Clinical trial results:
Ferrous Acetyl-Aspartylated Casein Formulation Evaluation over Ferrous Sulfate in Iron Deficiency Anemia (Access): A Double-Dummy Randomized Clinical Trial

Summary

EudraCT number	2017-002972-15
Trial protocol	GR
Global end of trial date	08 January 2021

Results information

Result version number	v1 (current)
This version publication date	26 June 2022
First version publication date	26 June 2022

Trial information

Trial identification

Sponsor protocol code	Omalin-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03524651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A.
Sponsor organisation address	14th Km National Road 1, Kifissia, Greece, 14564
Public contact	Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., 30 2108072512374, soumelas@uni-pharma.gr
Scientific contact	Regulatory Affairs department, Uni-Pharma Kleon Tsetis Pharmaceutical Laboratories S.A., 30 2108072512374, soumelas@uni-pharma.gr

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	10 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 January 2021
Global end of trial reached?	Yes
Global end of trial date	08 January 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The scope of this study is to compare the efficacy of the new oral formulation of Fe-ASP to oral ferrous sulfate in patients with IDA for the restoration of decreased circulating Hb.

Protection of trial subjects:

No specific measures applied

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 April 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	Greece: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	26
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was admitted to the study on 01.04.2018 and the last on 08.01.2021. A total of n = 60 patients were recruited, who completed the study in 1 center: 4th Department of Internal Medicine ATTIKON University General Hospital, National and Kapodistrian University of Athens, Medical School, Greece.

Pre-assignment

Screening details:

From 387 patients screened for eligibility, 60 patients (30 per group) were randomized and 327 were excluded. The majority of them (125) were excluded because of RBC count over the limit set. 1 and 5 patients respectively withdrew consent and request removal of data leaving 29 and 25 patients respectively for the analysis of the primary endpoint.

Period 1

Period 1 title	Visit 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Patients were randomly 1:1 assigned to double-blind and double-dummy treatment with FeSO4 or Fe-ASP. Randomization was provided by a sealed envelope to the investigators. Investigator and patient were blind to the allocated intervention. Following randomization, every patient was delivered two different boxes, one for each month of treatment. The first box contained capsules with a three-digit number at the outside. The second box contained vials with a four-digit number at the outside.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferrous sulfate

Arm description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Arm type	Active comparator
Investigational medicinal product name	Microfer
Investigational medicinal product code	
Other name	Ferrous sulfate capsules
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin placebo
Investigational medicinal product code	
Other name	Fe-ASP placebo
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin.

Arm title	Fe-ASP

Arm description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Arm type	Experimental
Investigational medicinal product name	Microfer placebo
Investigational medicinal product code	
Other name	Ferrous sulfate capsules placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin
Investigational medicinal product code	
Other name	Fe-ASP vials
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-Asp preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Number of subjects in period 1	Ferrous sulfate	Fe-ASP
Started	29	25
Completed	29	25

Period 2	
Period 2 title	Visit 2 -4 weeks after start
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As per baseline period

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferrous sulfate

Arm description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Arm type	Active comparator
Investigational medicinal product name	Microfer
Investigational medicinal product code	
Other name	Ferrous sulfate capsules
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin placebo
Investigational medicinal product code	
Other name	Fe-ASP placebo
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin.

Arm title	Fe-ASP

Arm description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Arm type	Experimental
Investigational medicinal product name	Microfer placebo
Investigational medicinal product code	
Other name	Ferrous sulfate capsules placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin
Investigational medicinal product code	
Other name	Fe-ASP vials
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-Asp preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Number of subjects in period 2	Ferrous sulfate	Fe-ASP
Started	29	25
Completed	29	25

Period 3

Period 3 title	Visit 2 -12 weeks after start
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

As per baseline period

Arms

Are arms mutually exclusive?	Yes
Arm title	Ferrous sulfate

Arm description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Arm type	Active comparator
Investigational medicinal product name	Microfer
Investigational medicinal product code	
Other name	Ferrous sulfate capsules
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin placebo
Investigational medicinal product code	
Other name	Fe-ASP placebo

Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin.

Arm title	Fe-ASP

Arm description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Arm type	Experimental
Investigational medicinal product name	Microfer placebo
Investigational medicinal product code	
Other name	Ferrous sulfate capsules placebo
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal.

Investigational medicinal product name	Omalin
Investigational medicinal product code	
Other name	Fe-ASP vials
Pharmaceutical forms	Oral solution in single-dose container
Routes of administration	Oral use

Dosage and administration details:

The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-Asp preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Number of subjects in period 3	Ferrous sulfate	Fe-ASP
Started	29	25
Completed	18	15
Not completed	11	10
Lost to follow-up	11	10

Baseline characteristics

Reporting groups	
Reporting group title	Ferrous sulfate

Reporting group description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Reporting group title	Fe-ASP

Reporting group description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Reporting group values	Ferrous sulfate	Fe-ASP	Total
Number of subjects	29	25	54
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	11	26
From 65-84 years	14	14	28
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.5	62.7	
standard deviation	± 16.1	± 21.2	-
Gender categorical Units: Subjects			
Female	19	14	33
Male	10	11	21

End points

End points reporting groups

Reporting group title	Ferrous sulfate

Reporting group description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Reporting group title	Fe-ASP

Reporting group description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Reporting group title	Ferrous sulfate

Reporting group description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Reporting group title	Fe-ASP

Reporting group description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Reporting group title	Ferrous sulfate

Reporting group description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Reporting group title	Fe-ASP

Reporting group description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Primary: Absolute change of baseline Hb

End point title	Absolute change of baseline Hb[1]

End point description:

The primary study endpoint was the non-inferiority of the increase of baseline Hb in the FeSO4 and in the Fe-ASP group after the first 4 weeks of treatment. Since the daily amount of elementary iron delivered with the ferrous sulfate regimen was 94 mg and with the Fe-ASP regimen 80 mg, the increase of baseline Hb was adjusted per mg of delivered elementary iron.

End point type	Primary

End point timeframe:

After the first 4 weeks of treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: N/A

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: gram/dl				
arithmetic mean (standard error)	0.76 (± 0.27)	0.83 (± 0.31)		

Statistical analyses

No statistical analyses for this end point

Primary: Relative % change of baseline Hb

End point title	Relative % change of baseline Hb[2]

End point description:

The primary study endpoint was the non-inferiority of the increase of baseline Hb in the FeSO4 and in the Fe-ASP group after the first 4 weeks of treatment. Since the daily amount of elementary iron delivered with the ferrous sulfate regimen was 94 mg and with the Fe-ASP regimen 80 mg, the increase of baseline Hb was adjusted per mg of delivered elementary iron.

End point type	Primary

End point timeframe:

After the first 4 weeks of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: N/A

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: percent change				
arithmetic mean (standard error)	10.3 (± 3.51)	10.99 (± 4.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of absolute RBC count from baseline

End point title	Absolute change of absolute RBC count from baseline

End point description:

Absolute change of the absolute red blood cell (RBC) count from baseline. Since the daily amount of elemental iron delivered with the ferrous sulfate regimen is 94 mg and with the Fe-ASP regimen 80 mg, all secondary study endpoints were adjusted per mg of delivered elemental iron.

End point type	Secondary

End point timeframe:

After 4 weeks

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: cells				
arithmetic mean (standard error)	0.23 (± 0.07)	0.37 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative % change of absolute RBC count from baseline

End point title	Relative % change of absolute RBC count from baseline

End point description:

Relative change of the absolute red blood cell (RBC) count from baseline. Since the daily amount of elemental iron delivered with the ferrous sulfate regimen is 94 mg and with the Fe-ASP regimen 80 mg, all secondary study endpoints were adjusted per mg of delivered elemental iron.

End point type	Secondary

End point timeframe:

After 4 weeks

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: percent change				
arithmetic mean (standard error)	6.61 (± 2.08)	13.65 (± 5.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change of the absolute reticulocyte count from baseline

End point title	Absolute change of the absolute reticulocyte count from baseline

End point description:

Absolute change of the absolute reticulocyte count from baseline. Since the daily amount of elemental iron delivered with the ferrous sulfate regimen is 94 mg and with the Fe-ASP regimen 80 mg, all secondary study endpoints were adjusted per mg of delivered elemental iron.

End point type	Secondary

End point timeframe:

After 4 weeks

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: cells				
arithmetic mean (standard error)	-43.7 (± 131.2)	116 (± 80.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Relative % change of the absolute reticulocyte count from baseline

End point title	Relative % change of the absolute reticulocyte count from baseline

End point description:

Relative change of the absolute reticulocyte count from baseline. Since the daily amount of elemental iron delivered with the ferrous sulfate regimen is 94 mg and with the Fe-ASP regimen 80 mg, all secondary study endpoints were adjusted per mg of delivered elemental iron.

End point type	Secondary

End point timeframe:

After 4 weeks

End point values	Ferrous sulfate	Fe-ASP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	25		
Units: percent				
arithmetic mean (standard error)	-3.9 (± 5.9)	11.8 (± 6.21)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Ferrous sulfate

Reporting group description:

Patients were taken every day for 12 weeks two oral capsules of 150 mg ferrous sulfate delivering 47 mg of active elementary iron. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were also taking every day on exactly the same time for 12 weeks two placebo vials of 15 ml volume with excipients contained in the commercially available formulation Fe-ASP Omalin (Uni-Pharma SA).

Reporting group title	Fe-ASP

Reporting group description:

Patients were taking every day for 12 weeks two oral placebo capsules. The capsules were containing the inactive excipients of Microfer. Patients were instructed to receive the capsules either two hours before meal or two hours after meal. The same patients were taking every day on the same time for 12 weeks two vials of 15 ml volume the Fe-ASP preparation Omalin (Uni-Pharma SA) delivering 40 mg of elementary iron.

Serious adverse events	Ferrous sulfate	Fe-ASP	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	6 / 25 (24.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Hospital admission due to abdominal pain		
subjects affected / exposed	5 / 29 (17.24%)	6 / 25 (24.00%)	
occurrences causally related to treatment / all	5 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ferrous sulfate	Fe-ASP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	7 / 25 (28.00%)	
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 29 (10.34%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Constipation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Helicobacter gastritis	Additional description: Helicobacter pylori gastritis		
subjects affected / exposed	1 / 29 (3.45%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Fungal oesophagitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	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

None reported