Clinical Study Report

1 TITLE PAGE

Study title:	Safety and efficacy of postoperative i.v. iron substitution with Polyglucoferron compared to Ferric Carboxymaltose and oral iron in patients with diagnosed iron deficiency anaemia pre- or postoperatively (IDA II)
Investigational product:	Polyglucoferron (Feramyl, once i.v., dosing according to Hb-levels and body weight) Ferric Carboxymaltose (Ferinject, i.v., dosing according to Hb-levels and body weight) Ferrous sulphate (Ferro Sanol Duodenal daily, p.o., dosing according to SmPC and allowed adjustment to highest tolerable dosage)
Indication studied / study population:	Iron deficiency with anaemia after surgery and iron deficiency anaemia (IDA) before surgery in patients with planned surgery who need replenishment of iron as judged by the treating physician
Study Design:	Parallel group, active-controlled, randomized, multi-centre, open label, interventional Phase IIIa trial
Sponsor:	Fraunhofer Society for its Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Executive director: Prof. Dr. med. Dr. rer. nat. Gerd Geisslinger, Theodor-Stern-Kai 7, 60590 Frankfurt a.M., Germany
Representative of the Sponsor	Prof. Dr. med. Frank Behrens Fraunhofer Institute for Translational Medicine and Pharmacology ITMP and Department of Rheumatology University Hospital, Goethe–University Frankfurt, Germany Theodor-Stern-Kai 7, 60590 Frankfurt a.M., Germany Phone: +49 (0)69 6301-7302 Fax: +49 (0)69-6301-5929 Email: Frank.Behrens@itmp.fraunhofer.de
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Protocol code:	TMP-0916_03
EudraCT-No.:	2017-003439-12
Phase:	IIIa
Study initiation date:	First patient 1st visit: 01.11.2018
Study completion date:	Closure date last study site: 21.10.2024 (Last patient last visit: 04.12.2023)
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Report date:	14.05.2025

The clinical trial was carried out in compliance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the applicable laws.

2 SYNOPSIS

Name of Sponsor	Fraunhofer Society for its Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Executive director: Prof. Dr. med. Dr. rer. nat. Gerd Geisslinger, Theodor-Stern-Kai 7, 60596 Frankfurt a.M., Germany
Representative of the sponsor	Prof. Dr. med. Frank Behrens Fraunhofer Institute for Translational Medicine and Pharmacology ITMP and Department of Rheumatology University Hospital, Goethe–University Frankfurt, Germany Theodor-Stern-Kai 7, 60590 Frankfurt a.M., Germany Phone: +49 (0)69 6301-7302 Fax: +49 (0)69-6301-5929 Email: Frank.Behrens@itmp.fraunhofer.de
Investigational product (IMP)	Feramyl Ferinject Ferro Sanol Duodenal
Active Ingredient	Polyglucoferron Ferric Carboxymaltose Ferrous glycerine sulphate
Title of study	Safety and efficacy of postoperative i.v. iron substitution with Polyglucoferron compared to Ferric Carboxymaltose and oral iron in patients with diagnosed iron deficiency anaemia pre- or postoperatively (IDA II)
Design	Parallel group, active-controlled, randomized, multi-centre, open label, interventional phase IIIa trial
Coordinating investigator	Prof. Dr. med. Dr. Phil. Kai Zacharowski, ML FRCA FESAIC Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Germany Theodor-Stern-Kai 7, 60590 Frankfurt a.M., Germany, Phone: +49 (0)69-6301-5998 Email: Zacharowski@med.uni-frankfurt.de
Study sites and location	Multicentre study (4 centres: 4 sites activated, 3 sites recruiting) Please find in Attachment 16.1.4 the list of participating investigators
Publication (reference)	Not yet published
Studied period	5 years 4 months First patient in: 01.11.2018 (date FPFV: 05.11.2018) Last patient out: 04.12.2023 (LPLV) Study end: 21.10.2024 (closure date last study site)
Phase of study	IIIa
Primary objective	Co-primary objectives for efficacy (at study end) and short-term safety (at interims analysis): 1) Demonstrate superiority in short term safety assessed by statistically significant lower levels of volume-corrected (v.c.) urine iron, estimated by the difference in v.c. iron urine measured before and after i.v.

	administration (first urine after the end of i.v. administration) - of Polyglucoferron compared to Ferric Carboxymaltose 2) Demonstrate superiority of i.v. iron substitution with Polyglucoferron compared to oral iron therapy with Ferrous sulphate in focus on proportion of patients who achieve normalized Hb-levels (according to WHO definition) or increased Hb-level with at least 1.5 g/dl at visit 4 compared to BL
Secondary objectives	Secondary efficacy assessment of and comparison between all groups: • Treatment effects on change in haematologic and serologic iron parameters (Hb, TSAT, s-iron, s-transferrin, s-ferritin) from BL until visit 4 • Proportion of patients with normalization (defined in WHO classification) of Hb at visit 4 Secondary objectives for safety (assessment for and comparison between all groups): • Treatment effects of Polyglucoferron i.v. and Ferric Carboxymaltose i.v. on s-phosphate levels at visit 4 (for i.v. groups only) • Overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs until 30 days after last IMP administration • Changes in laboratory parameters, vital signs, and physical exam on each available visit including blood pressure and heart rate • AEs related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions • All-cause mortality until visit 4 Exploratory efficacy objectives (assessment of and comparison between all groups): • The need of allogenic red blood cell transfusion (number of units) from BL until visit 4 • Number of patients with need of allogenic red cell blood transfusion from BL until visit 4 • Treatment effect on change in Quality of Life (SF-36) at visit 4 compared to BL Exploratory safety objectives (assessment of and comparison between all groups): • Duration of hospital stay (days) until visit 4 • Analysis of total iron levels in plasma at BL after end of i.v. iron administration (for the i.v. groups (safety analysis group) only)
Methodology	187 patients with iron deficiency anaemia (defined as S-ferritin <100 ng/mL and Hb <12 g/dL for female and <13 g/dL for male) were screened for eligibility. 148 patients were randomized to Ferinject (Polyglucoferron) group, Ferro Sanol Duodenal (Ferrous sulfate) group or Ferinject (Ferric Carboxymaltose) group. For short term safety analysis change of iron in urine was measured before and in the first urine after the end of i.v. administration in the first 35 patients from whom eligible samples for analysis are collected in each i.v. treatment group. The two treatment groups were compared with a

	two-sided nonparametric Wilcoxon-Mann-Whitney U test with significance level alpha=5%. The Feramyl treatment arm was closed, after sufficient number of patients with eligible samples was included for short term safety analysis. The study was continued for assessment of co-primary efficacy endpoint: The effectiveness of postoperative i.v. iron substitution with Feramyl compared to conventional oral iron substitution with Ferro Sanol Duodenal (treatment 28 – 35 days) to normalize Hb-values or to increase Hb values by at least 1.5 g/dl until visit 4 was evaluated. Rates of achieving normalized Hb-levels or an increased Hb of at least 1.5 g/dl at V4 compared to baseline was compared with a two-sided chi-square test at a significance level of alpha=5%. In addition, safety and efficacy outcomes, such as the decreased need for allogenic blood transfusions, haematologic and serologic iron parameters and the well-being of the patient using the SF36 questionnaire were compared between treatment groups.
Number of patients (planned and analysed)	Planned sample size: 407 (248 Feramyl group, 124 Ferro Sanol Duodenal group, 35 Ferinject) Number of patients screened: 187 Randomized patients: 148 (72 Feramyl group, 38 Ferro Sanol Duodenal group, 38 Ferinject) Analysed at interim: N=70 (Feramyl 35; Ferinject 35; mITT safety subset) Analysed at study end: 146 (safety set size), 130 (mITT set size),122 (per protocol set size) Drop-outs: 7 Screening failures: 36
Diagnosis and main criteria for inclusion	Patients with confirmed and documented iron deficiency and anaemia 10 days before surgery or until 72h after start of surgery and with confirmed anaemia before randomization at baseline, were included in the trial. Feramyl was administered once i.v., Ferinject according to SmPC once or two-times at a one-week interval i.v., and Ferro Sanol Duodenal as oral iron substitution daily until visit 4 (28-35 days after BL).
Test Product, dose and mode of administration, batch number, duration of treatment:	In this study, three IMPs were differentiated: Feramyl Ferinject Ferro Sanol Duodenal Patients were randomized to one of the three groups to receive either Feramyl i.v. once (adjusted to Hb-level and weight), Ferinject (according to SmPC adjusted to Hb-level and weight, once or max. a second dose after one week) or daily oral iron substitution with Ferro Sanol Duodenal (according to SmPC and with allowed adjustment to the highest tolerable dosage, 28-35 days after BL) in a 2:2:1 distribution. The Ferinject group was closed after samples of the first 35 patients in each i.v. treatment group were collected for short term safety analysis. **Table 1 Feramyl dosage and batches**

Active substance	Polyglucoferron
Dosage form	solution
Single dose	Dependent on weight and Hb concentration (500 –

	2000 mg)
Duration of treatment	once
Mode of application	i.v.
Batch number:	IRON03/202148 IRON03/201939 IRON03/201930 IRON03/201829

Table 2: Ferro Sanol Duodenal dosage and batches

Active substance	Ferrous glycine sulphate
Dosage form	capsules
Single dose	1-4 capsules (50 -200 mg) daily
Duration of treatment	28-35 days
Mode of application	oral
Batch number:	9972401 7619001

Table 3: Ferinject dosage and batches

Active substance	Ferric Carboxymaltose
Dosage form	solution
Single dose	Dependent on weight and Hb concentration (500 – 2000 mg, max. single dose of 1000 mg)
Duration of treatment	Once (a second administration was allowed)
Mode of application	i.v.
Batch number	9802012EA 9901012EA 9950012EA 8813012AA 7881012AA 675201YA

Criteria for evaluation (as stated and planned in the protocol and SAP)

Analyses sets

Participants with confirmed and documented non-anaemic iron deficiency (ID) before surgery who develop anaemia within 12 to 72h after start of surgery and with confirmation at baseline, were included in the trial.

While not defined in the study protocol, all randomized participants were used to assess subject disposition from the defined analyses sets and to list participants excluded from analysis.

Modified Intent-to-Treat Population (mITT)

The modified Intent-to-treat population (mITT) is defined to include all participants who received at least one dose of study medication and where

	the laboratory values were measured at least once under study medication. This population will be the basis for confirmatory testing. Participants who violated the definitions for allogenic red blood cell transfusion were analysed within the mITT population (see 4.4). The **mITT safety subset** of 70 eligible participants samples included in the primary short-term safety analysis was used for the confirmatory interims analysis. **Per Protocol Population (PP)** The per protocol population is defined to include the modified intent-to treat population excluding those participants with major protocol violations occurring up to visit 4. Specific reasons for warranting exclusion were agreed upon in the data review meeting (DRM) and documented in the data review meeting minutes and possibly in a statistical analysis plan prior to the closing of the database. Not all protocol deviators and violators were necessarily excluded from the per protocol population. As a result, not all patients with a major protocol deviation (PD) may have been excluded from the PP set if the PD did not affect the statistical analysis and interpretation as agreed upon in the DRM. Patients with several minor PDs may have been excluded from the PP set, if the degree of deviation was too large to ensure "per protocol behaviour". **Safety Population (SAS)** The safety population is defined to include all participants who received at least one dose, or any part of one dose, of the study medication. This population was the basis for the general safety analysis. For the primary safety analysis, the first 35 participants in the i.v. arms were utilised, corresponding to all participants who were randomized at the time of interim analyses. This set is a subset of the safety set and also a subset of the mITT. <u>Endpoints:</u> <u>Co-primary endpoints:</u> 1. Proportion of participants who achieve normalized Hb-levels (according to WHO definition) (1) or increased Hb-level by at least 1.5 g/dl at visit 4 compared to BL. 2. Pre-post difference of volume-corrected urine iron levels measured before and after i.v. iron administration (in the first urine after the end of i.v. administration) in the first 35 participants included in each i.v. treatment arms, eligible for analysis. Volume corrected iron urine is defined as the ratio between urine iron and urine creatinine. <u>Secondary and explorative efficacy endpoints:</u> • Proportion of participants who achieve normalized Hb-levels (according to WHO definition) • Absolute levels and changes to BL of Hb, TSAT, s-iron, s-transferrin, s-ferritin and s-phosphate at V4 • Proportion of units of allogenic red blood cell transfusion from BL until visit 4 (rules for RBC transfusion as described in 4.4) • Proportion of participants in need of allogenic red blood cell transfusions (i.e., who received RBC transfusions at least once) from BL until V4.

	• SF-36 composite scores for physical and mental health (derived) and SF-36 domain scores (derived).
	
	<u>Secondary and explorative safety endpoints:</u>
	<u>Adverse Events</u>
	• Overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs until 30 days after last IMP administration
	• AEs related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions
	• All-cause mortality until visit 4 - The number of deaths would have been summarized by phase and treatment group (no deaths occurred)
	• Outcome of and actions taken for AE
	
	<u>Length of hospital stay</u>
	• Length of hospital stay: The mean number of hospital days will be displayed by treatment group at visit 4.
	
	<u>Laboratory</u>
	• Mean change in s-phosphate from BL to visit 4 (for i.v. groups only)
	• Total iron in plasma levels at BL (only for i.v. groups (safety analysis group)) as the mean levels of total iron in plasma will be displayed by treatment group at BL (only for the i.v. groups in the safety analysis)
	• Absolute levels and changes to BL in other laboratory parameters at all available visits.
	  o Haemoglobin (Hb), haematocrit, red blood cell count, white blood cell count and thrombocytes (measured at BL (V2) and visit 4).
	  o Blood chemistry (measured at central laboratory): CRP, urea nitrogen, ALT, AST, GGT and serum creatinine (measured at BL (V2) and visit 4).
	• Listing of abnormal laboratory values
	
	<u>Other safety assessments</u>
	• Vital signs (pulse, blood pressure (syst. and diast.), temperature)
	• Physical examinations
	• Extent of exposure / drug application resp. intake
	• WOCBP and pregnancies (no pregnancies occurred)
	
	<u>Other</u>:
	• Subject disposition (drop-outs)
	• Assessments of demographics, medical history, concomitant medication, concomitant diseases
	• Compliance of drug intake

Statistical methods	<u>Primary efficacy analysis:</u> 1) Primary aim was to demonstrate superiority of i.v. iron substitution with Feramyl compared to oral iron therapy with Ferro Sanol Duodenal in focus on proportion of patients who achieve normalized Hb-levels (according to

	WHO definition) or at least increased Hb with 1.5 g/dl at visit 4 compared to BL. The patients who achieve normalized Hb-levels (according to WHO definition) or at least an increased Hb of 1.5 g/dl at visit 4 compared to BL were displayed by treatment group. Rates of achieving normalized Hb-levels or an increased Hb of at least 1.5 g/dl at V4 compared to baseline was compared with a two-sided chi-square test at a significance level of alpha=5%. The mITT population was used for confirmatory efficacy analysis. For sensitivity purposes, the analysis was additionally performed with the per protocol set. Sensitivity analysis using missing value imputation, which have been described in SAP, were not required as Hb values are available for all patients allocated to mITT population. <u>Primary short-term safety analysis (at interims analysis):</u> 2) Primary aim was also to demonstrate superiority in short term safety assessed by statistically lower levels of volume corrected iron in urine measured by the pre-post difference in v.c. urine iron obtained before and after i.v. administration (first urine after the end of i.v. administration) of Feramyl i.v. compared to Ferinject i.v. (E(treat-diff) = E(iron-diffPOLY) – E(iron-diffFC); with iron-diff = Fe/CrAFTER – Fe/CrPRE). The pre-post difference of v.c. urine iron measured before and in the first urine after the end of i.v. study medication administration was displayed by treatment group (for the first 35 patients in each i.v. group, eligible for analysis). The pre-post difference in v.c. urine iron levels was compared between treatments with a two-sided nonparametric Wilcoxon-Mann-Whitney U test with significance level alpha=5%. The mITT safety subset was the basis for hypothesis testing. We expected that missing values did not have to be accounted as laboratory assessments will be performed only on eligibility testing samples. Handling of values below the LOQ was described in the interim analysis (IA) SAP. <u>Secondary Efficacy Analysis</u> Secondary endpoints were compared between the treatment groups with appropriate tests (chi-square test or exact Fisher test for categorial variables, t-test or rank-tests for continuous variables). All tests were two-sided using a significance level of alpha=5%. Efficacy comparison were performed between all treatment groups, with a focus on the comparison of Feramyl and Ferro Sanol Duodenal. Rates and 95% confidence intervals as well as mean and standard deviation or median and interquartile range was given. Subgroup analyses was performed for primary and selected secondary efficacy analyses by centres, sex, age class and need for allogenic red blood cell transfusion (RBC) stratified by treatment. The mITT population was the basis for all efficacy analyses. Multiple imputation method (accounting for missing data) was not required, as Hb levels are available for all patients allocated to mITT population. Therefore, all efficacy analysis has been done with observed case data and sensitivity analysis were performed for the PP set. **Safety Analysis** All safety analyses were performed for the safety population (unless specified for specific subgroups, see co-primary short-term safety analysis). General safety and tolerability of IMP were assessed by adverse events, laboratory values, extent of exposure, pregnancies, vital signs and physical

	examination was described for safety assessment. Summary statistics have been produced for all safety assessments. Short term safety (interims analysis) is focused on comparison between i.v. groups (Feramyl vs. Ferinject). Safety was compared between all treatment groups as stated in the SAP. All analyses were of explorative nature. For the comparison of treatment groups, a significance level of 5% was used, unless stated otherwise, all test were performed in a 2-sided manner. A detailed description of all planned statistical methods is given in the study SAP and Interims-SAP.
Efficacy Conclusion	The primary aim to demonstrate superiority of i.v. iron substitution with Feramyl compared to oral iron therapy with Ferro Sanol Duodenal in focus on proportion of patients with normalized Hb-levels or increased Hb with at least 1.5 g/dl at visit 4 compared to baseline was not met. However, regarding achievement of Hb level increase of at least 1.5 g/dl at visit 4 was reached more frequently with Feramyl, and the treatment difference of i.v. iron substitution with Feramyl and oral iron (Ferro Sanol Duodenal) was statistically significant. The comparison of normalization of Hb levels at day 30 between two i.v. treatments, namely Feramyl and Ferinject, and a single oral treatment, Ferro Sanol Duodenal demonstrated that normalization was most frequently achieved in the Feramyl group (64.6%, 42/65), followed by the Ferinject group (59.4%, 19/32) and finally the Ferro Sanol Duodenal group (48.5%, 16/33). However, statistical analysis did not result in any significant difference between treatment groups. Treatment difference for median change from baseline until visit 4 in haematologic and serologic iron parameters were statistically significant between all three treatment groups (Kruskal-Wallis Test) and also for pairwise comparison (Wilcoxon Test) of Feramyl and Ferro Sanol Duodenal. Mean change from baseline to V4 was greater for i.v. treatment groups (Feramyl and Ferinject) compared to oral iron substitution (Ferro Sanol Duodenal). Statistical pairwise comparison (Wilcoxon Test) of median changes in hematologic and serologic parameters from baseline to V4 resulted in significant differences for all parameters (haemoglobulin, iron, ferritin, transferritin and sat. transferritin) between Ferro Sanol and Feramyl, and for all parameters except iron between Ferro Sanol and Ferinject. Pairwise treatment comparison (Wilcoxon-Test) of i.v. treatment groups (Feramyl and Ferinject) did not show any significant differences in changes from baseline to V4 for haemoglobulin, ferritin and transferritin levels, while change of iron and transferrin saturation was significantly different, with higher changes from baseline to V4 in the Feramyl group. In total, 12% (16/130) of the overall study population needed an allogenic RBC transfusion at any visit. The majority of patients requiring an RBC transfusion were observed within the Feramyl group. No statistically significant differences could be shown between treatment groups with regard to RBC transfusion need. Mean number of sum of units of RBC transfusions after baseline until day 30 (V4) revealed similar results for Feramyl (0.25; maximum: 3) and Ferinject (0.22, maximum: 4), and lower

	mean number of units of RBC transfusions for Ferro Sanol Duodenal (0.09, maximum: 1). Treatment effect on quality of life, assessed by questionnaire (SF-36) at baseline and day 30 (V4) showed no significant differences between treatment groups for both, Mental Health Composite Score (MCS) and Physical Health Composite Score (PCS). Changes of PCS and MCS were only minor. The PCS from baseline to V4 was similarly increased for Ferro Sanol Duodenal and Ferinject and decreased for Feramyl. Change of mean MCS from baseline to V4 was negative for all treatment groups, with the strongest reduction for Ferro Sanol and the lowest change for Feramyl. Median duration of hospitalization after surgery until day 30 (V4) (or early termination visit) was found to be similar across all treatment groups, with a slightly longer period for the Ferinject group (Feramyl: 8.0 days vs. Ferro Sanol Duodenal: 8.0 days vs. Ferinject: 8.5 days). Slightly more male patients in the Feramyl group achieved the primary endpoint compared to female patients. Contrary results were observed for the other treatment groups.
Safety Conclusions	**Interim's analysis** The interim analyses validated our assumption on preliminary safety effects with regard to Feramyl by demonstrating a smaller pre-post i.v. difference in volume-corrected (v.c.) urine iron, which here corresponds to less post i.v. v.c. urine iron II after administration than for Ferinject. Overall, the Feramyl patients showed an inflation of v.c. urine iron levels of zero (below the limit of quantification) after IMP administration, which indicates a better absorption of iron through i.v. intake in the Feramyl group compared to the Ferinject group. The European Medicines Agency (EMA) has classified free iron as a surrogate marker for toxicity measurement. Therefore, a lower concentration of urine iron levels may indicate a lower toxicity. **Final study analysis** Feramyl was administered once, thus treatment compliance was 100%. For Ferinject, the majority of patients required a second administration (91.9%, 34/37), of which for about a quarter (N=8/34) no information about the second IMP administration is available, resulting in a treatment compliance for Ferinject of 78.4% (29/37 patients). For Ferro Sanol Duodenal, treatment compliance was reported in 100% of patients. Complications during administration were reported in two cases (2.8%, 2/72) for Feramyl, while the majority of patients (97.2%, 70/72) exhibited good tolerance to the infusion. For Ferinject, the rate of complication at infusion was strongly increased for the second administration (29.7%, 11/37) compared to initial administration at baseline (2.7%, 1/37). These findings highlight the benefits of a single i.v. administration of IMP compared to multiple administrations. At least one AE occurred in 102 patients (102/146, 69.86%) during the course of the study. In total 449 adverse events were observed based on the safety set, whereof 34 (34/449, 7.6%) were serious adverse events (SAE) reported for 22 patients (22/146, 15.07%).

	AEs were observed less frequently in patients treated with Feramyl (42/72, 58.3%), followed by patients treated with Ferinject (28/37, 75.7%) and most frequently in patients treated with Ferro Sanol Duodenal (32/37, 86.5%). The comparison of treatments revealed that a significantly lower proportion of patients treated with Feramyl reported adverse events (AE) in contrast to Ferro Sanol Duodenal. The most common observed AEs by system organ class (SOC) were "Gastrointestinal disorders", occurring most prevalent in Ferrosanol Duodenal (Ferrosanol Duodenal: 51 events in 24/37 patients (64.9%) vs. Ferinject: 28 events in 14/37 patients (37.8%) vs. Feramyl: 33 events in 20/72 patients (27.8%). The second most common AE type by patient and SOC were "Respiratory, thoracic and mediastinal disorders" (Ferrosanol Duodenal: 12 events in 7/37 patients (18.9%) vs. Ferinject: 13 events in 8/37 patients (21.6%) vs. Feramyl: 23 events in 15/72 patients (20.8%). For Feramyl, the most common reported AEs were within the SOC "Gastrointestinal disorders" at a rate of 27.8% (n=20/72), which was still less than what was reported for this SOC in the other treatment groups (Ferro Sanol: 64.9%; Ferinject: 37.8%). With regard to the severity of adverse events, Ferinject treatment was associated with the highest proportion of severe AEs (33 events in 12 patients (32.4%, 12/37) compared to 14 severe AEs in 7 patients (18.9%, 7/37) in Ferro Sanol Duodenal group and 22 severe AEs in 10 patients (13.9%, 10/72) in Feramyl group. At study end, 75 AEs were ongoing in 30 patients in the Feramyl (30/72; 41.7%) group and 43 AEs were ongoing in 17 patients in the Ferinject (17/37; 45.9%) groups, while in the Ferro Sanol Duodenal treatment group only 14 AEs in 10 patients were ongoing (10/37; 27.0%). Most AEs in all treatment groups were considered unlikely related to treatment. A total of 18 events in 15 patients were considered to be certainly related to treatment. The frequency of patients with certain related adverse events (AEs) reported for Feramyl (5/72, 6.9%) and Ferinject (3/37, 8.1%) was approximately equal, while a greater number of patients in the Ferro Sanol Duodenal group (7/37, 18.9%) reported those. As per SAP, AEs of special interest (AESIs) were injection/infusion site reactions and hypersensitivity reactions only applicable within the i.v. groups Feramyl and Ferinject. AESIs were reported for nine events in seven patients, in particular three events in two patients (2.8%, 2/72) of the Feramyl group and six events in five patients (13.5%, 5/37) patients of the Ferinject group. None of the AESIs were serious AEs. A total of 34 SAEs in 22 patients were distributed evenly among patients in all three treatment groups (Feramyl: 15.3% (11/72) vs Ferro Sanol Duodenal: 13.5% (5/37) vs. Ferinject: 16.2% (6/37)). No SAE was considered related to study treatment. Iron in plasma was measured in Feramyl and Ferinject directly after i.v. administration. Iron levels were significantly higher for the Feramyl (371.3 µg/mL) than for Ferinject (240.1 µg/mL), but were also more rapidly reduced

	by Feramyl than by Ferinject as shown by second measurement for samples that were collected after first urine was sampled (Feramyl: 202.2 µg/ml; Ferinject: 221.7 µg/ml). Transient hypophosphatemia is known to be a common AE after treatment of iron deficiency anaemia with Ferinject. Measurement of phosphate in serum was done at baseline and V4 and showed an increase in median phosphate levels from BL until V4 (positive change) within the Feramyl group, while the Ferinject group showed a decrease in median phosphate levels from BL until V4 (negative change). The treatment difference for Feramyl vs. Ferinject in median change from BL was statistically significant. Overall, the safety evaluation showed that Feramyl is generally well tolerated, changes in serum phosphate after 30 days is more beneficial than for Ferinject and one-time administration is more advantageous in regards of treatment compliance.
Overall Conclusion	The co-primary aim to demonstrate the superiority of i.v. iron substitution with Feramyl compared to oral iron substitution with Ferro Sanol Duodenal in increasing Hb levels by at least 1.5g/dl or proportion of patients with normalized Hb levels was not met. The treatment difference between Feramyl and oral iron (Ferro Sanol Duodenal) for achieving an Hb level increase of at least 1.5 g/dl at visit 4, was statistically significant. Thus, Feramyl was more effective in achieving Hb level increase of at least 1.5 g/dl over a 30-day period compared to Ferro Sanol Duodenal. Normalization of Hb levels at day 30 were most frequently achieved in the Feramyl group compared to the other treatments, however, statistical analysis did not reveal any significant difference. In addition, over the period of 30 days, Feramyl increases haematologic and serologic levels (haemoglobulin, s-iron, s-ferritin and transferritin saturation) at least as well as Ferinject and more effectively than Ferro Sanol Duodenal. The single-dose regimen has been demonstrated to be both convenient and safe, thereby enhancing treatment compliance compared to multiple dosing regimens. The safety profile of Feramyl is comparable to Ferinject, and even superior to Ferro Sanol Duodenal. Frequency of observed infections was comparable between i.v. treatments and only slightly higher than for the oral treatment with Ferro Sanol Duodenal. No considerable differences were evident among the treatment groups with respect to the RBC transfusion rate and volume, length of hospital stay and quality of life assessment.
Report date:	14.05.2025