia (IDA) or renal anemia. Primary variables were the distribution of $^{52}Fe$ and incorporation of $^{59}Fe$ into RBCs. In addition, iron status and safety parameters were assessed.

**Study Population and Main Criteria for Inclusion**

Three subjects with IDA and 3 subjects with renal anemia were selected for the study. Main criteria for inclusion were hemoglobin concentrations between 90 and 130 g/L, serum ferritin *<30 µg/L* (IDA subjects) or <200 µg/L (subjects with renal anemia), serum cyanocobalamin <115 pmol, serum folate <3.7 nmol/L, serum aluminum <20 µg/L, and age between 18 and 75 years. The presence of any infections, severe diseases of the liver or cardiovascular system, or clinical suspicion of iron overload was excluded. All 6 subjects satisfied all inclusion and exclusion criteria.

**Treatment**

Each subject received a test dose of 25 mg iron as a 0.5 mL solution of VIT-45 at least I week prior to receiving study medication in order to test for serious adverse events. Study medication was administered as an IV injection bolus of 20 mL, containing 100 mg iron as $^{52}Fe$ and $^{59}Fe$-labeled VIT-45, delivered over 10 minutes using a constant infusion pump.

**Pharmacokinetic Measurements and Analysis**

Using the PET technique, the distribution of $^{52}Fe$ was assessed from 0 to 8 hours post-dose in the liver, spleen, bone marrow and heart ventricle (for blood activity). Standard uptake values (SUVs) for the tissue organs were calculated as tissue activity ($MBq/cm^3$) in relation to the injected activity per gram body weight (MBq/g), considering a tissue density of 1 $g/cm^3$. Thus, the SUV represents a dimensionless value that is comparable among individual subjects. A multiple graphical plotting method was used to determine the rate of $^{52}Fe$ flow from the blood into the tissue compartments. The linear regression of the slope and the intercept were calculated. Radioiron (Fe-59) RBC utilization was assessed from blood samples taken 3 times per week in the first week and then twice weekly over the following 3

weeks (until Day 24). Radioiron RBC utilization was determined by calculating the fraction of injected Fe-59 radioactivity that was circulating in the blood, based on whole blood samples. Iron status was assessed from measurements of hemoglobin, plasma iron, total iron binding capacity, transferrin saturation and serum ferritin.

**PET Imaging Results:**

**Blood Kinetics:**

The time span in kinetic studies ranged from 7.87 to 8.14 hours (target 8 hours). In all subjects, there was a rapid increase in the SUVs of radioactivity in the blood reaching a maximum value after about 10 to 20 minutes. The radioactivity in the blood was found to have an initial clearance phase during 100 minutes following the peak. This was followed by as lower clearance phase for the rest of the investigation time, reaching 20 to 30% of the peak value after 3 to 4 hours, and between 5 and 20% of the peak value after the nominal 8 hours of the PET study.

**Liver Kinetics**: In the liver, a rapid increase in SUVs was observed for the first 25 minutes for 4 of the subjects, followed by a slower increase. In Subjects 4 and 6, there was an increasing uptake throughout the first scanning session, followed by a slight decrease toward the end of the study when radioactivity reached 75% of the peak value (Figure 14).

**Bone marrow Kinetics**: In bone marrow, all subjects showed an initial rapid increase in the SUVs of radioactivity in the first 10 minutes, followed by an influx into the bone marrow at a decreased, but steady rate until the end of the study.

**Spleen Kinetics:** Peak SUV in the spleen was reached for all subjects after 16 to 25 minutes. Thereafter, SUV declined steadily (Table IX). The profile of the relative distribution of VIT -45 indicated a much higher uptake by the bone marrow than by the liver and spleen.

Table IX. Mean Peak Standard Uptake Values for various organs

| Region of Interest | Mean Peak SUV |
|---|---|
| Bone Marrow | 60 |
| Liver | 27 |
| Spleen | 16 |

The blood to bone marrow transfer rate was steady, irrespective of the blood-iron concentration, indicating that there was no saturation of the transport system to the bone marrow at the administered dose level. For the liver, equilibration could be seen after about 20 minutes, while for the spleen equilibration varied among subjects. The shorter

equilibration time for the liver (25 minutes) indicated a minimal role for the liver in direct distribution of the complex. Splenic uptake reflected the uptake of the complex by the reticulo-endothelial system (RES), illustrating the safety of VIT-45 in that it is not distributed to the parenchyma of tissue and organs.

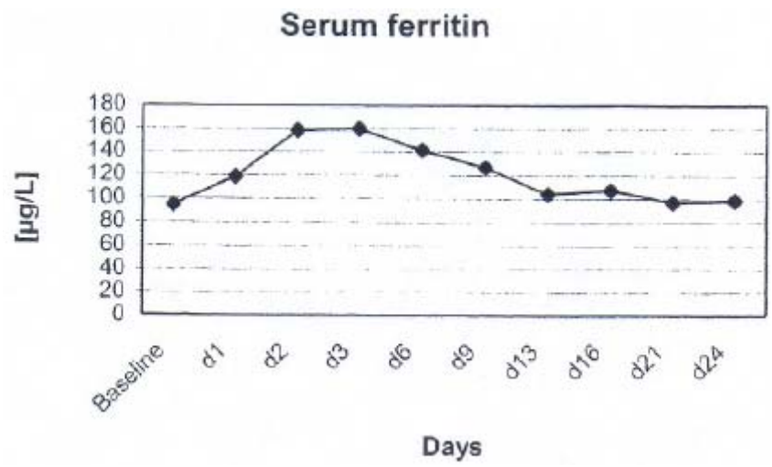



Figure 13. Serum Ferritin values during the course of study

Figure 14. Transferrin saturation during the course of study

A notable increase in transferrin saturation was measurable on Day 1 (74.18±15.25% at the baseline). After Day 1, values decrease as shown in Figure 14.

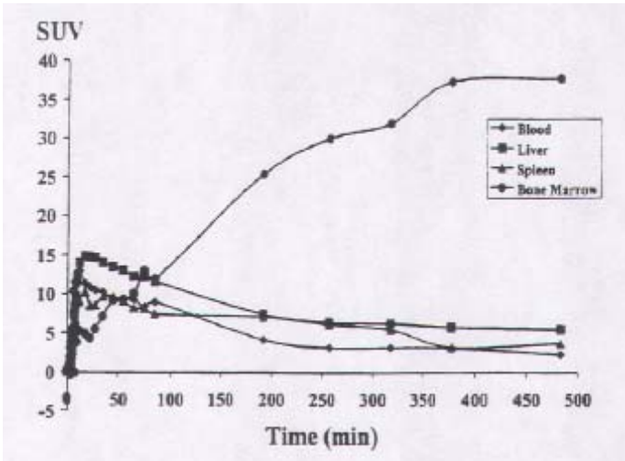



Figure 15. Kinetics of Ferinject in blood and other organs

| $^{59}$Fe Utilization (%) | | | | | | |
|---|---|---|---|---|---|---|
| Number of days from injection | IDA Subjects | | | Renal Anemia Subjects | | |
| | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 | Subject 6 |
| 1 | 7 | 7 | 8 | 5 | 5 | 5 |
| 2 | 18 | 17 | 24 | 6 | 15 | 6 |
| 3 | 34 | 33 | 42 | 15 | 32 | 11 |
| 6 | 69 | 72 | 84 | 47 | 50 | 34 |
| 9 | 76 | 78 | 89 | 52 | 73 | 48 |
| 13 | 86 | 88 | 93 | 55 | 79 | 56 |
| 16 | 86 | 92 | 96 | 58 | 79 | 61 |
| 21 | 85 | 94 | 97 | 63 | 81 | 58 |
| 24 | 91 | 95 | 99 | 68 | 84 | 59 |
| | | | | | | |

Table X. % Iron-59 Utilization over time by different patient groups

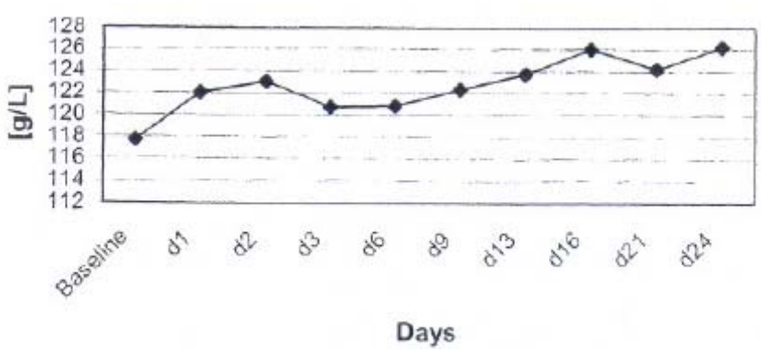



Figure 17. Hemoglobin values during the course of study

**Conclusion:**

Pharmacokinetic evaluation of VIT-45 using PET techniques showed a rapid distribution in the systemic circulation. During the observation period of 8 hours, the majority of 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 the spleen and liver (target organs) reflects its safety. Incorporation of radioiron into RBC increased rapidly during first 6 to 9 days, indicating the potential efficacy of VIT-45 as an iron supplementation treatment. After 24 days, iron utilization was greater in IDA (91-99%) than in renal anemia subjects (61-84%). The transient increase in serum ferritin levels illustrated the replenishment of the depleted iron stores. According to the sponsor, VIT-45 was shown to be safe and well-tolerated.

**OVERVIEW OF EFFICACY:**

The aim of the development program was to demonstrate the safety and effectiveness of parenteral VIT-45 in treatment of IDA in a variety of patient populations. In the clinical program, the effectiveness of VIT-45 was evaluated in 7 studies as follows:

A) Patients with postpartum IDA (2 Studies)
B) Anemic patients undergoing regular hemodialysis (2 Studies)
C) Patients with IDA secondary to GI disorders (2 Studies)
D) Patients with IDA secondary to heavy uterine bleeding

Four of the seven studies provide the primary evidence of effectiveness of VIT-45 for the treatment of IDA. These four pivotal studies are 1VIT03001 (postpartum anemia), VIT-IV-CL-009 (postpartum anemia), VIT-IVCL-008 (GI disorder associated anemia), and 1VIT04002/1VIT04003 (anemia due to heavy uterine bleeding). Supportive evidence of efficacy is provided by 3 studies, including VIT-IV-CL-015 (hemodialysis-associated anemia), VIT-53214 (hemodialysis-associated anemia), and VIT-IV-CL-003 (GI disorder-associated anemia). A summary of clinical studies is reported in Table XI.

Differences among the studies in endpoints led to a common analysis population in order to facilitate comparing studies and pooling studies. The Modified Intent-to-Treat set included all subjects who received at least 1 dose of study medication and had at least 1 post-baseline hemoglobin assessment. The Week 4 visit was chosen for analysis since it was the latest visit shared by Studies 1VIT03001, VIT-IV-CL-009, VIT-IV-CL-008, and 1VIT04002/1VIT04003. Responder analyses were based on an increase from baseline in hemoglobin of >2.0 g/dL, an increase from baseline in hemoglobin >3.0 g/dL, and hemoglobin level >12 g/dL on or before Week 4. These criteria represent increasing magnitude of hemoglobin response, and hemoglobin levels >12 g/dL indicate that subjects have achieved hemoglobin levels within or approaching normal range.

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Table XI. Summary of Clinical Efficacy Studies

| Study | Treated Subjects | | Efficacy Endpoint(s) |
|---|---|---|---|
| **Postpartum Anemia** | | | |
| | **VIT-45 Group** | **Oral Iron Group** | |
| 1VIT03001 | 174 | 178 | The primary measure of efficacy defined "success" as an increase in hemoglobin of ≥2 g/dL anytime between Baseline and End of Study or time of intervention. |
| VIT-IV-CL-009 | 227 | 117 | The primary efficacy endpoint was change from baseline levels of hemoglobin to Week 12. |
| **Gastrointestinal Disorder–Associated Anemia** | | | |
| | **VIT-45 Group** | **Oral Iron Group** | |
| VIT-IV-CL-008 (Inflammatory Bowel Disease) | 137 | 63 | The primary efficacy endpoint was change from baseline levels of hemoglobin to Week 12. |
| VIT-IV-CL-003 | 20 (500 mg) 26 (1000 mg) | - | Efficacy endpoints included mean hemoglobin levels by visit, proportion of subjects achieving >20 g/L increase in hemoglobin at any time during the study, proportion of subjects achieving normal hemoglobin levels (males: 140-180 g/L; females: 120-160 g/L) by visit, mean serum ferritin levels by visit, and proportion of subjects achieving normal serum ferritin (20-500 ng/mL). |
| **Hemodialysis-Associated Anemia** | | | |
| | **VIT-45 Group** | **Venofer® Group** | |
| VIT-IV-CL-015 | 137 | 63 | The primary efficacy endpoint was the percentage of subjects reaching an increase in hemoglobin of ≥10 g/L at 4 weeks after baseline. |
| VIT-53214 | 162 | - | Treatment responders were defined as subjects who had an increase of hemoglobin >1 g/dL from baseline at any point during the study. |
| **Anemia Due to Heavy Uterine Bleeding** | | | |
| | **VIT-45 Group** | **Oral Iron Group** | |
| 1VIT04002/1VIT04003 | 174 | 178 | The primary endpoint for efficacy was the proportion of subjects achieving success. Success for each subject was defined as an increase in hemoglobin of ≥2.0 g/dL anytime between baseline and end of study or time of intervention. |

**Hemoglobin >12 g/dL up to Week 4:**

Among subjects in the Modified Intent-to-Treat Population in the pivotal studies (1VIT03001, VIT-IV-CL-009, VIT-IV-CL-008, and 1VIT04002/1VIT04003) combined, a statistically significant greater proportion of VIT-45 subjects (485/748; 64.8%) achieved a >12 g/dL hemoglobin up to Week 4 compared to oral iron subjects (266/563; 47.2%).

Table XII. Summary of the Proportion of Subjects with hemoglobin >12 g/dL Up to Week 4 by Treatment Group Overall (Modified Intent-to-Treat Population in the Pivotal Studies Combined)

| Hemoglobin >12 g/dL up to Week 4 | Number (%) Subjects VIT-45 n/N (%) | Oral Iron n/N (%) | Fisher's Exact p-value | 95% CI |
|---|---|---|---|---|
| Overall | 485/748 (64.8) | 266/563 (47.2%) | <0.0001 | 12.23, 22.95 |

n= number of subjects with response, N=number of subjects in group

Among subjects in the Modified intent-to-Treat Population in the postpartum anemia studies combined (1VIT03001 and VIT-IV-CL-009) and the heavy uterine bleeding study (1VIT04002/1VIT04003), a statistically significantly greater proportion of VIT-45 subjects achieved a >12 g/dL increase in hemoglobin up to 4 Week compared to oral iron subjects. Among the subjects in Modified Intent-to-Treat Population in Inflammatory Bowel Disease Study (VIT-IV-008), no statistically significant difference was observed between the VIT-45 and oral iron groups in the proportion of subjects who achieved an increase in hemoglobin of >12 g/dL up to Week 4. A summary is provided in Table XII, XIII, XIV.

Table XIII. Summary of the Proportion of Subjects with hemoglobin >12 g/dL Up to Week 4 by Treatment Group Overall (Modified Intent-to-Treat Population in the Pivotal Studies Combined)

| Hemoglobin >12 g/dL up to Week 4 | Number (%) Subjects VIT-45 n/N (%) | Oral Iron n/N (%) | Fisher's Exact p-value | 95% CI |
|---|---|---|---|---|
| Postpartum Anemia Studies Combined | 285/356 (80.1%) | 160/263 (60.8%) | <0.0001 | 12.01, 26.43 |
| Inflammatory Bowel Disease Study | 60/136 (44.1%) | 21/60 (35.0%) | 0.2718 | -5.56, 23.79 |
| Heavy Uterine Bleeding Study | 114/228 (50.0%)) | 72/225 (32.0%) | <0.0001 | 9.10, 26.90 |

**Hemoglobin Increase >2.0 g/dL up to Week 4.**

Among subjects in Modified Intent-to-Treat Population in the postpartum anemia study combined (1VIT03001 and VIT-IV-CL-009), no statistically significant difference was observed between the VIT-45 and oral iron groups in the proportion of subjects who achieved an increase in hemoglobin of >2.0 g/dL up to Week 4.

Table XIV. Summary of the Proportion of Subjects with hemoglobin >2 g/dL Up to Week 4 by Treatment Group Overall (Modified Intent-to-Treat Population in the Pivotal Studies Combined)

| >2 g/dL Increase from baseline in hemoglobin up to Week 4 | Number (%) Subjects VIT-45 n/N (%) | Oral Iron n/N (%) | Fisher's Exact p-value | 95% CI |
|---|---|---|---|---|
| Postpartum Anemia Studies Combined | 321/356 (90.2%) | 226/263 (85.9%) | 0.1277 | -9.8, 9.45 |
| Inflammatory Bowel Disease Study | 101/136 (74.3%) | 32/60 (53.3%) | 0.0049 | 6.33, 35.54 |
| Heavy Uterine Bleeding Study | 150/228 (65.8%) | 105/225 (46.7%) | <0.0001 | 10.16, 28.09 |

## 4.3 Consult Reviews: N/A

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/s/
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5/30/2007 03:52:11 PM
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