Clinical Study Report Synopsis

1 TITLE PAGE

Study title:	Randomised, open lable, active controlled clinical trial to demonstrate safety and efficacy of an i.v. administration of Polyglucoferron compared to i.v. Ferric Carboxymaltose and oral iron substitution in preoperative treatment of iron deficiency anaemia in patients with elective noncardiac surgery (IDA I)
Investigational product:	Polyglucoferron Ferric Carboxymaltose Ferrous sulfate
Indication studied / study population:	Patients with iron deficiency anaemia (IDA) prior to elective non-cardiac surgery who need fast replenishment of iron as judged by the treating physician, e.g. when it is not appropriate to postpone surgery.
Study Design:	Randomised, active-controlled, open-labelled, parallel group, multicentre study to demonstrate superiority of Polyglucoferron i.v. compared to oral iron substitution for the treatment of iron deficient anaemic patients who need fast replenishment of iron stores as judged by the treating physician, e.g. if it is not appropriate to postpone surgery, before elective non-cardiac surgery and superiority of Polyglucoferron i.v. vs Ferric Carboxymaltose in short term safety monitoring
Sponsor:	Fraunhofer Gesellschaft for its Institute for Translational Medicine and Pharmacology (ITMP), Prof. Dr. med. Dr. rer. nat. Gerd Geisslinger, Theodor-Stern-Kai 7, 60596 Frankfurt a.M., Germany
Representative of the Sponsor / Coordinating investigator:	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
Protocol code:	TMP-0916_02
EudraCT-No.:	2017-003416-38
Phase:	IIIa
Study initiation date:	First site initiated: 05.02.2019 // 0 patients enrolled
Study completion date:	Closure date of last site: 28.07.2022 (0 patients enrolled)
Responsible medical officer:	Dr. med. Michaela Köhm Fraunhofer Institute for Translational Medicine and Pharmacology ITMP and Department of Rheumatology University Hospital, Goethe–University Frankfurt, Germany Theodor-Stern-Kai 7, 60590 Frankfurt/Main, Germany Phone: +49 (0)69-6301-7302 Fax: +49 (0)241-6085 50040

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Responsible for the study report / sponsor's contact person:	Dr. Tanja Roßmanith Fraunhofer Institute for Translational Medicine and Pharmacology ITMP Theodor-Stern-Kai 7, 60596 Frankfurt/Main, Germany Phone: +49 (0)69 6301-80208 Fax: +49 (0)241-6085 50040 E-Mail: Tanja.Rossmanith@itmp.fraunhofer.de
Report date:	21.07.2023

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 Gesellschaft for its Institute Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Institute Management: Prof. Dr. med. Dr. rer. nat. Gerd Geisslinger, Theodor-Stern-Kai 7, D-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 of 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)	Ferinject Ferramyl Ferro Sanol mite
Active Ingredient	Polyglucoferron Ferric Carboxymaltose Ferrous sulfate
Title of Study	Randomised, open lable, active controlled clinical trial to demonstrate safety and efficacy of an i.v. administration of Polyglucoferron compared to i.v. Ferric Carboxymaltose and oral iron substitution in preoperative treatment of iron deficiency anaemia in patients with elective noncardiac surgery (IDA I)
Design	Phase IIIa, parallel, 3-arm (including stratification), randomized, multi-centre, open label, interventional trial
Coordinating Investigator	Prof. Dr. med. Dr. Kai Zacharowski, FRCA Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Germany D-60590 Frankfurt / Main, Phone: +49 (0)69-6301-5998 Email: Kai.Zacharowski@kgu.de
Study sites and location	Multicentre Study (2 centres) Prof. Dr. med. Dr. Kai Zacharowski, FRCA Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Germany

	D-60590 Frankfurt / Main, Phone: +49 (0)69-6301-5998 Email: Kai.Zacharowski@kgu.de Prof. Dr. med. David Baron Medizinische Universität Wien (MUW) Universitätsklinik für Anästhesie, Allgemeine Intensivmedizin und Schmerztherapie Klinische Abteilung für Allgemeine Anästhesie und Intensivmedizin Tel.: +43 1 40400 41030 Währinger Gürtel 18-20 1090 Wien, Österreich
Publication (reference)	Not applicable
Studied Period	5 years First patient in: not applicable Last patient out: not applicable Study end: 28.07.2022 (closure date last study site)
Phase of study	IIIb
Primary objective	1) To demonstrate superiority of i.v. iron substitution with Polyglucoferron compared to oral iron therapy with Ferrous sulfate in focus on proportion of patients who achieve normalized Hb-levels (according to WHO definition) or an increased Hb-level of at least 1.5 g/dl at day before surgery compared to BL 2) To demonstrate superiority in short term safety assessed by measurements of statistically significant lower levels of urine iron after i.v. administration of Polyglucoferron compared to Ferric Carboxymaltose, measured in the first urine after the end of i.v. administration
Secondary objectives	Secondary objectives for efficacy (assessment for and comparison between all groups) Assessment of: - The need of allogenic red blood cell transfusion (number of units andnumber of patients receiving red blood cell transfusion) from BL until 28 days after surgery (visit 5) (rules for RBC transfusion as described in 4.4) - Treatment effects on change in haematologic and serologic iron parameters (Hb, TSAT, s-iron, s-ferritin, s-transferrin) from baseline (BL) until day before surgery (=visit 4) and visit 5 Secondary objectives for safety (assessment for and comparison between all groups) - Overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs until 28 days after surgery - Changes in laboratory parameters, vital signs, and physical exam on each visit including blood pressure and heart rate - Aes related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions - All-cause mortality within 28 days after surgery Exploratory objectives (assessment for and comparison between all groups): - Treatment effect on change in Quality of Life (SF36) at visits 4 and 5 compared to BL

	- Duration of hospital stay (days) until 28 days after surgery - Number of patients with normalized Hb-values after iron substitution (n, %) at visits 4 and 5 - Analysis of total iron levels in plasma at BL after end of iron administration (for the i.v. groups (safety analysis group) only)
Methodology	It was planned that patients will be recruited from those scheduled for elective surgery. Those patients with identified IDA within 28 to 42 days before surgery and need of fast replenishment of iron stores as judged by the treating physician (e.g., if it is not appropriate to postpone surgery) should have been supplemented with iron, starting 28-35 days before surgery. Patients were planned to be randomised either to receive Ferric Carboxymaltose i.v. (according to SmPC adjusted to Hb-level and weight), Polyglucoferron i.v. once (according to IB adjusted to Hb-level and weight) or oral iron substitution with Ferrous sulfate (according to SmPC and with allowed adjustment to the highest tolerable dose with a minimum of 50mg every 48h) in a 2:2:1 distribution. No patient was able to be screened /enrolled into this clinical study.
Number of patients (planned and analysed)	Planned sample size: 407 Number of patients screened: 0 Randomized patients: 0 Analysed: 0 Drop-outs: 0 Screening failures: 0
Diagnosis and main criteria for inclusion	Patients with iron deficiency (defined as s-ferritin <100 ng/mL and s-transferrin saturation <20%) and relevant anaemia (defined as haemoglobin of <12 g/dL for female and <13 g/dL for men) who need fast replenishment of iron stores within 28 to 42 day before a planned elective non-cardiac surgery were should have been included into this study. Unfortunately, it was not possible to recruit any patient into this clinical trial as patients do not see their physicians within 28 to 42 days before a planned elective non-cardiac surgery.
Test product, dose and mode of administration, batch number, duration of treatment:	In this study, three IMPs were differentiated: Open label IMP: Feramyl (Polyglucoferron) Open label IMP: Ferinject (Ferric Carboxymaltose) Open label IMP: Ferro Sanol Duodenal (Ferrous sulfate) Each patient was randomized in either Feramyl or Ferinject or Ferro Sanol Duodenal (2:2:1). After first 35 patients are randomized in Feramyl group and first 35 patients are randomized in Ferinject group an interim analysis will be performed an the Ferinject group is plnned to be closed. Randomisation will be done afterwards 2:1 for Feramyl : Ferro Sanol.

Table 1: Feramyl dosage and batches

Active Substance	Polyglucoferron
Dosage form	solution
Single Dose	Dependent on Hb value and weight 500 mg – 2000 mg
Duration of treatment	once
Mode of application	i.v.
Batch number:	0 patients were included in this study; no IMP Batch was allocated to a patient

Table 2: Frrinject dosage and batches

Active Substance	Ferric Carboxymaltose
Dosage form	solution
Single Dose	Dependent on Hb value and weight 500 mg- 2000 mg
Duration of treatment	Max. single dose of 1000 mg per week
Mode of application	i.v.
Batch number:	0 patients were included in this study; no IMP Batch was allocated to a patient

Table 3: Ferro Sanol Dudenal dosage and batches

Active Substance	Ferrous sulfate
Dosage form	tablets
Single Dose	Max. tolerable dose 50 mg – 200 mg
Duration of treatment	28 to 35 days
Mode of application	oral
Batch number:	0 patients were included in this study; no IMP Batch was allocated to a patient

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

Primary efficacy analysis:

- normalized Hb-levels (according to WHO definition) or an increased Hb of at least 1.5 g/dl at day before surgery (visit 4) compared to BL
- levels of iron urine after i.v. iron administration in the first urine after the end of i.v. administration in the first 35 patients included in the i.v. treatment arms, eligible for analysis

Secondary efficacy analyses

- The following set of secondary variables will be presented (assessment for and comparison between all groups):

Assessment of:

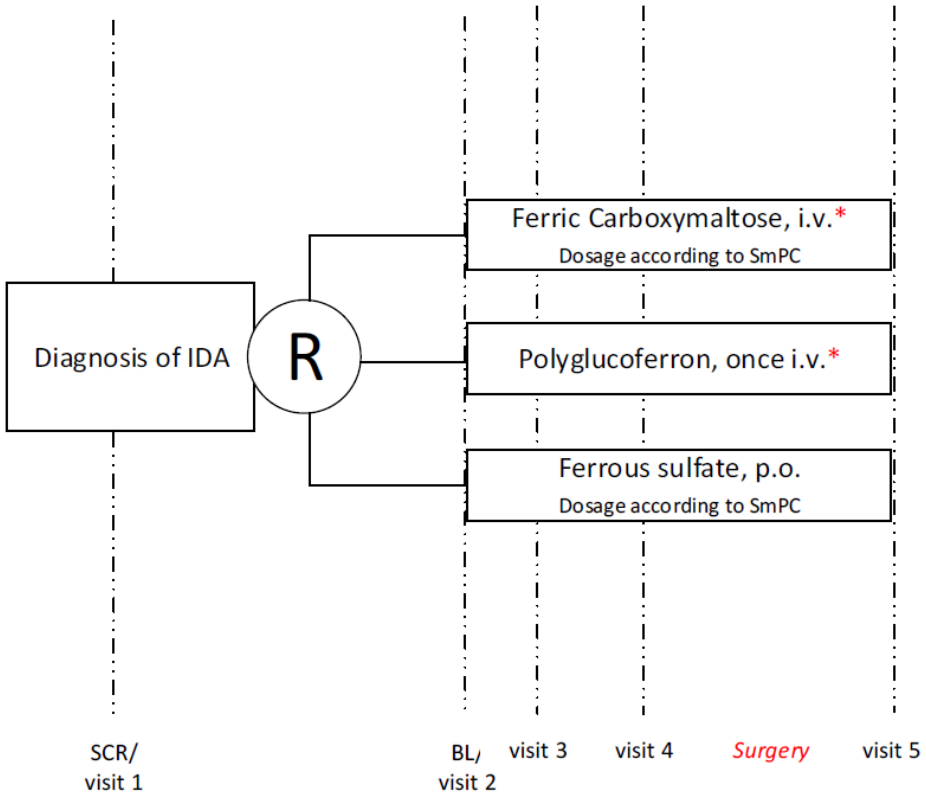
- The need of allogenic red blood cell transfusion (number of units and number of patients receiving red blood cell transfusion) from BL until 28 days after surgery (visit 4)

	• Treatment effects on change in haematologic and serologic iron parameters (Hb, TSAT, siron, s-ferritin, s-transferrin) from baseline (BL) until day before surgery (visit 4) and V5 - Secondary variables for safety (assessment for and comparison between all groups): • Overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs until 28 days after surgery • Changes in laboratory parameters, vital signs, and physical exam on each visit including blood pressure and heart rate • AEs related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions • All-cause mortality within 28 days after surgery - Exploratory variables (assessment for and comparison between all groups): • Treatment effect on change in Quality of Life (SF36) at visits 4 and 5 compared to BL • Duration of hospital stay (days) until 28 days after surgery • Number of patients with normalized Hb-values after iron substitution (n, %) at V4 and V5 • Analysis of total iron levels in plasma at BL after end of iron administration (for the i.v. groups (safety analysis group) only) The mITT population will be the basis for other efficacy analyses accounting for missing data using LOCF. As sensitivity analysis observed case analysis on the mITT will be performed. Interim Analysis: After inclusion of the first 35 eligible patients of each i.v. treatment arm, analysis of urine iron will be performed for the first urine after the end of administration for assessment of urine iron levels (co-primary safety endpoint). If the co-primary safety endpoint is achieved, the Ferric Carboxymaltose treatment arm will be closed and randomisation will be continued for the Polyglucoferron and oral iron treatment arm for efficacy assessment (co-primary efficacy endpoint). If the result for the co-primary safety endpoint is negative or any safety relevant issues occur, a data safety monitoring board will advise about study continuation.
Statistical methods	<u>Primary efficacy analysis:</u> 1) Primary aim is to demonstrate superiority of i.v. iron substitution with Polyglucoferron compared to oral iron therapy in focus on proportion of patients who achieve normalized Hb-levels (according to WHO definition) or an increased Hb of at least 1.5 g/dl at day before surgery compared to baseline. The patients who achieve normalized Hb-levels (according to WHO definition) or an increased Hb of at least 1.5 g/dl at day before surgery compared to BL will be displayed by treatment group at day before surgery. Rates of achieving normalized Hb-levels or an increased Hb of at least 1.5 g/dl at the day before surgery compared to baseline will be compared with a two-sided chi-square test at a significance level of alpha=5%. The mITT population will be used for confirmatory efficacy analysis. For sensitivity purposes, the

	analysis will be additionally performed with the safety analysis set using missing value imputation and with the mITT population without using missing value imputation. 2) Primary aim is also to demonstrate superiority in short term safety assessed by statically lower levels of iron in urine after the i.v. administration of Polyglucoferron i.v. compared to Ferric Carboxymaltose i.v. measured in the first urine after the end of i.v. administration. The levels of urine iron in the first urine after the end of i.v. product administration will be displayed by treatment group at BL (for the first 35 patients in each i.v. group, eligible for analysis). Iron urine levels will be compared with a two-sided nonparametric Wilcoxon-Mann-Whitney U test with significance level alpha=5%. For the second confirmatory analysis, all patients receiving at least part of the i.v. product and available iron in urine levels will be analysed. For sensitivity purposes, the analysis will be additionally performed with the safety analysis set using missing value imputation and with the mITT population without using missing value imputation. <u>Secondary efficacy analyses (assessment for and comparison between all groups):</u> Secondary endpoints will be compared between the groups with appropriate tests (chi-square test or exact Fisher test for categorial variables, t-test or rank-tests for continuous variables). All tests will be two-sided using a significance level of alpha=5%. Rates and 95% confidence intervals as well mean and standard deviation or median and interquartile range will be given. - Number of units of allogenic red blood cell transfusions until visit 5 Mean number of units of allogenic red blood cell transfusions will be displayed by treatment until visit 5. - Number of patients who receive allogenic red blood cell transfusions until visit 5 Mean number of patients of allogenic red blood cell transfusions will be displayed by treatment group until visit 5. - Mean change in haematologic and serologic iron parameters (Hb, TSAT, s-iron, stransferrin, and s-ferritin) from BL to day before surgery (visit 4) and V5 The mean change in Hb, TSAT, s-iron, s-transferrin, and s-ferritin values will be displayed by treatment group from BL to visits 4 and 5. <u>Secondary safety analysis (assessment for and comparison between all groups):</u> - Overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs until 28 days after surgery Summary statistics for overall tolerability and number, incidence, seriousness, severity, and relationship of AEs/SAEs will be displayed by treatment group until 28 days after surgery. - Changes in laboratory parameters, vital signs, and physical exam on each visit including blood pressure and heart rate

	Summary statistics for changes in laboratory parameters, vital signs, and physical exam on each visit including blood pressure and heart rate will be displayed until 28 days after surgery. - AEs related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions Summary statistics for AEs related to injection/infusion site reactions (i.v. groups only) and hypersensitivity reactions will be displayed. - All cause mortality within 28 days after surgery Summary statistics for all cause mortality will be displayed until 28 days after surgery. <u>Other efficacy analyses (assessment for and comparison between all groups):</u> - Treatment effect on change in QoL (SF36) as indicated in flowchart Summary statistics for the change in QoL (SF36) will be displayed by treatment group at visits 4 and 5 compared to BL. - Duration of hospital stay (days) until 28 days after surgery The mean number of hospital stay (days) until 28 days after surgery will be displayed by treatment group at visit 5. - Number of patients with normalized Hb-values after iron substitution (n, %) at visits 4 and 5 The mean number of patients with normalized Hb-values will be displayed by treatment group at visits 4 and 5. - Total iron in plasma levels at BL (only for i.v. groups (safety analysis group)) The mean levels of total iron in plasma will be displayed by treatment group at BL (only for the i.v. groups (safety analysis group))
Efficacy Conclusion	As no patient could be enrolled into this clinical trial no analysis of efficacy data could be peformed.
Safety Conclusions	No safety data could be analysed as no patient was enrolled into this trial.
Overall Conclusion	During the study the protocol was amended to adopt the study population. This did not lead to the inclusion of a patient. The major obstacle was, that the comparator IMP Ferro Sanol Duodenal needs to be taken around four weeks before the planned surgery to improve the Hb value. However, that was not feasible, because patients are not seen by their physicians that long before their planned surgery.
Report date:	21.07.2023

Flowchart – Study Design



**Co-primary safety endpoint: Interims Safety Analysis with evaluation in the Polyglucoferron and Ferric Carboxymaltose treatment arm after the first 35 patients in each i.v. arm (with delay for inclusion for co-primary efficacy endpoint until analysis is performed); if primary safety endpoint is not fulfilled a Data Safety Monitoring Board will advise about study continuation; 2:2:1 Randomisation (Polyglucoferron : Ferric Carboxymaltose : oral iron) will be performed until 35 eligible patients are included in both i.v. treatment arms. If co-primary safety endpoint is achieved, the Ferric Carboxymaltose arm will be closed and the study will be continued for assessment of efficacy endpoint with 2:1 distribution (Polyglucoferron i.v. : Ferrous sulfate p.o.).*

2.1.1 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

Author:

Place and Date

Dr. Tanja Roßmanith
Lead Project Manager

Author:

Place and Date

Dr. Anita Bulczak-Schadendorf
Project Manager

Statement of coordinating investigator and sponsor's representative

I have read this clinical study report and confirm that to the best of my knowledge it describes accurately the conduct and results of the study. This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996 (CPMP/ICH/135/95), the Declaration of Helsinki (revised version Declaration of Helsinki (revised version Fortaleza 2013), German Drug Law (AMG), and applicable national regulations and laws of the country in which the study was carried out.

Coordinating Investigator:

Fr, 24.07.2023

Place and Date

Prof. Dr. med. Dr. Kai Zacharowski

Sponsor's Representative:

Place and Date

Prof. Dr. med. Frank Behrens

2.1.1 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

Author:

Place and Date

Dr. Tanja Roßmanith
Lead Project Manager

Author:

Place and Date

Dr. Anita Bulczak-Schadendorf
Project Manager

Statement of coordinating investigator and sponsor's representative

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Coordinating Investigator:

25.07.23
Place and Date

Prof. Dr. med. Dr. Kai Zacharowski

Sponsor's Representative:

25.07.23
Place and Date

Prof. Dr. med. Frank Behrens

2.1.1 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement

Author:

25.7.2023 FTN
Place and Date

Dr. Tanja Roßmanith
Lead Project Manager

Author:

Place and Date

Dr. Anita Bulczak-Schadendorf
Project Manager

Statement of coordinating investigator and sponsor's representative

I have read this clinical study report and confirm that to the best of my knowledge it describes accurately the conduct and results of the study. This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996 (CPMP/ICH/135/95), the Declaration of Helsinki (revised version Declaration of Helsinki (revised version Fortaleza 2013), German Drug Law (AMG), and applicable national regulations and laws of the country in which the study was carried out.

Coordinating Investigator:

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Prof. Dr. med. Dr. Kai Zacharowski

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Author:

Place and Date	Dr. Tanja Roßmanith Lead Project Manager

Author:

Frankfurt, 24.07.2023	Anita Bulczak-Schadendorf Digital unterschrieben von Anita Bulczak-Schadendorf DN: c=DE, o=Fraunhofer, ou=ITMP, ou=People, sn=Bulczak-Schadendorf, givenName=Anita, cn=Anita Bulczak-Schadendorf Datum: 2023.07.24 11:34:33 +02'00'
Place and Date	Dr. Anita Bulczak-Schadendorf Project Manager

Statement of coordinating investigator and sponsor's representative

I have read this clinical study report and confirm that to the best of my knowledge it describes accurately the conduct and results of the study. This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996 (CPMP/ICH/135/95), the Declaration of Helsinki (revised version Declaration of Helsinki (revised version Fortaleza 2013), German Drug Law (AMG), and applicable national regulations and laws of the country in which the study was carried out.

Coordinating Investigator:

Place and Date	Prof. Dr. med. Dr. Kai Zacharowski

Sponsor's Representative:

Place and Date	Prof. Dr. med. Frank Behrens