1 TITLE PAGE

ABBREVIATED CLINICAL STUDY REPORT

Study Title:

A phase IV study to explore the safety of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with heart failure carrying Left Ventricular Assist Devices (ORION-LVAD-1)

Short title:	**OR**al **I**r**ON** supplementation with ferric maltol in patients with heart failure carrying **L**eft **V**entricular **A**ssist **D**evices (**ORION-LVAD-1)**
EudraCT number:	2016-005101-39
Protocol code number:	ORION-LVAD-1
Investigational product:	Feraccru® (ferric maltol)
Indication studied:	Patients with heart failure and left ventricular assist device and iron deficiency anemia
Study design:	Open-label, uncontrolled monocenter phase IV study
Development phase of study:	Phase IV
Study initiation date:	18.03.2019
Date of early study termination:	29.11.2019
Study completion date:	28.11.2019
Name and affiliation of principal investigator:	[redacted] Hannover Medical School Dept. of Cardiac, Thoracic, Transplantation and Vascular Surgery Carl-Neuberg-Str. 1 30625 Hannover, Germany
Sponsor:	Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover, Germany
Good Clinical Practice Statement:	This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP)

	guidelines. Essential documents will be retained in accordance with ICH GCP.
Version and date of report:	3.0 final, 09.04.2021

1.1 Signatures

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Prof. Dr. med. [redacted] Principal investigator Dept. of Cardiac, Thoracic, Transplantation and Vascular Surgery Hannover Medical School	Date
[redacted], MPH Trial statistician BREATH - **B**iomedical **R**esearch in **E**ndstage **A**nd Obs**T**ructive Lung Disease **H**annover Standort des Deutschen Zentrums für Lungenforschung Hannover Medical School	Date
Prof. Dr. med. [redacted] Sponsor representative of Hannover Medical School	Date

2 SYNOPSIS OF CLINICAL STUDY REPORT

Name of Sponsor/Company: Hannover Medical School Carl-Neuberg-Str. 1 30625 Hannover Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Feraccru® 30 mg hard capsules	Volume:	
Name of Active Ingredient: Iron (as ferric maltol)	Page:	

Title of study:

ORal **I**r**ON** supplementation with ferric maltol in patients with heart failure carrying **L**eft **V**entricular **A**ssist **D**evices (**ORION-LVAD-1)**

EudraCT no.: 2016-005101-39

Protocol code no.: ORION-LVAD-1

Information about study protocol version(s):

First submission:
Version 1.4, 17.10.2018

Subsequent substantial amendments:
n/a

Investigator(s) and study centre(s): Name(s) and address(es):

Prof. Dr. [redacted]
Hannover Medical School
Dept. of Cardiac, Thoracic, Transplantation and Vascular Surgery
Carl-Neuberg-Str. 1
30625 Hannover, Germany

Publication (reference):

None.

Studied period: 03/2019 – 11/2019 date of first enrolment: 18.03.2019 date of last completed: 28.11.2019 **Information about temporary halt(s) and premature termination of the trial:** No temporary halt	**Phase of development:** Phase IV

Premature termination on 29.11.2019	

Objectives:

Primary objective(s):

- To detect AEs and SAEs with a relative frequency of at least 11.5% in LVAD patients with iron deficiency anemia treated with oral ferric maltol for 12 weeks

Secondary objectives:

- To assess the effects of oral ferric maltol on hemoglobin levels in LVAD patients with iron deficiency anemia
- To assess the effects of oral ferric maltol on hemoglobin levels, serum ferritin, transferrin saturation, 6 min walking distance, serum NT-proBNP, right and left ventricular function (determined by echocardiography), liver and renal function and NYHA class in LVAD patients with iron deficiency anemia

Methodology:

Phase IV, open-label, uncontrolled monocenter study to explore the safety of oral ferric maltol in treating iron deficiency in patients with heart failure and left ventricular assist device.

Number of patients (planned and analysed):

Planned: 25

Analysed: 6 (patients who completed week 12)

Diagnosis and main criteria for inclusion:

Diagnosis:

Patients with iron deficiency anemia and heart failure carrying left ventricular assist devices (LVAD)

Main Inclusion criteria:

1. Signed written informed consent prior to any study-related procedure and willingness to comply with treatment and follow-up procedures
2. Male and female patients ≥18 years at day of inclusion
3. Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial
4. Patients that have an LVAD implanted for chronic heart failure and which are clinically stable for at least 6 months after LVAD implantation in the opinion of the investigator
5. 6 min walk distance >50 m
6. Mild-to-moderate iron-deficiency anemia as defined by a hemoglobin concentration ≥7 g/dl and <12 g/dl in females or ≥8 g/dl and <13 g/dl in males, and serum ferritin <100 µg/l, or 100-300 µg/l and transferrin saturation <20% at screening
7. Women of childbearing potential must:
   - Have a negative pregnancy test at screening
   - Agree to use reliable methods of contraception during the course of the study

Exclusion criteria:

1. Active hematological disorders other than iron-deficiency anemia
2. Other medical condition that according to the investigator's assessment is causing or contributing to anemia

3. Active malignancy
4. Active infectious disease
5. Active bleeding
6. Severe renal insufficiency (requiring dialysis)
7. Severe liver injury as indicated by serum aminotransferases >3 x upper limit of normal or bilirubin levels >50 µmol/l
8. Ongoing oral or intravenous iron supplementation
9. Concomitant erythropoietin medication
10. Pregnancy or lactation period
11. Subject has received any investigational medication or any investigational devices within 30 days prior to the first dose of study medication or is actively participating in any investigational drug/ devices trial, or is scheduled to receive investigational drug/devices during the course of the study.
12. Known or suspected hypersensitivity to any of the active substances or any excipients of the investigational medicinal product
13. Known haemochromatosis or other iron overload syndromes
14. Patients who have been receiving repeated (>1) blood transfusions during the past 6 months

Test product, dose and mode of administration, batch number:

Test product:	Feraccru® 30 mg hard capsules (Ferric maltol 30 mg)
Dose:	60 mg/day (one capsule twice daily, morning and evening)
Mode of administration:	oral (on an empty stomach)
Batch number(s):	B19694

Duration of treatment:

12-week treatment period followed by a 4-weeks safety follow-up period after discontinuation of study medication

Reference therapy, dose and mode of administration, batch number:

n/a

Criteria for evaluation:

Primary endpoint:

- Relative and absolute frequency of AEs and SAEs
  - n=8 of 11 included patients (73%) had a total of n=15 AEs and n=1 (9%) patient had an SAE

Secondary endpoint(s):

- Change in hemoglobin level from baseline to week 12
  - Hemoglobin level from 11.0 (±1.3) to 11.5 (±2.1) g/dl from baseline to week 12, p 0.534, Median 10.9 (9.3-12.2) to 11.3 (9.4-14.1) g/dl from baseline to week 6, Min/Max was 9.2/12.6 to 9.1/15.1 g/dl from baseline to week 12.
- Change in hemoglobin level from baseline to week 6

- Hemoglobin level from 11.0 (±1.3) to 12.1 (±1.9) g/dl from baseline to week 12, p = 0.063, Median 10.9 (9.3-12.2) to 12.2 (10.6-14) g/dl from baseline to week 6, Min/Max was 9.2/12.6 to 9.2/14.3 g/dl from baseline to week 6.

- Change in serum ferritin levels and transferrin saturation from baseline to week 6 and 12
  - Ferritin level from 28.3 ±20.1 to 41.1 (±27) µg/l for baseline to week 6, p = 0.176, Median 33 (19-67) to 41 (16-62) µg/l from baseline to week 6, Min/Max was 13/279 to 5.7/78 µg/l from baseline to week 6.
  - Ferritin level from 28.3 ±20.1 to 42.0 (±27.2) µg/l for baseline to week 12, p = 0.115, Median 33 (19-67) to 37.5 (19-61.8) µg/l from baseline to week 12, Min/Max was 13/279 to 16/88 µg/l from baseline to week 12.
  - 9.0 (±5.8) to 13 (±6.6) transferrin saturation (%) for baseline to week 6, p = 0.042, Median 8 (6-18) to 12 (9-20) % from baseline to week 12, Min/Max was 4/27 to 4/23 % from baseline to week 12.
  - 9.0 (±5.8) to 12.2 (±5.7) transferrin saturation (%) for baseline to week 12, p = 0.249, Median 8 (6-18) to 13 (6-17.5) % from baseline to week 12, Min/Max was 4/27 to 5/19 % from baseline to week 12.

- Change in 6 min walking distance from baseline to week 12
  - 295 (±158) to 429 (±150) m from baseline to week 12, p = 0.043, Median 340 (108-375) to 372 (338-551) m from baseline to week 12, Min/Max was 70/585 to 307/689 from baseline to week 12.

- Change in serum NT-proBNP from baseline to weeks 6 and 12
  - 1209 ±1162 to 805 (±586) ng/l from baseline to week 6, p = 0.674, Median 1017 (156-1862) to 861 (197-1408) ng/l from baseline to week 6, Min/Max was 85/3672 to 80/1485 ng/l from baseline to week 12.
  - 1209 ±1162 to 1374 ±1341 ng/l from baseline to week 12, p = 0.424, Median 1017 (156-1862) to 835 (215-2804) m from baseline to week 12, Min/Max was 85/3672 to 56/3986 from baseline to week 12.

- Change in echocardiographic markers of right ventricular function (right atrial area, right ventricular diameter, fractional area change, tricuspid annular plane systolic excursion) and left ventricular function (left ventricular ejection fraction, left atrial area, left ventricular diameter, fractional area change, tricuspid annular plane systolic excursion), change from baseline to week 12.
  - Right atrial area (cm^2) from 16.1 ±4.5 to 18.0 ±6.3, p = 0.684, Median 16.5 (11.4-19.3) to 17 (13-21.5) from baseline to week 12, Min/Max was 11.3/23 to 10/31 from baseline to week 12.
  - Right ventricular diameter (mm) from 40.8 ±15.7 to 41.8 ±13.7, p = 1.0, Median 36.5 (29-49.3) to 41 (33-56) from baseline to week 12, Min/Max was 25/76 to 14/58 from baseline to week 12.
  - Left ventricular ejection fraction from 20.9 ±8.3 to 19.1 ±7.4, p = 0.103, Median 15 (15-25) to 15 (15-25) from baseline to week 12, Min/Max was 15/40 to 10/30 from baseline to week 12.
  - Left atrial area (cm^2) from 25.1 ±7.1 to 23.1 ±7.3, p = 0.307, Median 23.4 (21.2-31.8) to 21 (16-25) from baseline to week 12, Min/Max was 13.4/35 to 12/36 from baseline to week 12.

- Left ventricular diameter (mm) from 61.6 ±11.1 to 62.4 ±12.5, p = 0.735, Median 62 (54.8-69.5) to 58 (55-74) from baseline to week 12, Min/Max was 38/76 to 40/80 from baseline to week 12.

- Liver: Change in Albumin, ALT, AST and Bilirubin from baseline to week 6 and 12
  - Albumin from baseline to week 6 42.1 ±3.8 to 48.4 ± 19.4, p = 1.0, Median 42 (40-44) to 41.5 (36.8-52) g/l from baseline to week 6, Min/Max was 36/49 to 35/94 from baseline to week 6.
  - Albumin from baseline to week 12 42.1 ±3.8 to 40.5 ±2.1, p = 0.414, Median 42 (40-44) to 40.5 (39.3-42.3) g/l from baseline to week 12, Min/Max was 36/49 to 37/43 from baseline to week 12.
  - ALT from baseline to week 6 26.1 ±16.6 to 21.8 ±11.3, p = 0.197, Median 21 (18-26) to 17.5 (12-33.8) U/ from baseline to week 6, Min/Max was 12/74 to 11/74 from baseline to week 6.
  - ALT from baseline to week 12 26.1 ±16.6 to 25.1 ± 21.7, p = 0.217, Median 21 (18-26) to 18 (16-20) U/l from baseline to week 12, Min/Max was 12/74 to 15/53 from baseline to week 12.
  - AST from baseline to week 6 27.1 ±11.9 to 28.5 ±8.1, p = 0.679, Median 22 (18-30) to 20 (17.5-37.5) U/ from baseline to week 6, Min/Max was 14/54 to 16/69 from baseline to week 6.
  - AST from baseline to week 12 27.1 ±11.9 to 25.1 ± 18.3, p = 1.0, Median 22 (18-30) to 23 (19-31) U/ from baseline to week 12, Min/Max was 14/54 to 14/43 from baseline to week 12.
  - Bilirubin from baseline to week 6 14.3 ±18.8 to 9.5 ± 6.0, p = 0.649, Median 8 (6-12) to 7 (5-12) µmol/l from baseline to week 6, Min/Max was 5/70 to 4.8/22 from baseline to week 6.
  - Bilirubin from baseline to week 12 14.3 ±18,8 to 12.1 ±12.5, p = 0.791, Median 8 (6-12) to 7 (5-13) µmol/l from baseline to week 12, Min/Max was 5/70 to 5/48 from baseline to week 12.

- Kidney: Change in Creatinine (+GFR) and Urea from baseline to week 6 and 12
  - Creatinine from baseline to week 6 139.5 ± 63.7 to 110.0 ± 47.5, p = 0.364, Median 140 (96-176) to 104 (71.8-161.3) µmol/l from baseline to week 6, Min/Max was 35/240 to 42/174 from baseline to week 6.
  - Creatinine from baseline to week 12 139.5 ± 63.7 to 143.5 ± 97.5, p = 0.699, Median 140 (96-176) to 123 (93-167) µmol/l from baseline to week 12, Min/Max was 35/240 to 42/405 from baseline to week 12.
  - Creatinine Clearance (eGFR) from baseline to week 6 61.2 ±42.2 to 71.6 ± 39.0, p = 0.385, Median 49 (35-77) to 61.5 (39.8-91.3) ml/min/1.73m² from baseline to week 6, Min/Max was 22/166 to 34/152 from baseline to week 6.
  - Creatinine Clearance (eGFR) from baseline to week 12 61.2 ±42.2 to 63.6 ± 39.4, p = 0.562, Median 49 (35-77) to 55 (37-81) ml/min/1.73m² from baseline to week 12, Min/Max was 22/166 to 14/153 from baseline to week 12.

- Urea from baseline to week 6 12.1 ±10.8 to 12.1 ± 10.8, p = 0.186, Median 9.6 (4.6-14.6) to 6.8 (5.4-7.7) mmol/l from baseline to week 6, Min/Max was 2.7/41.3 to 2.1/13.2 from baseline to week 6.
- Urea from baseline to week 12 12.1 ± 10.8 to 12.1 ± 15.6, p = 0.478, Median 9.6 (4.6-14.6) to 6.8 (6-10.9) mmol/l from baseline to week 12, Min/Max was 2.7/41.3 to 2.4/58 from baseline to week 12.

- Change in NYHA from baseline to week 12
  - 6 Patients with NYHA Class I to 5 (83%) NYHA Class I and 1 (17%) NYHA Class II, p = 0.296

Statistical methods:

Continuous variables are stated as mean and standard deviation, categorical variables as numbers (n) and percent (%). Comparisons of continuous parameters are assessed via paired Wilcoxon-Test and categorical variables via Chi^2-Test.

Major changes in the conduct of the study and planned analyses:

Conduct of the study:

No amendments were made to the original study protocol.

Changes to analyses:

Hence the study was aborted and only 11 of the 25 planned patients could be enrolled and n=6 patients completed week 12, the originally planned analysis was withdrawn and descriptive statistics with comparisons over time as described above have been conducted.

Summary – Conclusions:

Efficacy Results:

Hence the study was aborted (due to a low recruitment rate) no efficacy analysis has been conducted.

Safety Results:

Hence the study was aborted prematurely the safety analysis was not conducted as initially planned. Instead, safety results are presented descriptively:

The majority of patients (eight of eleven, 73%) suffered from at least one AE. Four patients (36%) experienced more than one AE. The most frequent non-serious AEs were diarrhea (4 cases, 36%), nausea (3 cases, 27%) and abdominal pain or cramps (3 cases, 27%). These gastrointestinal symptoms are well-known side effects that occur frequently with the use of ferric maltol as specified in the reference document (Fachinformation Feraccru®).

The majority of AEs (13 of 15, 87%) – all of them non-serious - were assessed by the investigator to be related to the IMP ferric maltol. The IMP application was withdrawn in five patients.

One non-serious AE and the single SAE that occurred in this trial (right ventricular failure) were assessed as not related to the IMP.

All patients recovered from all AEs, including the single SAE. No patient died during the trial.

Conclusion:

In terms of safety, the number and spectrum of adverse reactions is within the well-known safety profile of ferric maltol. Thus, no new safety signal was detected in this trial.

3 TABLE OF CONTENTS

3.1 List of figures

3.2 List of tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
CRF	Case report form
ECG	Electrocardiogram
eCRF	Electronic case report form
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
ITT	Intention-to-treat
n/a	Not applicable
NT-proBNP	N-terminale pro brain natriuretic peptide
PP	Per protocol
SAE	Serious adverse event

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

This was a prospective, open-label, uncontrolled monocenter phase IV clinical trial to explore the safety of oral iron supplementation with ferric maltol in treating iron deficiency in patients with heart failure carrying Left Ventricular Assist Devices.

Feraccru® 30 mg hard capsules were given twice daily.

The study duration per subject was approximately 18 weeks including 2 weeks screening period, 12 weeks treatment period and 4 weeks safety follow-up period after discontinuation of study medication.

Eleven patients were enrolled over a period of 8 months.
The first patient was enrolled on 18.03.2019 and the last patient was completed on 28.11.2019 (study period: 03/2019 – 11/2019). The clinical trial was prematurely terminated due to a low recruitment rate on 29.11.2019. No temporary halt took place.

In the course of the clinical trial the primary submitted and approved study protocol version 1.4 of 17.10.2018 remained unchanged throughout the clinical trial (see Appendix 15.1).

A representative sample of case report form (CRF) is presented in Appendix 15.2 and of SAE form in Appendix 15.4.

Publications:

None.

9.8 Changes in the Conduct of the Study or Planned Analyses

Changes to conduct of the study:
No amendments were made to the original study protocol (1.4 of 17.10.2018).

Changes to analyses:

Hence the study was aborted prematurely and only 11 of the 25 planned patients could be enrolled and n=6 patients completed week 12, the originally planned analysis was withdrawn and descriptive statistics with comparisons over time as described above have been conducted.

10 STUDY PATIENTS

10.1 Disposition of Patients

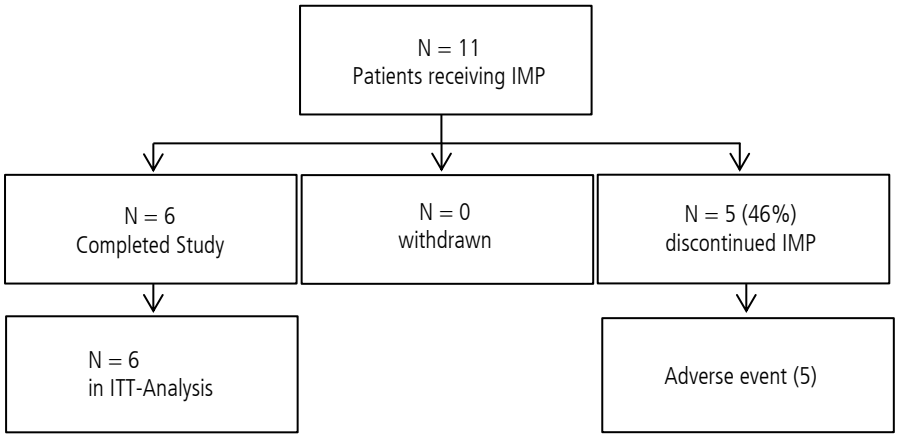

Figure 1: Patient flow chart

A listing of all discontinued patients is provided in Section 12.1.

10.2 Protocol Deviations

Table 1 gives an overview of the frequency of important study protocol deviations. For further details of protocol deviations see Appendix 15.3.

Table 1: Overview of frequency of study protocol deviations

Site	Violation of entry criteria	Violation of withdrawal criteria	Wrong treatment or incorrect dose	Excluded concomitant treatment	Other
01-MHH	1	-	-	-	4

One subject violated the entry criteria because she was included into the study due to a lab error (Exclusion criterion Bilirubin >50 umol/l violated). Four subjects violated the study protocol due to other reasons (ECG not done at baseline visit; visit at week 6 not performed; Borg test and 6 min walk test not performed at week 12 and a not immediately reported SAE).

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

N=11 patients were included and n=6 patients which concluded the study were analysed. However, hence the study was aborted prematurely a descriptive efficacy analysis has been conducted.

11.2 Demographic and Other Baseline Characteristics

N=11 patients were enrolled.

N=2 female (18%) and n=9 male (82%), median age was 55 (Q_{25}-Q_{75} = 48-60) years.

11.3 Efficacy Results and Tabulations of Individual Patient Data

11.3.1 Analysis of Efficacy

- Ferritin level from 28.3 ±20.1 to 41.1 (±27) µg/l for baseline to week 6, p = 0.176, Median 33 (19-67) to 41 (16-62) µg/l from baseline to week 6, Min/Max was 13/279 to 5.7/78 µg/l from baseline to week 6.
- Ferritin level from 28.3 ±20.1 to 42.0 (±27.2) µg/l for baseline to week 12, p = 0.115, Median 33 (19-67) to 37.5 (19-61.8) µg/l from baseline to week 12, Min/Max was 13/279 to 16/88 µg/l from baseline to week 12.
- 9.0 (±5.8) to 13 (±6.6) transferrin saturation (%) for baseline to week 6, p = 0.042, Median 8 (6-18) to 12 (9-20) % from baseline to week 12, Min/Max was 4/27 to 4/23 % from baseline to week 12.
- 9.0 (±5.8) to 12.2 (±5.7) transferrin saturation (%) for baseline to week 12, p = 0.249, Median 8 (6-18) to 13 (6-17.5) % from baseline to week 12, Min/Max was 4/27 to 5/19 % from baseline to week 12.

11.3.2 Statistical/Analytical Issues

The per protocol analysis could not be conducted because of the small number of participants due to the premature termination of this study. Analysis was changed to the following methodology: Continuous variables are stated as mean and standard deviation, categorical variables as numbers (n) and percent (%). Comparisons of continuous parameters are assessed via paired Wilcoxon-Test and categorical variables via Chi^2-Test.

11.3.2.1 Adjustments for Covariates

No adjustment conducted / necessary.

11.3.2.2 Handling of Dropouts or Missing Data

Dropouts or missing data were not replaced.

11.3.2.3 Multiple Comparisons/Multiplicity

There was no adjustment for multiple comparisons.

11.3.3 Efficacy Conclusions

No efficacy conclusion could be made.

12 SAFETY EVALUATION

12.1 Extent of Exposure

A total amount of eleven patients was included in this trial. The planned dose of the IMP was two capsules of Feraccru® (each containing 30 mg ferric maltol) on a daily basis for twelve weeks. The following table displays the number of ingested IMP for each of the participants:

Table 2: Amount of ingested IMP for each of the participants

Patient ID	Ingested IMP	Comment
01-001	2 capsules on daily basis for 12 weeks	-
01-002	2 capsules on daily basis for 12 weeks	-
01-003	3 capsules for 4 days	Dropout on day 5
01-004	2 capsules on daily basis for 12 weeks	-
01-005	2 capsules day 1-7, 2 capsules day 9	Patient stopped IMP on day 8 (see 12.2.2), dropout on day 10
01-006	2 capsules for day 1-14	Dropout on day 15
01-007	2 capsules on daily basis for 12 weeks	-
01-008	2 capsules for day 1-7	Dropout on day 8
01-009	2 capsules on daily basis for 12 weeks	-
01-010	2 capsules for day 1-14	Dropout on day 15
01-011	2 capsules on daily basis for 12 weeks	-

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

Eight of eleven included patients (73%) had a total amount of fifteen AEs (fourteen non-serious and one serious AEs) during the trial (see Table in Section 12.2.2).

The most frequent non-serious AEs were diarrhea (4 cases, 36% of the 11 patients), nausea (3 cases, 27%) and abdominal pain or cramps (3 cases, 27%). Thirteen non-serious AEs were assessed by the investigator to be related to the IMP ferric maltol. The IMP application was withdrawn in five patients. One non-serious AE and the single SAE that occurred in this trial (right ventricular failure, see Section 12.3.1 below for details) had no causal relationship with the IMP.

All patients recovered from all AEs, including the single SAE. No patient died during the trial.

12.2.2 Display of Adverse Events

Table 3: Listing of Adverse events

Patient ID	AE term	Serious?	Outcome	Causality as per investigator	IMP withdrawn?
01-001	Diarrhea	no	recovered	related	no
01-001	Stomach pain	no	recovered	related	no
01-001	Stomach intestine flu	no	recovered	related	no
01-001	Melena	no	recovered	related	no

01-002	Mild Nausea	no	recovered	related	no
01-003	Nausea	no	recovered	related	yes
01-003	Heartburn	no	recovered	related	yes
01-005	Abdominal cramps	no	recovered	related	yes
01-005	Diarrhea,	no	recovered	related	yes
01-006	Diarrhea	no	recovered	related	yes
01-007	Nose bleeding	no	recovered	not related	no
01-008	Nausea	no	recovered	related	yes
01-010	Diarrhea	no	recovered	related	yes
01-010	Abdominal pain	no	recovered	related	yes
01-010	Right ventricular failure	yes	recovered	not related	yes

12.2.3 Analysis of Adverse Events

The majority of patients (eight of eleven, 73%) suffered from at least one AE. Four patients (36%) experienced more than one AE. The most frequent non-serious AEs were diarrhea (4 cases, 36%), nausea (3 cases, 27%) and abdominal pain or cramps (3 cases, 27%). These gastrointestinal symptoms are well-known side effects that occur frequently with the use of ferric maltol as specified in the reference document (Fachinformation Feraccru®).
The majority of AEs (13 of 15, 87%) – all of them non-serious - were assessed by the investigator to be related to the IMP ferric maltol. The IMP application was withdrawn in five patients.
One non-serious AE (nose bleeding) had no causal relationship with the IMP according to the investigator. Likewise, the single SAE that occurred in this trial (right ventricular failure) was definitely not related to the IMP (see Section 12.3.1 below for details).
All patients recovered from all AEs, including the single SAE. No patient died during the trial.

Taken together, the number and spectrum of adverse reactions is within the well-known safety profile of ferric maltol. Thus, no new safety signal was detected in this trial.

12.2.4 Listing of Adverse Events by Patient

See 12.2.2 above.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Not applicable.

12.3.1 Listing of Deaths, other Serious Adverse Events, other Significant Adverse Events

Not applicable.

12.3.1.1 Deaths

No deaths occurred in this trial.

12.3.1.2 Other Serious Adverse Events

Table 4: Listing of SAEs

Patient ID	SAE term	Outcome	Causality as per investigator	Causality as per sponsor	IMP withdrawn?
01-010	right ventricular failure	recovered	not related	not related	no

12.3.1.3 Other Significant Adverse Events

No adverse events of special interest (AESI) were defined in the protocol. No other significant adverse events occurred in this trial.

12.3.2 Narratives of Deaths, other Serious Adverse Events, and Certain Other Significant Adverse Events

Patient 01-010, right ventricular failure

This case reports about a 49 year-old male participant in the ORION-LVAD-1 study (A phase IV study to explore the safety of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with heart failure carrying Left Ventricular Assist Devices (ORION-LVAD-1) who had received a left ventricular assist device (LVAD) on 19JUL2012 for heart failure and who suffered from iron deficiency anaemia (since 18JUN2019).

The patient had been treated with open-label IMP ferric maltol (2x30 mg/day p.o.) as per the ORION-LVAD-1 protocol from 19JUN2019 10:00 a.m.. However, the patient had permanently stopped IMP intake on 03JUL2019 due to non-serious diarrhoea and abdominal pain, which no longer occurred after IMP withdrawal.

One month later on 01AUG2019 he was admitted to hospital with refractory ventricular fibrillation and several unsuccessful ICD triggers which led to right ventricular heart failure. The event was initially treated by cardioversion (successful) and finally by heart transplantation on 21SEP2019 at which date he was considered completely recovered from the event.

The report provides no information about concomitant medication.

Both the investigator and the sponsor's delegate for pharmacovigilance assessed the event "right ventricular failure" as not related to IMP ferric maltol (withdrawn on 03JUL2019 before event onset) but to the underlying disease.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

The single SAE that occurred in this trial was definitely not related to IMP ferric maltol as the SAE occurred 4 weeks after the IMP had been already withdrawn due to a non-serious adverse event.

12.4 Clinical Laboratory Evaluation

Because of the small number of participants due to the premature termination of this trial, no data is shown here.

12.4.1 Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

See above.

12.4.2 Evaluation of Each Laboratory Parameter

See above.

12.4.2.1 Laboratory Values Over Time

See above.

12.4.2.2 Individual Patient Changes

See above.

12.4.2.3 Individual Clinically Significant Abnormalities

See above.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

See above.

12.6 Safety Conclusions

Most of the observed adverse events that occurred in this trial were assessed to be related with the IMP ferric maltol. The single serious adverse event that occurred in this trial was assumed to be not related with the IMP ferric maltol.

However, regarding all the AEs that occurred in this trial, the CTCAE (Common Terminology Criteria of Adverse Events) Grading was 1 (mild) for all of the events. We conclude, that the number and spectrum of AEs for which a causal relationship with the IMP was assumed is within the well known safety profile of ferric maltol. Thus, no new safety signal was detected in this trial.

13 DISCUSSION AND OVERALL CONCLUSIONS

Iron deficiency is common in patients suffering from heart failure. The underlying pathomechanisms are complex and include impaired iron absorption, elevated hepcidin levels, augmented gastrointestinal loss and reduced availability from the reticuloendothelial system. Currently available oral iron formulations are often poorly tolerated in this cohort. Thus, in this study we tried to investigate is ferric maltol is an alternative to conventional iron formulations in this patient cohort.

The cohort of left ventricular assist device patients is a large and diverse group of patients with a multitude of underlying diseases and a high multi-morbidity. Unfortunately, recruitment for the study was low among this cohort. Thus, in future studies in this patient cohort, inclusion and exclusion criteria need to be re-evaluated.

Furthermore, the dropout rate in the study due to AE was high. The majority of AEs (13 of 15, 87%) – all of them non-serious - were assessed by the investigator to be related to the IMP ferric maltol. However, all patients recovered from all AEs, including the single SAE. No patient died during the trial. Yet, the IMP application was withdrawn in five patients. The most frequent non-serious AEs were diarrhea (4 cases, 36%), nausea (3 cases, 27%) and abdominal pain or cramps (3 cases, 27%). These gastrointestinal symptoms are well-known side effects that occur frequently with the use of ferric maltol as specified in the reference document (Fachinformation Feraccru®), This AE might have been effected by the general high intake of medications and possible contributing side effects in this cohort.

By design, our study had several limitations, including small sample size, open-label design, heterogeneous patient population and the lack of a control group. The objective of the study was to generate preliminary data on the safety, tolerability and efficacy of ferric maltol in patients supported by left ventricular assist devices. However, the study was aborted early. Thus, in conclusion, in this exploratory open-label study in patients supported by left ventricular assist devices and iron deficiency anaemia, we were not able to significantly prove the effects of iron supplementation due to a low recruitment rate. Further larger cohort studies are needed to compare oral and intravenous iron supplementation in this highly interesting cohort of patients.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Age (median, Q25-Q75) 55 (48-60)
Female/male n=2 female (18%) / n=9 male (82%)

14.2 Efficacy Data

Not applicable.

14.3 Safety Data

Not applicable.

14.3.1 Displays of Adverse Events

Not applicable.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Not applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

Not applicable.

15 APPENDICES

The following appendices are parts of the abbreviated clinical study report and are available as separate documents. Additional information can be obtained on request from Hannover Medical School.

15.1 Study protocol vs.1.4_2018_10_17_ORION-LVAD-1

15.2 Sample Case Report Form_2019_08_28_ORION-LVAD-1

15.3 Protocol deviations_ORION-LVAD-1

15.4 SAE-Formblatt_ORION-LVAD-1