Clinical trial results:
Iron deficiency and heart failure

A Phase II study open-label, non-controlled, non-randomized single-center study to evaluate the efficacy of Succifer® to increase iron deposits in non-anemic patients with iron deficiency and heart failure.

Summary

EudraCT number	2018-000874-31
Trial protocol	SE
Global end of trial date	01 February 2019

Results information

Result version number	v1 (current)
This version publication date	16 March 2022
First version publication date	16 March 2022
Summary attachment (see zip file)	Publication (WJCD.pdf)

Trial information

Trial identification

Sponsor protocol code	DRUGSSON-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mimer Medical AB
Sponsor organisation address	Svärdvägen 3B, Danderyd, Sweden, 18233
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 February 2019
Global end of trial reached?	Yes
Global end of trial date	01 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our primary aim was to evaluate whether Succifer®, given as one(1) 100mg tablet orally in the morning and at bedtime for 12 weeks, could significantly increase iron deposits as indicated by ferritin levels in patients with Heart Failure after 12 weeks of treatment. A second aim was to explore iron uptake after 6 weeks.

Iron deficiency (ID) is often present (32% - 65%) in patients with heart failure (HF). Oral iron absorption in patients with HF is generally poor. This is the reason why oral treatment is not recommended. The aim is to test whether Succifer® significantly increases iron deposits in non-anemic patients with HF. We want to emphasize that we did not aim to study outcomes in the present study, rather challenge the statement that oral iron therapy cannot be adequately taken up in patients with HF.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Before each subject was admitted to the study, a signed and dated informed consent was obtained from the subject. No investigations specifically required for the study were conducted until valid consent was obtained. The Investigator explained the aims, methods, reasonably anticipated benefits, data protection, potential hazards of the study, and any potential discomforts. The results and samples from each patient were coded with a numeric code so neither the results nor the samples would be identifiable. Only the student doctor and the student nurse could link the code with the patient.

Patients were identified from the case records who might be eligible for participation, based on the following inclusion criteria: case record diagnosis of HF based on symptoms, echocardiography (ECHO) verified reduced cardiac function as systolic and/or diastolic dysfunction, ferritin < 100 µg/L or 100 - 299 µg /L with transferrin saturation (TSAT) < 20%. Both preserved ejection fraction (EF) and reduced EF were potentially eligible provided there were no contraindications to participate. Those with an EF ≤ 40% were classified as HFrEF, and those with EF > 40% were classified as HF with preserved EF (HFpEF). When EF was described as normal or mildly reduced, these patients were classified as having HFpEF. Those with moderately or severely reduced EF were classified as HFrEF. Patients with a primary diagnosis of cancer, dementia, or some other terminal disease were excluded, as were patients planning to undergo intravenous iron treatment or to take part in another study. Patients with anemia (hemoglobin < 120 g/L for females and <130 g/L for males) were also excluded because the new indication for treatment of HF is ID regardless of the presence of anemia.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential subjects were selected from the population (2017-2019) at the Swedish center with a primary or secondary diagnosis of HF. The potential subjects that might be eligible based on the inclusion criteria were called by phone and informed of the study. Written informed consent was obtained before conducting any study-specific assessments.

Pre-assignment

Screening details:

Potential subjects were screened for eligibility to participate based on their demographics, medical/surgical history, physical examination, concomitant medications, vital signs, clinical laboratory tests(Hemoglobin, hsCRP, Ferritin, Iron, TSAT, Transferrin, and Hepcidin), and Iron Deficiency status.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Succifer®

Arm description:

Active treatment arm with Succifer®

Arm type	Experimental
Investigational medicinal product name	Ferrous Succinate
Investigational medicinal product code	Succifer®
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dosing of Succifer® was one(1) tablet in the morning and one tablet at bedtime for at least 12 weeks, and not with ordinary meals. Patients were instructed not to change their dietary habits. Compliance was checked at Visit 1 (Week 6) and EOT (Week 12) by pill counting. One(1) tablet contains 100 mg Ferrous Succinate(equivalent to 32.48 mg Fe2+), and 100 mg Succinic Acid. The total amount of iron per day in our study was 65.96 mg

Blood sampling was performed before 10 AM according to local and current guidelines. The blood was centrifuged, divided into aliquots, and stored at -80°C in a safe deposit box (Biobank Norr) until analysis. Ferritin, hsCRP, plasma iron, TSAT, and hepcidin samples were taken at baseline, at week 6, and at week 12. Hemoglobin was analyzed locally at each visit. At EOT, hepcidin was analyzed at Laboratory Medicine, Skåne, by LC-MS/MS, and plasma ferritin, iron, TSAT, and transferrin were analyzed and calculated at Laboratory Medicine, Uppsala.

Number of subjects in period 1	Succifer®
Started	20
Visit 1 (Week 6)	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
Active treatment arm with Succifer®	

Reporting group values	Overall trial	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
From 65-84 years	20	20	
Age continuous Units: years			
arithmetic mean	72.7		
standard deviation	± 8.6	-	
Gender categorical Units: Subjects			
Female	5	5	
Male	15	15	
Ejection Fraction (EF)			
HFrEF = heart failure with reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction. Those with an EF ≤ 40% were classified as HFrEF, and those with EF > 40% were classified as HF with preserved EF (HFpEF). When EF was described as normal or mildly reduced, these patients were classified as having HFpEF. Those with moderately or severely reduced EF were classified as HFrEF.			
Units: Subjects			
HFpEF > 40%	9	9	
HFrEF ≤ 40%	11	11	
Class of Heart Failure (NYHA)			
NYHA = New York Heart Association			
Units: Subjects			
NYHA Class 1	1	1	
NYHA Class 2	9	9	
NYHA Class 3	8	8	
NYHA Class 4	1	1	
Missing Info about NYHA Class	1	1	
Iron Deficiency Status Units: Subjects			
Iron Deficiency	17	17	
Functional Iron Deficiency	3	3	
Medical history: Hypertension Units: Subjects			
Yes	12	12	
No	8	8	
Medical history: Atrial Fibrillation Units: Subjects			
Yes	9	9	
No	11	11	
Medical history: Type II Diabetes			

Units: Subjects			
Yes	9	9	
No	11	11	
Medical history: Valvular Disorder Units: Subjects			
Yes	1	1	
No	19	19	
Symptoms: Breathlessness Units: Subjects			
Yes	18	18	
No	2	2	
Symptoms: Tiredness Units: Subjects			
Yes	16	16	
No	4	4	
Symptoms: Stomach Pain Units: Subjects			
Yes	2	2	
No	18	18	
Symptoms: Constipation Units: Subjects			
Yes	4	4	
No	16	16	
Symptoms: Diarrhea Units: Subjects			
Yes	1	1	
No	19	19	

End points

End points reporting groups

Reporting group title	Succifer®

Reporting group description:

Active treatment arm with Succifer®

Subject analysis set title	Baseline
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: All patients enrolled in the study at Baseline (Week 0). The Baseline is defined as the pre-dose values measured at the start. 16 patients completed the study without major protocol deviations and the study compliance was >80%. One(1) patient stopped the study medication after 3.5 weeks and three(3) patients took only one tablet per day for 2.5, 6, or 7.5 weeks. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Week 6 (N = N Baseline)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: The patients that attended Visit 1 (Week 6) and whose data were compared with the data of the same 20 patients who attended Baseline (Week 0). Due to the system limitation with the EudraCT system, EudraCT does not allow single-arm for paired statistical analysis. This set is a workaround for that limitation. 16 patients completed the study without major protocol deviations and the study compliance was >80%). One(1) patient stopped the study medication after 3.5 weeks and three(3) patients took only one tablet per day for 2.5, 6, or 7.5 weeks. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Week 12 (N = N Baseline)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: The patients that attended EOT (Week 12) and whose data were compared with the data of the same 20 patients who attended Baseline (Week 0). Due to the system limitation with the EudraCT system, EudraCT does not allow single-arm for paired statistical analysis. This set is a workaround for that limitation. 16 patients completed the study without major protocol deviations and the study compliance was >80%. One(1) patient stopped the study medication after 3.5 weeks and three(3) patients took only one tablet per day for 2.5, 6, or 7.5 weeks. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Baseline - HFpEF Subset
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: This subset consists of all subjects (characterized with HFpEF) at Baseline (Week 0). The Baseline is defined as the pre-dose values measured at the start. No subjects were excluded from the population even if major protocol deviations occurred. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Week 12 (N = N Baseline) - HFpEF subset
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: This subset consists of all subjects (characterized with HFpEF) at EOT (Week 12) and whose data were compared with the data of the same 9 subjects who attended Baseline (Week 0). Due to the system limitation with the EudraCT system, EudraCT does not allow single-arm for paired statistical analysis. This set is a workaround for that limitation. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Baseline - HFrEF subset
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Population: This subset consists of all subjects (characterized with HFrEF) at Baseline (Week 0). The Baseline is defined as the pre-dose values measured at the start. Following the intention-to-treat principle, no subjects were excluded from the population.

Subject analysis set title	Week 12 (N = N Baseline) - HFrEF subset
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Population: This subset consists of all subjects (characterized with HFrEF) at EOT (Week 12) and whose data were compared with the data of the same 11 subjects who attended Baseline (Week 0). Due to the system limitation with the EudraCT system, EudraCT does not allow single-arm for paired statistical analysis. This set is a workaround for that limitation. Following the intention-to-treat principle, no subjects were excluded from the population.

Primary: Ferritin - Baseline to Week 12

End point title	Ferritin - Baseline to Week 12

End point description:

Primary efficacy endpoint, defined as the median ferritin from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose ferritin measured at the start. The power calculation was based on the primary endpoint: a non-parametric test with 95% power and a p-value < 0.05 required at least 16 patients. All analyses were performed according to the intention-to-treat analysis

End point type	Primary

End point timeframe:

Baseline (Week 0) to EOT (Week 12)

End point values	Baseline	Week 12 (N = N Baseline)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	47 (32 to 78)	85 (62 to 171)		

Statistical analyses

Statistical analysis title	Ferritin evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To assess the evolution in median ferritin between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 12 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.001 [2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[1] - Previous investigations showed patients with HF had median ferritin of approximately 50 µg/L. We hypothesized that a clinically meaningful increase should be 25 µg/L, a relative increase of 50%. The null hypothesis for the primary efficacy analysis will be rejected (i.e., Succifer® will be deemed to significantly increase iron deposits as indicated by ferritin levels in patients with HF after 3 months of treatment) if there is a significant increase in median ferritin by 25 µg/L at Week 12.

[2] - There was a highly significant increase in median ferritin level from a baseline of 47 µg/L to 85 µg/L following 12 weeks of Succifer® treatment. Thus, the null hypothesis was rejected

Secondary: Ferritin - Baseline to Week 6

End point title	Ferritin - Baseline to Week 6

End point description:

Secondary efficacy endpoint, defined as the ferritin from Baseline (Week 0) to Visit 1 (Week 6). The baseline was defined as the pre-dose ferritin measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Secondary

End point timeframe:

Baseline (Week 0) to Visit 1 (Week 6)

End point values	Baseline	Week 6 (N = N Baseline)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	20		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	47 (32 to 78)	78 (57 to 113)		

Statistical analyses

Statistical analysis title	Ferritin evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used for related or independent data. To observe the evolution of Ferritin between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.009 [4]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[3] - From an earlier investigation, we had found that patients with HF had a median ferritin value of approximately 50 µg/L. We hypothesized that a clinically meaningful increase should be 25 µg/L, a relative increase of 50%.
[4] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median ferritin level from a baseline of 47 µg/L to 78 µg/L following 6 weeks of Succifer® treatment.

Other pre-specified: Iron

End point title	Iron

End point description:

Exploratory endpoint, defined as Iron from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose Iron measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (Week 12)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: µmol/L				
median (inter-quartile range (Q1-Q3))	13.5 (10.2 to 19.8)	16.5 (13.2 to 23.0)	16.0 (13.0 to 24.0)	

Statistical analyses

Statistical analysis title	Iron evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Iron between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Week 12 (N = N Baseline) v Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096 [5]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[5] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Iron evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Iron between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)

Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.102 [6]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[6] - Since the p-value is over 0.05, there is no significant difference.

Other pre-specified: Transferrin Saturation (TSAT%)

End point title	Transferrin Saturation (TSAT%)

End point description:

Exploratory endpoint, defined as Transferrin Saturation (TSAT%) from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose Transferrin Saturation (TSAT%) measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to End Of Study (12 weeks)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: percent				
median (inter-quartile range (Q1-Q3))	20 (15 to 30)	27 (21 to 33)	25 (21 to 44)	

Statistical analyses

Statistical analysis title	TSAT% evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Transferrin Saturation (TSAT%) between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 12 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [7]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[7] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median TSAT% level from a baseline of 20% to 25% following 12 weeks of Succifer® treatment.

Statistical analysis title	TSAT% evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Transferrin Saturation (TSAT%) between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [8]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[8] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median TSAT% level from a baseline of 20% to 27% following 6 weeks of Succifer® treatment.

Other pre-specified: Hepcidin

End point title	Hepcidin

End point description:

Exploratory endpoint, defined as Hepcidin from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose Hepcidin measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (Week 12)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: nmol/L				
median (inter-quartile range (Q1-Q3))	2.5 (0.8 to 4.4)	4.8 (3.0 to 7.4)	4.2 (2.0 to 8.8)	

Statistical analyses

Statistical analysis title	Hepcidin evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Hepcidin between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of p<0.05 and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Week 12 (N = N Baseline) v Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [9]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[9] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median hepcidin level from a baseline of 2.5 nmol/L to 4.2 nmol/L following 12 weeks of Succifer® treatment.

Statistical analysis title	Hepcidin evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Hepcidin between Baseline (Week 0) and Visit1 (Week 6), Mann–Whitney U test was used with a significance level of p<0.05 and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006 [10]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[10] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median hepcidin level from a baseline of 2.5 nmol/L to 4.8 nmol/L following 6 weeks of Succifer® treatment.

Other pre-specified: high sensitive C-reactive protein (hsCRP)

End point title	high sensitive C-reactive protein (hsCRP)

End point description:

Exploratory endpoint, defined as high-sensitivity C-reactive protein (hsCRP) from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose high-sensitive C-reactive protein (hsCRP) measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (12 weeks)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: mg/L				
median (inter-quartile range (Q1-Q3))	2.0 (0.9 to 4.2)	2.0 (1.2 to 5.5)	1.9 (0.8 to 4.1)	

Statistical analyses

Statistical analysis title	hsCRP evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of high-sensitivity C-reactive protein (hsCRP) between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 12 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.841 [11]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[11] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	hsCRP evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of high-sensitivity C-reactive protein (hsCRP) between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.565 [12]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[12] - Since the p-value is over 0.05, there is no significant difference.

Other pre-specified: Transferrin

End point title	Transferrin

End point description:

Exploratory endpoint, defined as Transferrin from baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose Transferrin measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (12 weeks)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: g/L				
median (inter-quartile range (Q1-Q3))	2.6 (2.4 to 2.9)	2.4 (2.2 to 2.7)	2.3 (2.0 to 2.5)	

Statistical analyses

Statistical analysis title	Transferrin evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Transferrin between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Week 12 (N = N Baseline) v Baseline
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [13]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[13] - Since the p-value is under 0.05, there is a significant difference. There was a significant decrease in median transferrin level from a baseline of 2.6 g/L to 2.3 g/L following 12 weeks of Succifer® treatment.

Statistical analysis title	Transferrin evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Transferrin between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.038 [14]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[14] - Since the p-value is under 0.05, there is a significant difference. There was a significant decrease in median transferrin level from a baseline of 2.6 g/L to 2.4 g/L following 6 weeks of Succifer® treatment.

Other pre-specified: Hemoglobin (Hb)

End point title	Hemoglobin (Hb)

End point description:

Exploratory endpoint, defined as Hemoglobin (Hb) from Baseline (Week 0) to EOT (Week 12). The Baseline was defined as the pre-dose Hemoglobin (Hb) measured at the start. All analyses were performed according to the intention-to-treat analysis

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (12 weeks)

End point values	Baseline	Week 6 (N = N Baseline)	Week 12 (N = N Baseline)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	20	20	
Units: g/L				
median (inter-quartile range (Q1-Q3))	144 (135 to 155)	138 (129 to 150)	142 (131 to 152)	

Statistical analyses

Statistical analysis title	Hemoglobin evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%,

a non-parametric test was used. To observe the evolution of Hemoglobin (Hb) between Baseline (Week 0) and EOT (Week 12), Mann–Whitney U test was used with a significance level of p<0.05 and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 12 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 [15]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[15] - Since the p-value is over 0.05, there is no significant difference.

Statistical analysis title	Hemoglobin evolution between Baseline and Week 6

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Hemoglobin (Hb) between Baseline (Week 0) and Visit 1 (Week 6), Mann–Whitney U test was used with a significance level of p<0.05 and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the subjects in this analysis are 20.

Comparison groups	Baseline v Week 6 (N = N Baseline)
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301 [16]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[16] - Since the p-value is over 0.05, there is no significant difference.

Other pre-specified: Ferritin - Baseline to Week 12 (HFpEF Subset)

End point title	Ferritin - Baseline to Week 12 (HFpEF Subset)

End point description:

Exploratory endpoint, defined as the median ferritin from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose ferritin measured at the start. Analysis was performed on HFpEF Subset and all analyses were performed according to the intention-to-treat analysis.

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (Week 12)

End point values	Baseline - HFpEF Subset	Week 12 (N = N Baseline) - HFpEF subset		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	9		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	40 (28 to 85.50)	100 (70 to 167.50)		

Statistical analyses

Statistical analysis title	Ferritin evolution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT%, a non-parametric test was used. To observe the evolution of Ferritin between Baseline (Week 0) and EOT (Week 12), the Wilcoxon signed-rank test for paired differences was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the number of subjects in this analysis is 9

Comparison groups	Baseline - HFpEF Subset v Week 12 (N = N Baseline) - HFpEF subset
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.008 [18]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[17] - From an earlier investigation, we had found that patients with HF had a median ferritin value of approximately 50 µg/L. We hypothesized that a clinically meaningful increase should be 25 µg/L, a relative increase of 50%.
[18] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median ferritin level in patients(HFpEF Subset) from a baseline of 40 µg/L to 100 µg/L following 12 weeks of Succifer® treatment.

Other pre-specified: Ferritin - Baseline to Week 12 (HFrEF Subset)

End point title	Ferritin - Baseline to Week 12 (HFrEF Subset)

End point description:

Exploratory endpoint, defined as the ferritin from Baseline (Week 0) to EOT (Week 12). The baseline was defined as the pre-dose ferritin measured at the start. Analysis was performed on HFrEF Subset and all analyses were performed according to the intention-to-treat analysis.

End point type	Other pre-specified

End point timeframe:

Baseline (Week 0) to EOT (Week 12)

End point values	Baseline - HFrEF subset	Week 12 (N = N Baseline) - HFrEF subset		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	11		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	48 (32 to 62)	79 (62 to 215)		

Statistical analyses

Statistical analysis title	Ferritin eovlution between Baseline and Week 12

Statistical analysis description:

Performed according to the Intention-To-Treat analysis. Due to skewed variables for ferritin and TSAT, a non-parametric test was used. To observe the evolution of Ferritin between Baseline (Week 0) and EOT (Week 12), Wilcoxon signed-rank test for paired differences was used with a significance level of $p<0.05$ and 95% power. Due to the system limitation with the EudraCT system, EudraCT does not allow a single arm for paired statistical analysis so the number of subjects in this analysis is 11.

Comparison groups	Baseline - HFrEF subset v Week 12 (N = N Baseline) - HFrEF subset
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.003 [20]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[19] - From an earlier investigation, we had found that patients with HF had a median ferritin value of approximately 50 µg/L. We hypothesized that a clinically meaningful increase should be 25 µg/L, a relative increase of 50%.

[20] - Since the p-value is under 0.05, there is a significant difference. There was a significant increase in median ferritin level in patients(HFrEF Subset) from a baseline of 48 µg/L to 79 µg/L following 12 weeks of Succifer® treatment.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded at Visit 1 (Week 6), EOT (Week 12), and followed by a 2-week monitoring period after EOT for administrative reasons.

Adverse event reporting additional description:

Four patients stopped the study medication before EOT; three patients because of vomiting or diarrhea and one patient because of hospitalization for a disease other than Heart Failure. The adverse effects reported in our study were few but well-known and expected. No serious adverse events were found.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	2017

Reporting groups

Reporting group title	Succifer®

Reporting group description:

Active treatment arm with Succifer® (Ferrous Succinate, Succinic Acid)

Serious adverse events	Succifer®		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Succifer®		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)		
Gastrointestinal disorders			
Obstipation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Heartburn			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Stomach pain			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This is a small pilot single-center study and selection bias cannot be excluded. Lack of a placebo control is an important limitation, but placebo did not significantly increase uptake in other studies. For example, Lewis et al.

Notes: