Clinical trial results:
Doubleblind, randomised, placebo-controlled clinical trial to evaluate the safety and efficacy of Gerolsteiner Heilwasser in NERD patients with heartburn

Summary

EudraCT number	2016-000994-19
Trial protocol	DE
Global end of trial date	07 December 2018

Results information

Result version number	v1 (current)
This version publication date	25 June 2021
First version publication date	25 June 2021

Trial information

Trial identification

Sponsor protocol code	GER/026115

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gerolsteiner Brunnen GmbH & Co. KG
Sponsor organisation address	Vulkanring, Gerolstein, Germany, 54567
Public contact	Dr. Thomas Hens, Gerolsteiner Brunnen GmbH & Co. KG, +49 659114423, drthomas.hens@gerolsteiner.com
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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	10 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigation of the efficacy and tolerability of Gerolsteiner Heilwasser in NERD-patients with heartburn.

Efficacy parameters:
-Changes for dimension 'heartburn', 'GERD', 'regurgitation' and 'dyspepsia' of questionnaire RDQ
-Changes in number of days with heartburn-episodes per week according to patient diary
-Changes in HSI
-Intake of rescue medication during treatment
-Changes in QOLRAD scores
-Changes in GLQI scores
-Changes in subjective perception of well-being (SF-12 questionnaire)
-"Overall Treatment Evaluation" (OTE) by patient and investigator

Tolerability parameters:
-Adverse events
-Difference in blood pressure / pulse
-Differences in safety laboratory parameters
-Global assessment of tolerability by patient and investigator

Protection of trial subjects:

The investigators ensured that the subjects were given full and adequate oral and written information (subject information) about the nature, purpose, consequences and possible risk of the clinical study. The subjects were given the opportunity to ask questions and were allowed sufficient time to consider the information provided. Subjects provided informed consent before the conduct of any study specific procedure. The collected data were made available to the CRO and the study’s sponsor only in pseudonymous form to minimize the chances of matching the data to an individual person. Rescue medication was provided to subjects with instructions in case they experience intolerable NERD discomfort.

Background therapy:

Rescue medication in case of intolerable NERD discomfort:
Maaloxan (Magnesium hydroxide and Aluminium hydroxide) 25 mVal;
at heartburn with intensity "moderate to strong" (in patient diary);
max. 2 times per day, max. 7 times per week;
to be documented for efficacy analysis

Evidence for comparator: -

Actual start date of recruitment	06 September 2016
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	Germany: 80

Worldwide total number of subjects	80
EEA total number of subjects	80

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)	73
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment details:
Recruitment period: September 2016 - September 2018
Subjects were recruited at four sites in Berlin, Germany.

Pre-assignment

Screening details:

88 patients were screened;
2 patients didn't meet in-/exclusion criteria;
3 patients withdrew their consent;
2 patients didn't meet randomisation criteria;
1 patient required enhanced medical treatment for heartburn

Period 1

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

Blinding implementation details:

The randomisation list was prepared by an independent statistician using a random number generator. Numbers were allocated 1:1 to both treatment groups (placebo/verum). The list was available to the person responsible for labelling and packaging as well as to sponsor's representative who wasn't part of the study team. The CRO was provided with the list only after database closure.

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Gerolsteiner Heilwasser
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

1,5 l of Gerolsteiner Heilwasser (at room temperature) per day:
3 times a day 300 ml before or with a meal; the remaining volume should be consumed over the day.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo water
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

1,5 l of Placebo water (at room temperature) per day:
3 times a day 300 ml before or with a meal; the remaining volume should be consumed over the day.

Number of subjects in period 1	Verum	Placebo
Started	40	40
Completed	38	38
Not completed	2	2
Consent withdrawn by subject	-	1
no delivery of IMP to patient	1	-
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Verum	Placebo	Total
Number of subjects	40	40	80
Age categorical			
Inclusion criteria (Protocol version 1.1, 27 June 2016): age 18-64 Inclusion criteria (Protocol version 2.0, 29 September 2017): age 18-85; changed due to recruitment difficulties			
Units: Subjects			
<30 years	2	5	7
30 - <40 years	8	4	12
40 - <50 years	12	9	21
50 - <60 years	11	15	26
60 - <70 years	6	6	12
70 - <80 years	0	1	1
Not recorded	1	0	1
Age continuous			
Units: years			
arithmetic mean	47.3	48.5	
standard deviation	± 12.3	± 13.1	-
Gender categorical			
Units: Subjects			
Female	25	30	55
Male	14	10	24
Not recorded	1	0	1
Race			
Units: Subjects			
Caucasian	37	39	76
Asian	1	1	2
Other	1	0	1
Not recorded	1	0	1

End points

End points reporting groups

Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: RDQ heartburn

End point title	RDQ heartburn
End point description:	
End point type	Primary
End point timeframe:	
V2 v. V4	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	2.1 (± 1.44)	1.71 (± 1.14)		
V4	1.13 (± 1.4)	0.69 (± 0.84)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.8338
Method	Wilcoxon (Mann-Whitney)

Notes:
[1] - Explorative

Primary: RDQ GERD

End point title	RDQ GERD
End point description:	
End point type	Primary

End point timeframe: V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	2.38 (± 1.14)	2.03 (± 0.9)		
V4	1.09 (± 1.09)	0.85 (± 0.8)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.6829
Method	Wilcoxon (Mann-Whitney)

Notes:
[2] - Explorative

Primary: RDQ regurgitation	
End point title	RDQ regurgitation
End point description:	

End point type	Primary
End point timeframe: V2 v. V4	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	2.67 (± 1.29)	2.35 (± 1.01)		
V4	1.04 (± 1.10)	0.93 (± 0.98)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Placebo v Verum
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.6357
Method	Wilcoxon (Mann-Whitney)

Notes:
[3] - Explorative

Primary: RDQ dyspepsia

End point title	RDQ dyspepsia

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	2.14 (± 1.39)	1.86 (± 1.23)		
V4	1.01 (± 1.28)	0.85 (± 0.93)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.6703
Method	Wilcoxon (Mann-Whitney)

Notes:
[4] - Explorative

Primary: Number of days with heartburn

End point title	Number of days with heartburn

End point description:
Last 7 days before visit date

End point type	Primary

End point timeframe: V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Days				
arithmetic mean (standard deviation)				
V2 V4	5.7 (± 1.4) 3.3 (± 2.5)	5.3 (± 1.4) 2.7 (± 2.2)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.5138
Method	Wilcoxon (Mann-Whitney)

Notes:
[5] - Explorative

Primary: Heartburn Severity Index	
End point title	Heartburn Severity Index
End point description:	

End point type	Primary
End point timeframe: V2 v. V4	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2 V4	47.3 (± 51.4) 13.9 (± 17.6)	25.3 (± 20.3) 9.6 (± 11.6)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0184
Method	Wilcoxon (Mann-Whitney)

Notes:
[6] - Explorative

Primary: Rescue medication days per week

End point title	Rescue medication days per week

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Days				
arithmetic mean (standard deviation)				
V2	1.6 (± 1.7)	1.7 (± 2.0)		
V4	0.5 (± 1.0)	0.5 (± 1.1)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.9493
Method	Wilcoxon (Mann-Whitney)

Notes:
[7] - Explorative

Primary: QOLRAD emotional stress

End point title	QOLRAD emotional stress

End point description:

End point type	Primary

End point timeframe: V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	28.58 (± 9.96)	30.95 (± 8.77)		
V4	36.76 (± 7.73)	37.03 (± 7.10)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.2006
Method	Wilcoxon (Mann-Whitney)

Notes:
[8] - Explorative

Primary: QOLRAD sleep disturbance	
End point title	QOLRAD sleep disturbance
End point description:	

End point type	Primary
End point timeframe: V2 v. V4	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	24.18 (± 7.81)	26.46 (± 6.74)		
V4	31.11 (± 5.76)	31.85 (± 4.37)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.4831
Method	Wilcoxon (Mann-Whitney)

Notes:
[9] - Explorative

Primary: QOLRAD food and drink

End point title	QOLRAD food and drink

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	26.22 (± 9.21)	28.46 (± 8.67)		
V4	36.31 (± 7.33)	36.12 (± 6.45)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.2024
Method	Wilcoxon (Mann-Whitney)

Notes:
[10] - Explorative

Primary: QOLRAD physical/social functioning

End point title	QOLRAD physical/social functioning

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	27.26 (± 6.86)	28.92 (± 5.4)		
V4	32.37 (± 4.78)	32.46 (± 3.32)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.1619
Method	Wilcoxon (Mann-Whitney)

Notes:
[11] - Explorative

Primary: QOLRAD vitality

End point title	QOLRAD vitality

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	13.26 (± 4.47)	13.54 (± 4.64)		
V4	17.64 (± 3.94)	17.92 (± 3.34)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.8338
Method	Wilcoxon (Mann-Whitney)

Notes:
[12] - Explorative

Primary: GLQI

End point title	GLQI

End point description:

End point type	Primary

End point timeframe:
V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Score				
arithmetic mean (standard deviation)				
V2	95.8 (± 22.3)	96.6 (± 17.9)		
V4	110.4 (± 22.7)	110.8 (± 18.5)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.9276
Method	Wilcoxon (Mann-Whitney)

Notes:
[13] - Explorative

Primary: SF-12 Physical Composite Scale

End point title	SF-12 Physical Composite Scale

End point description:

End point type	Primary

End point timeframe: V2 v. V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Score				
arithmetic mean (standard deviation)				
V2 V4	46 (± 9.2) 49 (± 7.3)	46.5 (± 8.1) 48.6 (± 8.7)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.9605
Method	Wilcoxon (Mann-Whitney)

Notes:
[14] - Explorative

Primary: SF-12 Mental Composite Scale	
End point title	SF-12 Mental Composite Scale
End point description:	

End point type	Primary
End point timeframe: V2 v. V4	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	37		
Units: Score				
arithmetic mean (standard deviation)				
V2 V4	46.2 (± 10.8) 51 (± 9.8)	47 (± 10.8) 50 (± 10.4)		

Statistical analyses

Statistical analysis title	Pre/post changes
Comparison groups	Verum v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.6478
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - Explorative

Primary: Overall Treatment Evaluation (Investigator)

End point title	Overall Treatment Evaluation (Investigator)

End point description:

0 = no change, +1 = marginally better, +2 = a little better, +3 = somewhat better, +4 = moderately better, +5 = clearly better, +6 = much better, +7 = very much better

Reporting group 1 (Verum; n=38): 4.0±1.9 (arithmetic mean; standard deviation)
Reporting group 2 (Placebo; n=38): 3.5±2.5 (arithmetic mean; standard deviation)

End point type	Primary

End point timeframe:

V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Patients				
no change	3	6		
marginally better	2	4		
a little better	3	6		
somewhat better	3	4		
moderately better	8	1		
clearly better	12	7		
much better	5	3		
very much better	2	7		
no data	1	1		

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

0 = no change, +1 = marginally better, +2 = a little better, +3 = somewhat better, +4 = moderately better, +5 = clearly better, +6 = much better, +7 = very much better

Comparison groups	Placebo v Verum

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.4638
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - Explorative

Primary: Overall Treatment Evaluation (Patient)

End point title	Overall Treatment Evaluation (Patient)

End point description:

0 = no change, +1 = marginally better, +2 = a little better, +3 = somewhat better, +4 = moderately better, +5 = clearly better, +6 = much better, +7 = very much better

Reporting group 1 (Verum; n=38): 4.0±2.0 (arithmetic mean; standard deviation)
Reporting group 2 (Placebo; n=38): 3.5±2.5 (arithmetic mean; standard deviation)

End point type	Primary

End point timeframe:

V4

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Patients				
no change	4	7		
marginally better	2	3		
a little better	3	5		
somewhat better	3	5		
moderately better	7	1		
clearly better	10	8		
much better	7	1		
very much better	2	8		
no data	1	1		

Statistical analyses

Statistical analysis title	Group comparison

Statistical analysis description:

0 = no change, +1 = marginally better, +2 = a little better, +3 = somewhat better, +4 = moderately better, +5 = clearly better, +6 = much better, +7 = very much better

Comparison groups	Verum v Placebo

Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.4867
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Explorative

Primary: AE/ADR (Patients)

End point title	AE/ADR (Patients)[18]

End point description:

End point type	Primary

End point timeframe:

V1-V4

Notes:

[18] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Patients				
AE	6	14		
ADR	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: AE/ADR (Occurrences)

End point title	AE/ADR (Occurrences)[19]

End point description:

End point type	Primary

End point timeframe:

V1-V4

Notes:

[19] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Occurrence AE/ADR				
AE	12	22		
ADR	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: AE Causality

End point title	AE Causality[20]

End point description:

End point type	Primary

End point timeframe:

V1-V4

Notes:

[20] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Patients				
Causality likely	0	1		
Causality unlikely	6	13		

Statistical analyses

No statistical analyses for this end point

Primary: AE Intensity

End point title	AE Intensity[21]

End point description:

End point type	Primary

End point timeframe:

V1-V4

Notes:

[21] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Patients				
Light	3	4		
Moderate	3	9		
Severe	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Blood pressure (systolic)

End point title	Blood pressure (systolic)[22]

End point description:

End point type	Primary

End point timeframe:

V2 v. V4

Notes:

[22] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: mmHg				
arithmetic mean (standard deviation)				
V2	123.3 (± 11.0)	125.7 (± 13.2)		
V4	121.5 (± 10.9)	120.6 (± 10.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Blood pressure (diastolic)

End point title	Blood pressure (diastolic)[23]

End point description:

End point type	Primary

End point timeframe:

V2 v. V4

Notes:

[23] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: mmHg				
arithmetic mean (standard deviation)				
V2	76.0 (± 5.7)	77.1 (± 9.4)		
V4	78.3 (± 6.0)	78.0 (± 7.6)		

Statistical analyses

No statistical analyses for this end point

Primary: Pulse

End point title	Pulse[24]

End point description:

End point type	Primary

End point timeframe:

V2 v. V4

Notes:

[24] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: Beats per minute				
arithmetic mean (standard deviation)				
V2	70.2 (± 6.7)	68.0 (± 5.2)		
V4	68.4 (± 5.4)	69.7 (± 6.7)		

Statistical analyses

No statistical analyses for this end point

Primary: ALT, 37°C

End point title	ALT, 37°C[25]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[25] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: U/L				
arithmetic mean (standard deviation)				
V1	28.43 (± 17.62)	33.00 (± 26.65)		
V4	27.29 (± 18.38)	32.85 (± 23.85)		

Statistical analyses

No statistical analyses for this end point

Primary: Alkaline phosphatase, 37°C

End point title	Alkaline phosphatase, 37°C[26]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[26] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: U/L				
arithmetic mean (standard deviation)				
V1	72.02 (± 19.2)	83.56 (± 31.79)		
V4	71.22 (± 19.07)	84.05 (± 31.68)		

Statistical analyses

No statistical analyses for this end point

Primary: AST, 37°C

End point title	AST, 37°C[27]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[27] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: U/L				
arithmetic mean (standard deviation)				
V1	26.00 (± 11.64)	28.84 (± 22.74)		
V4	25.73 (± 8.75)	25.86 (± 10.49)		

Statistical analyses

No statistical analyses for this end point

Primary: Bilirubin, total

End point title	Bilirubin, total[28]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[28] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: µmol/L				
arithmetic mean (standard deviation)				
V1	11.09 (± 4.74)	10.54 (± 5.77)		
V4	11.37 (± 6.91)	10.41 (± 5.19)		

Statistical analyses

No statistical analyses for this end point

Primary: Blood urea nitrogen

End point title	Blood urea nitrogen[29]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[29] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: mmol/L				
arithmetic mean (standard deviation)				
V1	4.56 (± 1.37)	4.81 (± 1.24)		
V4	4.99 (± 1.29)	5.12 (± 1.66)		

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine

End point title	Creatinine[30]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[30] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: µmol/L				
arithmetic mean (standard deviation)				
V1	71.96 (± 13.26)	67.19 (± 11.79)		
V4	72.18 (± 15.63)	66.09 (± 12.74)		

Statistical analyses

No statistical analyses for this end point

Primary: Gamma-GT, 37°C

End point title	Gamma-GT, 37°C[31]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[31] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: U/L				
arithmetic mean (standard deviation)				
V1	35.07 (± 30.53)	41.17 (± 68.46)		
V4	31.58 (± 24.34)	40.54 (± 74.51)		

Statistical analyses

No statistical analyses for this end point

Primary: Uric acid

End point title	Uric acid[32]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[32] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: µmol/L				
arithmetic mean (standard deviation)				
V1	324.57 (± 85.1)	295.55 (± 79.29)		
V4	323.61 (± 89)	293.87 (± 76.02)		

Statistical analyses

No statistical analyses for this end point

Primary: Hemoglobin

End point title	Hemoglobin[33]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[33] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: g/L				
arithmetic mean (standard deviation)				
V1	142.51 (± 9.86)	140.22 (± 14.59)		
V4	141.38 (± 10.37)	138.95 (± 14.09)		

Statistical analyses

No statistical analyses for this end point

Primary: Hematocrit

End point title	Hematocrit[34]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[34] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: L/L				
arithmetic mean (standard deviation)				
V1	0.42 (± 0.03)	0.42 (± 0.04)		
V4	0.42 (± 0.03)	0.42 (± 0.04)		

Statistical analyses

No statistical analyses for this end point

Primary: Platelets

End point title	Platelets[35]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[35] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: 10^9/L				
arithmetic mean (standard deviation)				
V1	270.79 (± 62.01)	259.86 (± 58.86)		
V4	273.56 (± 61.09)	261.32 (± 57.88)		

Statistical analyses

No statistical analyses for this end point

Primary: Red blood cells

End point title	Red blood cells[36]

End point description:

End point type	Primary

End point timeframe:

V1 v. V4

Notes:

[36] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: 10^12/L				
arithmetic mean (standard deviation)				
V1	4.64 (± 0.33)	4.58 (± 0.46)		
V4	4.64 (± 0.37)	4.57 (± 0.46)		

Statistical analyses

No statistical analyses for this end point

Primary: White blood cells

End point title	White blood cells[37]

End point description:

End point type	Primary

End point timeframe:

V1 V. V4

Notes:

[37] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	37		
Units: 10^9/L				
arithmetic mean (standard deviation)				
V1	7.47 (± 2.26)	6.92 (± 1.88)		
V4	7.62 (± 2.3)	6.78 (± 2.03)		

Statistical analyses

No statistical analyses for this end point

Primary: Overall tolerability evaluation (Investigator)

End point title	Overall tolerability evaluation (Investigator)[38]

End point description:

End point type	Primary

End point timeframe:

V4

Notes:

[38] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Patients				
very good	28	30		
good	9	8		
moderate	1	0		
poor	0	0		
no data	1	2		

Statistical analyses

No statistical analyses for this end point

Primary: Overall tolerability evaluation (Patient)

End point title	Overall tolerability evaluation (Patient)[39]

End point description:

End point type	Primary

End point timeframe:

V4

Notes:

[39] - 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: Based on the statistical analysis plan, no detailed statistical analysis (except from display of frequency tables) for this endpoint was foreseen and can therefore not be provided here.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	40		
Units: Patients				
very good	27	28		
good	10	8		
moderate	1	2		
poor	0	0		
no data	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: V1-V4	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19
Reporting groups	
Reporting group title	Verum
Reporting group description: 40 patients were enrolled, 39 patients received IMP	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 40 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 39 (15.38%)	14 / 40 (35.00%)	
Vascular disorders			
Blood pressure fluctuation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Nervous system disorders			
Migraine			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	3	0	
Headache			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal tenderness			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Aphthous ulcer			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menstrual discomfort			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Photosensitivity reaction			
subjects affected / exposed	1 / 39 (2.56%)	0 / 40 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Fibromyalgia			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 39 (5.13%)	2 / 40 (5.00%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 40 (0.00%)	
occurrences (all)	2	0	
Sinusitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 39 (0.00%)	2 / 40 (5.00%)	
occurrences (all)	0	2	

Acute sinusitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 39 (0.00%)	1 / 40 (2.50%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2017	1) Increase of maximum age for study participation from 64 years to 85 years. 2) Striking of one manager from project management list.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported