1 TITLE PAGE

ABBREVIATED CLINICAL STUDY REPORT

Study Title:

A pilot study to explore preliminary safety, tolerability and efficacy of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with pulmonary hypertension and iron deficiency anemia

Short title:	**OR**al **I**r**ON** supplementation with ferric maltol in patients with **P**ulmonary **H**ypertension (**ORION-PH-1)**
EudraCT number:	2016-005100-26
Protocol code number:	ORION-PH-1
Investigational product:	Feraccru® (ferric maltol)
Indication studied:	Patients with iron deficiency anemia and pulmonary hypertension
Study design:	Explorative, open-label, uncontrolled monocenter phase IIIb -study
Development phase of study:	Phase IIIb
First patient first visit:	09.05.2018
Last patient last visit:	09.03.2020
Date of early study termination:	19.03.2020
Name and affiliation of principal investigator:	[redacted] Hannover Medical School Department of Pneumology 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:	2.0 final, 25.02.2021

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 Department of Pneumology Hannover Medical School	Date
[redacted] 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
[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:

A pilot study to explore preliminary safety, tolerability and efficacy of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with pulmonary hypertension and iron deficiency anemia

EudraCT no.: 2016-005100-26

Protocol code no.: ORION-PH-1

Information about study protocol version(s):

First submission:
Version 1.2, 25.08.2017

Subsequent substantial amendments:

n/a

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

[redacted]
Hannover Medical School
Dept. of Pneumology
Carl-Neuberg-Str. 1
30625 Hannover, Germany

Publication (reference):

[redacted] Oral iron supplementation with ferric maltol in patients with pulmonary hypertension. Eur Respir J. 2020 Nov 12; 56(5):2000616.

Studied period: 05/2018 – 03/2020 date of first enrolment: 09.05.2018 date of last completed: 09.03.2020 **Information about temporary halt(s) and premature termination of the trial:** No temporary halt	**Phase of development:** Phase IIIb

Premature termination on 19.03.2020	

Objectives:

Primary objective(s):

- To assess the effects of oral ferric maltol on hemoglobin levels in patients with pulmonary hypertension and anemia caused by iron deficiency

Secondary objectives:

- To assess the effects of oral ferric maltol on serum ferritin, transferrin saturation, 6 min walking distance, NT-proBNP, right ventricular function (determined by echocardiography) and World Health Organization Functional Class (WHO FC) in patients with pulmonary hypertension and anemia caused by iron deficiency

Assessment of safety:

- To assess the safety and tolerability of oral ferric maltol in patients with pulmonary hypertension and anemia

Methodology:

Phase IIIb, open-label, uncontrolled monocenter study to explore the preliminary safety, tolerability and efficacy of oral ferric maltol in treating iron deficiency in patients with pulmonary hypertension and iron deficiency anemia

Number of patients (planned and analysed):

Planned: 25

Analysed: 22

Diagnosis and main criteria for inclusion:

Diagnosis:

Patients with iron deficiency anemia and pulmonary hypertension

Main Inclusion criteria:

- Signed written informed consent prior to any study-related procedure and willingness to comply with treatment and follow-up procedures
- Male and female patients ≥18 years at day of inclusion
- Patients capable of understanding the investigational nature, potential risks and benefits of the clinical trial
- Patients with a diagnosis of PH confirmed by a (historical) right heart catheterization showing a mean pulmonary artery pressure ≥25 mmHg at rest and stable PH medication for at least 3 months.
- 6 min walk distance >50 m
- 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
- Women of childbearing potential must:
  - Have a negative pregnancy test during screening
  - Agree to use reliable methods of contraception during the course of the study

Exclusion criteria:

- Active hematological disorders other than iron-deficiency anemia

- Other medical condition that according to the investigator's assessment is causing or contributing to anemia
- Active malignancy
- Active infectious disease
- Active bleeding
- Severe renal insufficiency (glomerular filtration rate <30 ml/min)
- Severe liver injury as indicated by serum aminotransferases >3 x upper limit of normal or bilirubin levels >50 µmol/l
- Ongoing oral or intravenous iron supplementation
- Hemoglobin <7 g/dl in females or <8 g/dl in males at screening
- Concomitant erythropoietin medication
- Pregnancy or lactation period
- Subject has received any investigational medication or any investigational device 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 an investigational drug/device during the course of the study.
- Known or suspected hypersensitivity to any of the active substances or any excipients of the investigational medicinal product
- Known haemochromatosis or other iron overload syndromes
- 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):	BM7736 and 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:

- Change in hemoglobin level from baseline to week 12
  - 10.7±0.9 $g \cdot dL^{-1}$ to 13.6±1.3 $g \cdot dL^{-1}$, p<0.001, n=18

Secondary endpoint(s):

- Change in hemoglobin from baseline to week 6
  - 10.7±0.9 $g \cdot dL^{-1}$ to 12.4 ±1.4 $g \cdot dL^{-1}$, p=0.001, n=15
- Change in serum ferritin levels and transferrin saturation from baseline to week 6 and 12
  - Baseline to week 6: 13.1 ±6.7 $\mu g \cdot L^{-1}$ to 29.3 ±16.6 $\mu g \cdot L^{-1}$, p<0.001, n=15

- Baseline to week 12: 13.1 ±6.7 µg·L^{-1} to 36.6 ±19.8 µg·L^{-1}, p<0.001, n=20

- Change in 6 min walking distance from baseline to week 12
  - 331±147 m to 381±131 m, p=0.004, n=20
- Change in serum NT-proBNP from baseline to weeks 6 and 12
  - Baseline to week 6: 496 (254–902) ng·L^{-1} to 382 (161-664) ng·L^{-1}, p=0.657, n=15
  - Baseline to week 12: 496 (254–902) ng·L^{-1} to 298 (160–484) ng·L^{-1}, p=0.003, n=20
- Change in echocardiographic markers of right ventricular function (right atrial area, right ventricular diameter, fractional area change, tricuspid annular plane systolic excursion) from baseline to week 12 in patients with pulmonary hypertension and anemia caused by iron deficiency.
  - Right atrial area: 23.7±8.4 cm^2 to 23.3±8.3 cm^2, p=0.070, n=17
  - Right ventricular diastolic diameter (four-chamber view): 45.4±8.9 mm to 42.3±8.4 mm, p=0.050, n=17
  - Right ventricular diastolic diameter (parasternal long axis): 38.7±7.3 mm to 35.0±6.3 mm, p=0.002, n=17
  - Right ventricular fractional area change: 30.5±12.8 % to 37.0±11.3 %, p=0.005, n=17
  - TAPSE: 21.6±5.6 mm to 21.3±5.6 mm, p=1.000, n=17

- Change in WHO FC from baseline to week 12
  - WHO FC I from 0 (0%) to 0 (0%)
  - WHO FC II from 4 (17%) to 9 (45%)
  - WHO FC III from 16 (83%) to 11 (55%)
  - WHO FC IV from 0 (0%) to 0 (0%)
  - p=0.091, n=20

Assessment of safety:

- Safety and tolerability by documentation of (serious) adverse events (AEs/SAEs)

Statistical methods:

Comparisons of baseline and week 12 data were performed with Chi-square tests or paired Wilcoxon tests, as appropriate. All p-values were exploratory and termed significant if the two-sided p-value fulfilled $p < 0.05$.

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:

None.

Summary – Conclusions:

Efficacy Results:

In the 20 patients who completed the 12-week study period, haemoglobin (median +2.9 g·dL^{-1}, interquartile range 2.6–3.7 g·dL^{-1}, p<0.001) and serum iron levels (5.4 µmol·L^{-1} ±2.0 vs 19.7 µmol·L^{-1} ±11.7, p<0.001)

significantly improved. In addition, we observed improvements in 6MWD 331±147 m vs 381±131 m; p=0.004) and NT-proBNP (496 ng/l, Q1; Q3, 254-902 ng/l) vs 298 ng/l; Q1; Q3, 298 (160-484 ng/l); p=0.003). Echocardiography showed decreased RV dimensions and increased RV fractional area change while tricuspid annular plane systolic excursion remained unchanged.

Safety Results:

Treatment with ferric maltol was well tolerated by the majority of patients. All but two patients completed the 12-week study period; the reasons for premature discontinuations were gastrointestinal side-effects (n=1, related to study medication) and pneumonia (n=1, unrelated to study medication). Twelve of the 22 patients (55%) experienced a total of 23 adverse events (Table 2). Five AEs were serious. The only treatment-emergent adverse events occurring in two or more patients – all of them non-serious - were diarrhoea (n=3, 14%, including the aforementioned patient who discontinued study medication because of diarrhoea), and common cold (n=2, 9%). Adverse events considered related to IMP ferric maltol were diarrhea and obstipation. 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®). Three SAE cases with a total of six SAE terms occurred during the trial. Two cases were fatal. One patient experienced a SAE of systemic inflammatory response syndrome which led to the withdrawal of the IMP and was complicated by a number of complications, including acute on chronic liver failure from which she ultimately died shortly after safety follow-up. Another patient died from right-sided heart failure during the 4-week safety follow-up. Both cases were considered unrelated to study medication. Thus, no new safety concern was detected for ferric maltol.

Conclusion:

In conclusion, in this exploratory, single arm, uncontrolled, open-label study in patients with pulmonary hypertension and iron deficiency anaemia, ferric maltol was well tolerated by the majority of patients with no new safety concerns detected and resulted in significant improvements in iron status and haemoglobin levels. These changes were accompanied by signs of improved right ventricular function and improved exercise capacity, supporting the notion that iron deficiency has detrimental effects in patients with pulmonary hypertension and that treating iron deficiency anaemia in these patients is important.

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
eCRF	Electronic case report form
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hb	Haemoglobin
Hk	Haematocrit
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
KCO	transfer coefficient of the lung for carbon monoxide
n/a	Not applicable
NT-proBNP	N-terminale pro brain natriuretic peptide
NYHA	New York Heart Association
RBC	Red blood corpuscles
WBC	White blood corpuscles
RV	Right ventricular
SAE	Serious adverse event
TLCO	Transfer factor of the lung for carbon monoxide
WHO FC	World Health Organization Functional Class

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

This was a prospective, open-label, uncontrolled, monocenter, phase IIIb clinical trial to explore the preliminary safety, tolerability and efficacy of oral ferric maltol in treating iron deficiency in patients with pulmonary hypertension and iron deficiency anemia.

Feraccru® 30 mg hard capsules were given twice daily.

The study duration per subject was approximately 16 weeks including a 12-week treatment period and 4 weeks safety follow-up period after discontinuation of study medication.

22 patients were enrolled over a period of 22 months.
The first patient was enrolled on 09.05.2018 and the last patient was completed on 09.03.2020 (study period: 05/2018 – 03/2020). The clinical trial was prematurely terminated due to a low recruitment rate on 19.03.2020. No temporary halt took place.

In the course of the clinical trial the primary submitted and approved study protocol version 1.2 of 25.08.2017 remained unchanged throughout the clinical trial (see Appendix 16.1).

A representative sample of case report form (CRF) is presented in Appendix 16.2 and of SAE form in Appendix 16.4.

Publications:
A publication with the title 'Oral iron supplementation with ferric maltol in patients with pulmonary hypertension' was published in November 2020 in the European Respiratory Journal (Eur Respir J. 2020 Nov; 56(5): 2000616.) by Karen M Olsson et al..

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 (1.2 of 25.08.2017).

Changes to analyses:
There were no changes to the planned analysis.

10 STUDY PATIENTS

10.1 Disposition of Patients

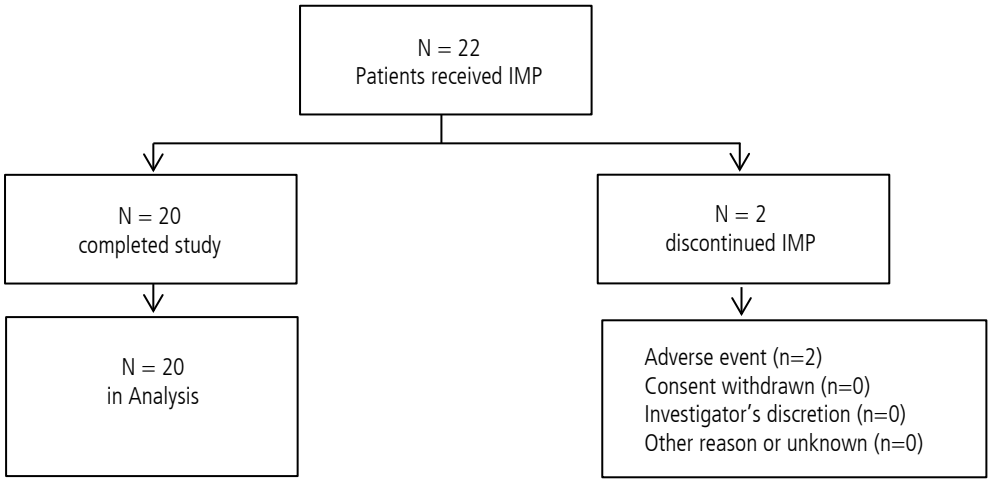

Figure 1: Patient flow chart

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 16.3.

Table 1: Overview of frequency of study protocol deviations

Site	Deviation from visit schedule	Deviation from correct application of study medication	Other protocol deviations
01 - MHH	3	1	7

In 6 subjects protocol deviations were observed:
In patient 01-002 laboratory diagnostics including Hb, Hk, RBC, WBC, platelets, lymphocytes, neutrophiles and albumine at screening were not performed (other deviation), Week 6 was not done (deviation from visit schedule), Week 12 was done 18 days early for reason of holyday (deviation from visit schedule) and study medication: Only 129 of 168 tablets were ingested because visit 12 was done too early (Deviation from correct application of study medication). In patient 01-005 determinations for lymphocytes, neutrophils and NT-proBNP were not performed at baseline (other deviation). In patient 01-010 lung function values TLCO (mmol / min / kPa) and KCO (mmol / min / kPa / l) at screening were not done (other deviation) and week 6 was not done (deviation from visit schedule). In patient 01-016 and 01-018 laboratory diagnostics for Albumin at week 6 was not done (other deviation). In patient 01-023 parameters for lung function testing was only partially determined (other deviation) and laboratory diagnostics for ALT/AST was not done at week 12 (other deviation).

11 EFFICACY EVALUATION

11.1 Data Sets Analysed

N=22 patients were enrolled in this study and n=20 patients were included in the per protocol analysis.

11.2 Demographic and Other Baseline Characteristics

The median (range) age of the enrolled patients was 57 (49–71) years; 82% were female. Underlying conditions were pulmonary arterial hypertension (n=14, 64%), pulmonary hypertension due to left heart disease (n=1, 5%) and inoperable chronic thromboembolic pulmonary hypertension (n=7, 32%). Haemodynamics at the time of diagnosis showed severe pre-capillary pulmonary hypertension with mean±SD pulmonary artery pressure of 50±11 mmHg, pulmonary artery wedge pressure of 10±4 mmHg and pulmonary vascular resistance of 875±385 dyn·s·cm^{-5}. The median (range) time from diagnosis to study inclusion was 4.5 (2.5–7.3) years. All patients received medical therapy for pulmonary hypertension; the majority (64%) received combination therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors.

11.3 Efficacy Results and Tabulations of Individual Patient Data

11.3.1 Analysis of Efficacy

Primary endpoint:

- Change in hemoglobin level from baseline to week 12
  - 10.7±0.9 g·dL^{-1} to 13.6±1.3 g·dL^{-1}, p<0.001

Secondary endpoint(s):

- Change in hemoglobin from baseline to week 6
  - 10.7±0.9 g·dL^{-1} to 12.4 ±1.4 g·dL^{-1}, p=0.001
- Change in serum ferritin levels and transferrin saturation from baseline to week 6 and 12
  - Baseline to week 6: 13.1 ±6.7 µg·L^{-1} to 29.3 ±16.6 µg·L^{-1}, p<0.001
  - Baseline to week 12: 13.1 ±6.7 µg·L^{-1} to 36.6 ±19.8 µg·L^{-1}, p<0.001
- Change in 6 min walking distance from baseline to week 12
  - 331±147 m to 381±131 m, p=0.004
- Change in serum NT-proBNP from baseline to weeks 6 and 12
  - Baseline to week 6: 496 (254–902) ng·L^{-1} to 382 (161-664) ng·L^{-1}, p=0.657
  - Baseline to week 12: 496 (254–902) ng·L^{-1} to 298 (160–484) ng·L^{-1}, p=0.003
- Change in echocardiographic markers of right ventricular function (right atrial area, right ventricular diameter, fractional area change, tricuspid annular plane systolic excursion) from baseline to week 12 in patients with pulmonary hypertension and anemia caused by iron deficiency.
  - Right atrial area: 23.7±8.4 cm^2 to 23.3±8.3 cm^2, p=0.070
  - Right ventricular diastolic diameter (four-chamber view): 45.4±8.9 mm to 42.3±8.4 mm, p=0.050
  - Right ventricular diastolic diameter (parasternal long axis): 38.7±7.3 mm to 35.0±6.3 mm, p=0.002
  - Right ventricular fractional area change: 30.5±12.8 % to 37.0±11.3 %, p=0.005
  - TAPSE: 21.6±5.6 mm to 21.3±5.6 mm, p=1.000
- Change in WHO FC from baseline to week 12

- WHO FC I from 0 (0%) to 0 (0%)
- WHO FC II from 4 (17%) to 9 (45%)
- WHO FC III from 16 (83%) to 11 (55%)
- WHO FC IV from 0 (0%) to 0 (0%)
- p=0.091

11.4 Statistical/Analytical Issues

None.

11.5 Efficacy Conclusions

In the 20 patients who completed the 12-week study period, haemoglobin (median +2.9 $g \cdot dL^{-1}$, interquartile range 2.6–3.7 $g \cdot dL^{-1}$, p<0.001) and serum iron levels (5.4 $\mu mol \cdot L^{-1}$ ±2.0 vs 19.7 $\mu mol \cdot L^{-1}$ ±11.7, p<0.001) improved. In addition, we observed improvements in 6MWD (331±147 m vs 381±131 m; p=0.004) and NT-proBNP (496 ng/l; interquartile range, 254-902 ng/l vs 298 ng/l; interquartile range, 298 ng/l interquartile range, 160-484 ng/l; p=0.003). Echocardiography showed decreased RV dimensions and increased RV fractional area change while tricuspid annular plane systolic excursion remained unchanged. Given the uncontrolled, exploratory, open-label design of the present study, these results have to be interpreted with caution and need to be confirmed by larger, randomized-controlled and blinded studies.

12 SAFETY EVALUATION

12.1 Extent of Exposure

22 Patients were treated with the IMP from 30.05.2018 (first disposal of IMP) to the 12.02.2020 (latest return of IMP Bottle). Every patient was provided with 3 bottles of IMP, all but 3 patients returned all bottles. One patient threw away all three bottles (after use), on patient accidently disposed two of three bottles at home and one patient disposed one bottle of IMP at home. Two patients returned tablets. Patient 01-015 returned 152 tablets due to discontinuation of IMP and patient 01-002 returned 39 IMP tablets hence week 12 visit was earlier due to holidays. Mean duration of IMP treatment was 83 (±19) days.

12.2 Adverse Events (AEs)

12.2.1 Brief Summary of Adverse Events

Twelve of the 22 patients (55%) experienced a total of 23 adverse events (Table 2). Five AEs were serious. The only treatment-emergent adverse events occurring in two or more patients were diarrhoea (n=3, 14% and common cold (n=2, 9%). Only three adverse events – none of them serious - were considered related to the IMP ferric maltol by the investigator. No deaths occurred during the main study period, but one patient died from right-sided heart failure during the 4-week safety follow-up. This death was considered unrelated to study medication.

12.2.2 Display of Adverse Events

Table 2: Listing of Adverse events

Patient ID	AE term	Serious	Outcome	Causality as per investigator	IMP withdrawn?
01-002	Heart failure	Yes	fatal	No	No
01-002	Nausea	No	not recovered (persistent)	No	No
01-002	Back Pain	No	not recovered (persistent)	No	No
01-005	suspected pneumonia	Yes	ongoing	No	Yes
01-005	Peritonitis bacterial	Yes	ongoing	No	No
01-005	Pancytopenia	Yes	completely recovered	No	No
01-006	Worsening of PAH	No	ongoing	No	No
01-006	Vertigo on exercise	No	completely recovered	No	No
01-006	Pain by osteochondrosis of the lumbar spine	Yes	completely recovered	No	No
01-008	Diarrhea	No	completely recovered	No	No
01-010	Obstipation	No	completely recovered	Yes	No
01-011	Common cold	No	completely recovered	No	No

01-012	Dry Cough	No	ongoing	No	No
01-013	Ulcus varicosis	No	completely recovered	No	No
01-013	Varicosis	No	completely recovered	No	No
01-013	Insufficiency vena saphena magna grade IV	No	completely recovered	No	No
01-014	Headache intermittent	No	completely recovered	No	No
01-014	Vomiting intermittent	No	completely recovered	No	No
01-016	Common cold	No	completely recovered	No	No
01-016	bleeding of haemorrhoids	No	completely recovered	No	No
01-017	Pain right knee	No	completely recovered	No	No
01-018	Diarrhea	No	completely recovered	Yes	No
01-018	Diarrhea	No	completely recovered	Yes	No

12.2.3 Analysis of Adverse Events

The only treatment-emergent adverse events occurring in two or more patients were diarrhea (n=3, 14%, and common cold (n=2, 9%). Adverse events considered related to IMP ferric maltol were diarrhea and obstipation. 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®).

12.2.4 Listing of Adverse Events by Patient

See above.

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

Three SAE cases with a total of six SAE terms occurred during the trial (see listing in 12.3.1).

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

Patient ID	SAE term (MedDRA preferred term)	Outcome	Causality as per investigator	Causality as per sponsor
01-002	Cardiac failure	Fatal	Not related	No reasonable possibility
01-005	Systemic inflammatory response syndrome	Fatal	Not related	No reasonable possibility
	Pancytopenia	Not recovered/ not resolved	Not related	No reasonable possibility
	Peritonitis bacterial	Recovering/ resolving	Not related	No reasonable possibility
	Acute on chronic liver failure	Fatal	Not related	No reasonable possibility

01-006	Osteochondrosis	Recovered/ resolved	Not related	No reasonable possibility

12.3.1.1 Deaths

Two cases were fatal. One patient experienced a SAE of systemic inflammatory response syndrome which led to the withdrawal of the IMP and was complicated by a number of complications, including acute on chronic liver failure from which she ultimately died shortly after safety follow-up. Another patient died from right-sided heart failure during the 4-week safety follow-up. Both cases were considered unrelated to study medication by both investigator and sponsor´s delegate for pharmacovigilance.

12.3.1.2 Other Serious Adverse Events

Not applicable.

12.3.1.3 Other Significant Adverse Events

Not applicable.

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

Patient 01-002, Cardiac failure:

This case reports about a 41 year-old female participant in the ORION-PH-1 study (A pilot Study to explore preliminary safety, tolerability and efficacy of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with Pulmonary Hypertension and iron deficiency anemia) who had been diagnosed with pulmonary hypertension on 15APR2010 and who had received the IMP ferric maltol (2x30 mg/day p.o.) as per the ORION-PH-1 protocol from 31MAY2018 till 03AUG2018 (the EOS visit has been brought forward).
On 23AUG2018 she experienced heart failure, that led to death on the same day. As communicated by her husband, the patient died at home and no autopsy has been performed.

Her medical history additionally comprised iron-deficiency anaemia (since 18MAY2018), tachycardia (start date unknown), COPD (start date unknown), thyrotoxicosis (M. Basedow - start date unknown) and oedema.
Concomitant medication consisted of ambrisentan 10mg/d (start date NOV2011), tadalafil 20 mg/d (start date NOV2011), i.v. trepostinil (start date FEB2018), phenprocoumon (start date 19DEC2017), pantoprazol 40mg/d (start date 19DEC2017), ivabradin 10mg/d (start date 18MAY2018), levothyroxin 175µg/d (start date 19DEC2017), formoterol (inhalative, start date 19DEC2017), ciclesonid 80µg/d (inhalative, start date 19DEC2017) and torasemide 10mg/d (start date 18MAY2018).

Both the investigator and the sponsor's delegate for pharmacovigilance assessed the event "cardiac failure" as not related to IMP ferric maltol but rather to the underlying disease.

Patient 01-005, Systemic inflammatory response syndrome, Pancytopenia, Peritonitis bacterial, and Acute on chronic liver failure:

This case reports about a 56 year-old female participant in the ORION-PH-1 study (A pilot Study to explore preliminary safety, tolerability and efficacy of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with Pulmonary Hypertension and iron deficiency anemia) who had been diagnosed with

pulmonary hypertension on 07JUN2007. She had been diagnosed with iron deficiency anemia on 26JUN2018 and had received IMP ferric maltol (2x30 mg/day p.o.) as per study protocol since that day.
The patient was hospitalized on 14SEP2018 due to a general worsening together with cough, diarrhoea and fever. Based on hypotension, leukopenia, tachypnoea and 39°C a systemic inflammatory response syndrome (SIRS) was diagnosed with suspected underlying bronchopulmonary infection. The IMP ferric maltol was permanently withdrawn (last dose on 14SEP2018, reason for withdrawal not known) and the event treated empirically with moxifloxacin. On 15SEP she became hypoxemic and was transferred to an intensive care unit where she received furosemide for cardiac decompensation. After being retransferred she developed fever on 26SEP and antibiotics were escalated to imipenem for 6 days. Acyclovir i.v. was added for 10 days after detection of herpes simplex in bronchial lavage fluid (BAL). On 25OCT the patient was transferred to a university hospital. An Addison crisis was suspected and treated with i.v. cortisone after concomitant medication with cortisone had been terminated. The clinical course was complicated by peritonitis (Klebsiella oxytoca, treated with tigecycline since 07NOV2018 and later ciprofloxacine since 14NOV2018), subdural hematoma in the setting of thrombocytopenia, and acute on chronic liver failure with encephalopathy and progredient right heart failure in which she died on 20NOV2018.
The cause of death was stated as 'portopulmonal decompensation by acute liver failure'. No autopsy was performed. The investigator stated that there was no indication that the IMP caused or contributed to the fatal outcome of the event.

The patients' medical history included primary biliary sclerosis with suspected overlap to scleroderma hepatitis type 3 (since 2007) and arterial hypertension, among others. Of note, she had experienced an episode of SIRS with detection of herpes simplex in BAL in JUN2018.
The patients' concomitant medication consisted of prednisolone 1x5 mg/d, ursodeoxycholic acid 2x500 mg/d, pantoprazole 1x40 mg/d, spironolactone 1x25 mg/d, sildenafil 3x20 mg/d, macitentan 1x10 mg/d and calcium/vitamin D3.

Both the investigator and the sponsor's delegate for pharmacovigilance assessed the initial event "SIRS" and the complicated course as not related to IMP ferric maltol but rather to the underlying diseases (pulmonary hypertension, primary biliary sclerosis).

Patient 01-006, Osteochondrosis:

This case reports about a 77 year-old female participant in the ORION-PH-1 study (A pilot Study to explore preliminary safety, tolerability and efficacy of ORal IrON supplementation with ferric maltol in treating iron deficiency in patients with Pulmonary Hypertension and iron deficiency anemia) who had been diagnosed with chronic thromboembolic pulmonary hypertension on 15MAR2011 and with iron deficiency anemia since 31JUL2018 and who had received open-label IMP ferric maltol (2x30 mg/day p.o. for 12 weeks) as per the ORION-PH-1 protocol from 20AUG2018 till 12NOV2018.
On 26NOV2018 she experienced pain of the lumbar spine, that led to hospitalization on the same day. Magnetic resonance tomography (26NOV2018) confirmed osteochondrosis of lumbar spine. The event was treated with i.v. triamcinolone (80mg frequency unknown, from 26NOV-05DEC2018) and 4x500mg/d novaminsulfon since 26NOV2018. Glucocorticoid treatment led to increased blood glucose levels. However, the patient was discharged completely recovered on 05DEC2018.

Her medical history was remarkable for pre-existing lumbar pain (start date unknown) and diabetes mellitus (start date unknown). Concomitant medication consisted of rivaroxaban, metoprolol, levothyroxine, pantoprazole, simvastatin, riociguat, macitentan, sitagliptine, insulin lispro, and insulin glargine.

Both the investigator and the sponsor's delegate for pharmacovigilance assessed the event "osteochondrosis" as not related to IMP ferric maltol but rather to a pre-existing disease.

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

All three SAE cases (with a total of six SAE terms) including the two fatal cases were considered not related to IMP ferric maltol by both, investigator and sponsor´s delegate for pharmacovigilance, but rather were attributed to the underlying disease under study or comorbidities.

12.4 Safety Conclusions

Treatment with ferric maltol was well tolerated by the majority of patients. All but two patients completed the 12-week study period; the reasons for premature discontinuations were gastrointestinal side-effects (n=1, related to study medication) and pneumonia (n=1, unrelated to study medication). Twelve of the 22 patients (55%) experienced a total of 23 adverse events (Table 2). Five AEs were serious. The only treatment-emergent adverse events occurring in two or more patients – all of them non-serious - were diarrhoea (n=3, 14%, including the aforementioned patient who discontinued study medication because of diarrhoea), and common cold (n=2, 9%). Adverse events considered related to IMP ferric maltol were diarrhea and obstipation. 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®). Three SAE cases with a total of six SAE terms occurred during the trial. Two cases were fatal. One patient experienced a SAE of systemic inflammatory response syndrome which led to the withdrawal of the IMP and was complicated by a number of complications, including acute on chronic liver failure from which she ultimately died shortly after safety follow-up. Another patient died from right-sided heart failure during the 4-week safety follow-up. Both cases were considered unrelated to study medication by both, investigator and sponsor´s delegate for pharmacovigilance. Thus, no new safety concern was detected for ferric maltol.

13 DISCUSSION AND OVERALL CONCLUSIONS

In conclusion, in this exploratory open-label study in patients with pulmonary hypertension and iron deficiency anaemia, ferric maltol was well tolerated by the majority of patients with no new safety concerns detected and resulted in significant improvements in iron status and haemoglobin levels. These changes were accompanied by signs of improved right ventricular function and improved exercise capacity, supporting the notion that iron deficiency has detrimental effects in patients with pulmonary hypertension and that treating iron deficiency anaemia in these patients is important. Despite the limitations of a small, uncontrolled and unblinded study, our results suggest that oral iron supplementation with ferric maltol might become a safe, effective and convenient treatment option for patients with pulmonary hypertension and iron deficiency. Further studies are needed to compare oral and intravenous iron supplementation in this cohort of patients.

14 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.

16.1 Studyprotocol vs_1.2_2017_08_25_ORION-PH-1

16.2 Sample CRF_ORION-PH-1_2020_12_08

16.3 Protocol deviations_ORION-PH-1

16.4 SAE-Formblatt_ORION-PH-1_1.0_final_2017-10-18