Clinical trial results:
Investigation of efficacy and tolerability of the healing water Staatl. Fachingen STILL in patients for symptomatic treatment of heartburn in comparison to placebo

Summary

EudraCT number	2017-001100-30
Trial protocol	DE
Global end of trial date	07 June 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	1334hew16ct

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fachingen Heil- und Mineralbrunnen GmbH
Sponsor organisation address	Brunnenstrasse 11, Birlenbach OT Fachingen/Lahn, Germany, 65626
Public contact	Clinical Trial Information, Fachingen Heil- und Mineralbrunnen GmbH, +49 6432983468, marketing@fachingen.de
Scientific contact	Clinical Trial Information, Fachingen Heil- und Mineralbrunnen GmbH, +49 6432983468, marketing@fachingen.de

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	30 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is:
• to demonstrate superiority of Staatl. Fachingen STILL compared to placebo with regard to the responder rate by means of change in RDQ score in the dimension heartburn

Protection of trial subjects:

Prior to recruitment of patients, all relevant documents of the clinical study were submitted and proved by the Independent Ethics Committees (IECs) responsible for the participating investigators. Written consent documents embodied the elements of informed consent as described in the Declaration of Helsinki, the ICH Guidelines for Good Clinical Practice (GCP) and were in accordance with all applicable laws and regulations. The informed consent form and patient information sheet described the planned and permitted uses, transfers and disclosures of the patient's personal data and personal health information for purposes of conducting the study. The informed consent form and the patient information sheet further explained the nature of the study, its objectives and potential risks and benefits as well as the date informed consent was given. Before being enrolled in the clinical trial, every patient was informed that participation in this trial was voluntary and that he/she could withdraw from the study at any time without giving a reason and without having to fear any loss in his/her medical care. The patient’s consent was obtained in writing before the start of the study. By signing the informed consent, the patient declared that he/she was participating voluntarily and intended to follow the study protocol instructions and the instructions of the investigator and to answer the questions asked during the course of the trial.

Background therapy:

Rennie Kautabletten was used as rescue medication only in cases when the patient came to the conclusion that the heartburn episode was no longer tolerable. Administration of Rennie Kautabletten was should be performed in accordance with the SmPC. Patients were instructed to use 1 tablet in cases when he/she came to the conclusion that the heartburn episode was no longer tolerable and to use the next dose earliest 0.5 to 1 h after previous intake. However, the maximum dose of 11 tablets was not allowed to be exceeded.
Use of rescue medication was assessed as secondary study objective.

Evidence for comparator:

As comparator a placebo water was used available on the market and bottled by the sponsor. To assure a blinding, a placebo product with a comparable amount of carbonic acid but low mineralisation was applied. Additionally, Verum and Placebo water were packed in identical bottles with the same label to perform blinding as far as possible.

Actual start date of recruitment	09 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 148

Worldwide total number of subjects	148
EEA total number of subjects	148

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)	103
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of 175 patients screened, 161 patients entered the run-in phase. Only 13 patients were excluded after the run-in phase and were not randomised. Of these, 7 patients were excluded due to violation of inclusion criteria 9 (N=2) or 10 (N=5).

Pre-assignment

Screening details:

In total 175 patients were screened:
N=14 patients excluded after V1 (screening) due to:
- violation of exclusion criteria (N=3)
- violation of inclusion criteria (N=7)
- withdrawal of ICF (N=2)
- other reason (N=2)

Pre-assignment period milestones

Number of subjects started	161[1]
Number of subjects completed	148

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not matching exclusion criteria: 2
Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Not matching inclusion criteria: 6
Reason: Number of subjects	Personal reason: 2

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 161 patients entered the run-in phase. Only 13 patients were excluded after the run-in phase and were not randomised. Of these, 7 patients were excluded due to violation of inclusion criteria 9 (N=2) or 10 (N=5). Randomsiation to one of the treatments were performed after sucsessfull performance of the run-in phase.

Period 1

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

Blinding implementation details:

Randomisation was performed in blocks. To prevent unintentional unblinding, the block size was withheld by the randomisation service provider until completion of the clinical part of the trial.
At study visit V2, eligible patients were randomised to receive Verum or Placebo according to a randomisation plan in a 1:1 ratio. The assignment was conducted in a blinded fashion via Clinical Supply Management.

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description: -

Arm type	Experimental

Investigational medicinal product name	Staatl. Fachingen STILL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

The treatment period with daily administration of the IMPs lasted for 6 weeks (i.e., 42 days).
Each patient was to asked to drink 2 bottles (1.5 L) of Staatl. Fachingen STILL per day.
Patients were instructed to drink a total of 1.5 L daily dispensed over the day. Recommendation for daily intake was given in the diary.
Any remaining amount of the 1.5 L Verum was estimated by the patient and documented daily.

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:

The treatment period with daily administration of the IMPs lasted for 6 weeks (i.e., 42 days).
Each patient was to asked to drink 2 bottles (1.5 L) of the Placebo water per day.
Patients were instructed to drink a total of 1.5 L daily dispensed over the day. Recommendation for daily intake was given in the diary.
Any remaining amount of the 1.5 L Placebo was estimated by the patient and documented daily.

Number of subjects in period 1	Verum	Placebo
Started	73	75
Completed	72	71
Not completed	1	4
Consent withdrawn by subject	-	3
Adverse event, non-fatal	1	-
Protocol deviation	-	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	73	75	148
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)	55	48	103
From 65-84 years	18	27	45
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	54.6	57.9	
standard deviation	± 13.4	± 13.5	-
Gender categorical Units: Subjects			
Female	46	51	97
Male	27	24	51

Subject analysis sets	
Subject analysis set title	SAS
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAS was defined as all patients randomised who received the investigational treatment or placebo at least once.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all patients randomised who received the investigational treatment or placebo at least once, and who provided any post-baseline data for the symptom score used for determining the primary outcome measure, and who did not violate against inclusion criteria.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS was defined as all patients included in the FAS:
• who completely passed the pre-defined treatment regimen, and
• whose relevant study variables were available, and

• who finished the study without major protocol deviations.
Protocol violations were classified as "major" when a significant influence on the assessment of the primary outcome measure of treatment efficacy was not excluded (e.g. no treatment-compliant day, no overall treatment compliance, no valid assessment of study variables RDQ and QOLRAD is given for all seven out of the seven (7/7) days prior to the day of the visit

Reporting group values	SAS	FAS	PPS
Number of subjects	148	146	103
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)	103	101	68
From 65-84 years	45	45	35
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	56.3	56.5	56.6
standard deviation	± 13.5	± 13.5	± 14.3
Gender categorical			
Units: Subjects			
Female	97	97	70
Male	51	49	33

End points

End points reporting groups

Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	SAS
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAS was defined as all patients randomised who received the investigational treatment or placebo at least once.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS was defined as all patients randomised who received the investigational treatment or placebo at least once, and who provided any post-baseline data for the symptom score used for determining the primary outcome measure, and who did not violate against inclusion criteria.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS was defined as all patients included in the FAS:
• who completely passed the pre-defined treatment regimen, and
• whose relevant study variables were available, and
• who finished the study without major protocol deviations.
Protocol violations were classified as "major" when a significant influence on the assessment of the primary outcome measure of treatment efficacy was not excluded (e.g. no treatment-compliant day, no overall treatment compliance, no valid assessment of study variables RDQ and QOLRAD is given for all seven out of the seven (7/7) days prior to the day of the visit

Primary: RDQ responder rate

End point title	RDQ responder rate[1]

End point description:

Responder rate was defined by percentage of patients with a reduction from baseline of at least 5 points in the RDQ score in the dimension "heartburn" after 6 weeks of treatment.

End point type	Primary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

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: As primary end point responder rate was defined, no additional analysis is given

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	74		
Units: percent				
number (not applicable)				
Responder	84.72	63.51		
Non-Responder	15.28	36.49		

Statistical analyses

No statistical analyses for this end point

Secondary: RDQ dimension heartburn

End point title	RDQ dimension heartburn

End point description:

For RDQ (Reflux Disease Questionnaire) dimension "heartburn", 2 questions regarding frequency and 2 questions regarding severity were provided, resulting in a maximal score of 20 points. A decreased RDQ score indicates an improvement in symptoms.

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[2]	74[3]		
Units: Score				
arithmetic mean (standard deviation)				
V2	13.56 (± 3.32)	12.59 (± 3.22)		
V5	4.43 (± 4.47)	6.26 (± 5.42)		

Notes:

[2] - N (V2) = 72 ; N (V5) = 71

[3] - N (V2) = 74; N (V5) = 72

Statistical analyses

Statistical analysis title	Changes RDQ dimension "heartburn" from baseline
Comparison groups	Placebo v Verum
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5843
upper limit	-1.078

Notes:

[4] - explorative

Secondary: RDQ dimension regurgitation

End point title	RDQ dimension regurgitation

End point description:

For RDQ (Reflux Disease Questionnaire) dimension "regurgitation", 2 questions regarding frequency and 2 questions regarding severity were provided, resulting in a maximal score of 20 points. A decreased RDQ score indicates an improvement in symptoms.

End point type	Secondary

End point timeframe:

V2(baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[5]	72[6]		
Units: Score				
arithmetic mean (standard deviation)				
V2	9.38 (± 5.54)	9.30 (± 5.67)		
V5	4.03 (± 5.18)	5.04 (± 5.00)		

Notes:

[5] - N(V2) = 71; N(V5) = 71

[6] - N(V2) = 74; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes RDQ dimension "regurgitation from baseline
Comparison groups	Placebo v Verum
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.0676
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2308
upper limit	0.0789

Notes:

[7] - explorative

Secondary: RDQ dimension dyspepsia

End point title	RDQ dimension dyspepsia

End point description:

For RDQ (Reflux Disease Questionnaire) dimension "dyspepsia", 2 questions regarding frequency and 2 questions regarding severity were provided, resulting in a maximal score of 20 points. A decreased RDQ score indicates an improvement in symptoms.

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[8]	72[9]		
Units: Score				
arithmetic mean (standard deviation)				
V2	10.07 (± 5.03)	8.87 (± 5.56)		
V5	4.43 (± 4.47)	6.26 (± 5.42)		

Notes:

[8] - N(V2) = 72; N(V5) = 71

[9] - N(V2) = 74; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes RDQ dimension "dyspepsia" from baseline
Comparison groups	Verum v Placebo
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.1194
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2692
upper limit	0.2627

Notes:

[10] - explorative

Secondary: RDQ total score

End point title	RDQ total score

End point description:

The RDQ (Reflux Disease Questionnaire) consists of 12 items within the 3 dimensions "heartburn", "regurgitation" and "dyspepsia" assessing the last 7 days. Each item was rated for frequency and severity from 0 (most positive option) to 5 (most negative option), with 2 questions per dimension regarding frequency and 2 questions regarding severity. Total score range: 0 to 60

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[11]	74[12]		
Units: Score				
arithmetic mean (standard deviation)				
V2	33.00 (± 10.90)	30.76 (± 11.59)		
V5	12.41 (± 12.60)	16.39 (± 12.74)		

Notes:
[11] - N(V2) = 71 ; N(V5) = 71
[12] - N(V2) = 74; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes in RDQ "total score" from baseline
Comparison groups	Verum v Placebo
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.005
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6901
upper limit	-1.3905

Notes:
[13] - explorative

Secondary: QOLRAD domain "emotional distress"

End point title	QOLRAD domain "emotional distress"

End point description:

The disease-specific QOLRAD (Quality of Life in Reflux and Dyspepsia Questionnaire) was used to assess the health-related quality of life of the patients during the last 7 days. Frequency and severity of the symptoms were rated on a 7-point Likert scale ranging from 1 (worst condition) to 7 (best condition).

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[14]	74[15]		
Units: Score				
arithmetic mean (standard deviation)				
V2	4.898 (± 1.249)	5.099 (± 1.479)		
V5	6.238 (± 1.067)	5.931 (± 1.022)		

Notes:
[14] - N(V2) = 70; N(V5) =72
[15] - N(V2) = 74 ; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes QOLRAD "emotional distress" from baseline
Comparison groups	Verum v Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.0147
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0704
upper limit	0.6344

Notes:

[16] - explorative

Secondary: QOLRAD domain "food/drink problems"

End point title	QOLRAD domain "food/drink problems"

End point description:

The disease-specific QOLRAD (Quality of Life in Reflux and Dyspepsia Questionnaire) was used to assess the health-related quality of life of the patients during the last 7 days. Frequency and severity of the symptoms were rated on a 7-point Likert scale ranging from 1 (worst condition) to 7 (best condition).

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[17]	74[18]		
Units: Score				
arithmetic mean (standard deviation)				
V2	4.119 (± 1.069)	4.513 (± 1.138)		
V5	5.761 (± 1.208)	5.500 (± 1.263)		

Notes:

[17] - N(V2) = 70; N(V5) = 72

[18] - N(V2) = 74 ; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes QOLRAD "food/drink problems" from baseline
Comparison groups	Verum v Placebo

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.0125
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0834
upper limit	0.6779

Notes:

[19] - explorative

Secondary: QOLRAD domain "physical/social functioning

End point title	QOLRAD domain "physical/social functioning

End point description:

The disease-specific QOLRAD (Quality of Life in Reflux and Dyspepsia Questionnaire) was used to assess the health-related quality of life of the patients during the last 7 days. Frequency and severity of the symptoms were rated on a 7-point Likert scale ranging from 1 (worst condition) to 7 (best condition).

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[20]	74[21]		
Units: Score				
arithmetic mean (standard deviation)				
V2	5.380 (± 1.115)	5.416 (± 1.211)		
V5	6.342 (± 0.920)	6.158 (± 0.972)		

Notes:

[20] - N(V2) = 69; N(V5) = 72

[21] - N(V2) = 74; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes QOLRAD "phys./soc. function" from baseline
Comparison groups	Placebo v Verum
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.1048
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0403
upper limit	0.4227

Notes:

[22] - explorative

Secondary: QOLRAD domain "sleep disturbance"

End point title	QOLRAD domain "sleep disturbance"

End point description:

The disease-specific QOLRAD (Quality of Life in Reflux and Dyspepsia Questionnaire) was used to assess the health-related quality of life of the patients during the last 7 days. Frequency and severity of the symptoms were rated on a 7-point Likert scale ranging from 1 (worst condition) to 7 (best condition).

End point type	Secondary

End point timeframe:

V2 (baseline) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[23]	74[24]		
Units: Score				
arithmetic mean (standard deviation)				
V2	4.937 (± 1.206)	4.989 (± 1.477)		
V5	6.103 (± 1.064)	5.939 (± 1.158)		

Notes:

[23] - N(V2) = 70; N(V5) = 72

[24] - N(V2) = 74 ; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes QOLRAD "sleep disturbance" from baseline
Comparison groups	Placebo v Verum
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.1604
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0851
upper limit	0.5095

Notes:

[25] - explorative

Secondary: QOLRAD domain "vitality"

End point title	QOLRAD domain "vitality"

End point description:

The disease-specific QOLRAD (Quality of Life in Reflux and Dyspepsia Questionnaire) was used to assess the health-related quality of life of the patients during the last 7 days. Frequency and severity of the symptoms were rated on a 7-point Likert scale ranging from 1 (worst condition) to 7 (best condition).

End point type	Secondary

End point timeframe:

V2 (baseline) vs V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[26]	74[27]		
Units: Score				
arithmetic mean (standard deviation)				
V2	4.290 (± 1.271)	4.369 (± 1.337)		
V5	5.898 (± 1.233)	5.495 (± 1.302)		

Notes:

[26] - N(V2) = 70 ; N(V5) = 72

[27] - N(V2) = 74; N(V5) = 72

Statistical analyses

Statistical analysis title	Changes QOLRAD "vitality" from baseline
Comparison groups	Placebo v Verum
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.0393
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.0164
upper limit	0.6409

Notes:

[28] - explorative

Secondary: TSQM-9 domain "effectiveness"

End point title	TSQM-9 domain "effectiveness"

End point description:

The TSQM-9 (Treatment Satisfaction Questionnaire for Medication version 9) was used for assessment of patient´s satisfaction during the last 2 to 3 weeks.

End point type	Secondary

End point timeframe:

V3 (study day 14) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[29]	72[30]		
Units: Score				
arithmetic mean (standard deviation)				
V3	65.664 (± 24.990)	51.003 (± 23.613)		
V5	74.100 (± 26.873)	54.851 (± 28.280)		

Notes:

[29] - N(V3) = 72 ; N(V5) = 71

[30] - N(V3) = 72 ; N(V5) = 71

Statistical analyses

No statistical analyses for this end point

Secondary: TSQM-9 domain "convenience"

End point title	TSQM-9 domain "convenience"

End point description:

End point type	Secondary

End point timeframe:

V3 (study day 14) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[31]	72[32]		
Units: Score				
arithmetic mean (standard deviation)				
V3	88.272 (± 15.079)	86.227 (± 16.518)		
V5	89.906 (± 14.064)	89.358 (± 14.202)		

Notes:

[31] - N(V3) = 72 ; N(V5) = 71

[32] - N(V3) = 72 ; N(V5) = 71

Statistical analyses

No statistical analyses for this end point

Secondary: TSQM-9 "global satisfaction"

End point title	TSQM-9 "global satisfaction"

End point description:

End point type	Secondary

End point timeframe:

V3 (study day 14) vs. V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[33]	72[34]		
Units: Score				
arithmetic mean (standard deviation)				
V3	69.345 (± 22.854)	53.174 (± 24.182)		
V5	79.376 (± 21.346)	59.184 (± 29.865)		

Notes:

[33] - N(V3) = 72 ; N(V5) = 71

[34] - N(V3) = 72 ; N(V5) = 70

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of effectiveness by investigator

End point title	Evaluation of effectiveness by investigator

End point description:

The investigator evaluated the effectiveness of the treatment by using a 4-point verbal rating scale (VRS).

End point type	Secondary

End point timeframe:

V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	74		
Units: percent				
number (not applicable)				
very good	59.72	35.14		
good	25.00	22.97		
moderate	8.33	29.73		
bad	5.56	9.46		
missing	1.39	2.70		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of tolerability by investigator

End point title	Evaluation of tolerability by investigator

End point description:

The investigator evaluated the tolerability of the treatment by using a 4-point verbal rating scale (VRS).

End point type	Secondary

End point timeframe:

V5 (study day 43)

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	74		
Units: percent				
number (not applicable)				
very good	70.83	52.70		
good	19.44	33.78		
moderate	4.17	5.41		
bad	4.17	5.41		
missing	1.39	2.70		

Statistical analyses

No statistical analyses for this end point

Secondary: Average number of heartburn episodes per day

End point title	Average number of heartburn episodes per day

End point description:

Weekly intervals were considered as observation periods.

End point type	Secondary

End point timeframe:

week 1 - week 6

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[35]	74[36]		
Units: number				
arithmetic mean (standard deviation)				
week 1	0.64 (± 0.77)	0.71 (± 0.67)		
week 2	0.56 (± 0.64)	0.58 (± 0.55)		
week 3	0.49 (± 0.68)	0.56 (± 0.53)		
week 4	0.49 (± 0.61)	0.60 (± 0.47)		

week 5	0.41 (± 0.59)	0.58 (± 0.46)		
week 6	0.48 (± 0.66)	0.58 (± 0.48)		

Notes:

[35] - Number of subjects for all weeks = 72

[36] - N(week 1) = 74 ; N(week 2) = 74 ; N(week 3) =73 ; N(week4) =72; N(week 4) = 71; N(week 6) = 71

Statistical analyses

No statistical analyses for this end point

Secondary: Average number of tablets of rescue medication per day

End point title	Average number of tablets of rescue medication per day

End point description:

End point type	Secondary

End point timeframe:

baseline - week 6

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[37]	74[38]		
Units: number				
arithmetic mean (standard deviation)				
baseline interval	0.73 (± 1.15)	0.56 (± 0.85)		
week 1	0.64 (± 1.51)	0.67 (± 1.19)		
week 2	0.59 (± 1.60)	0.60 (± 1.17)		
week 3	0.56 (± 1.48)	0.51 (± 1.25)		
week 4	0.54 (± 1.25)	0.55 (± 1.17)		
week 5	0.46 (± 1.31)	0.60 (± 1.21)		
week 6	0.47 (± 1.13)	0.60 (± 1.44)		

Notes:

[37] - Number of patients in all intervalls = 72

[38] - N (baseline & week 1 & week 2) = 74; N(week 3) =73; N(week 4) = 72; N(week 5 & week 6) =71

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The observation phase for AEs began with the start of the treatment (i.e. 1st administration of IMP) and ended with the discharge of the patient from the clinical trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

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

Reporting group description: -

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 73 (24.66%)	21 / 75 (28.00%)	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Vascular disorders			

Hot flush			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	17 / 73 (23.29%)	13 / 75 (17.33%)	
occurrences (all)	17	13	
Migraine			
subjects affected / exposed	2 / 73 (2.74%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Dizziness postural			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 73 (1.37%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Abdominal distension			

subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Defaecation urgency			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Dry mouth			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 73 (2.74%)	1 / 75 (1.33%)	
occurrences (all)	2	1	
Paraesthesia oral			
subjects affected / exposed	2 / 73 (2.74%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Toothache			
subjects affected / exposed	1 / 73 (1.37%)	2 / 75 (2.67%)	
occurrences (all)	1	2	
Dyspepsia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Epigastric discomfort			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Eructation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Reproductive system and breast			

disorders			
Dysmenorrhoea			
subjects affected / exposed	4 / 73 (5.48%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
breast pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Throat irritation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Somatic symptom disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Arthralgia			
subjects affected / exposed	0 / 73 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	0 / 73 (0.00%)	10 / 75 (13.33%)	
occurrences (all)	0	10	
Neck pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Infections and infestations			

Gastroenteritis			
subjects affected / exposed	1 / 73 (1.37%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Oral herpes			
subjects affected / exposed	1 / 73 (1.37%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 73 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 73 (0.00%)	4 / 75 (5.33%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2018	1. Upon request of the competant authorithy exclusion criteria Nos. 2, 3, and 26 were described more precisely by using threshold levels. No 2. severe renal impairment (i.e. eGFR < 59 mL/min/1.73 m2 determined from serum creatinine during screening) No. 3. severe heart failure (i.e. NYHA III/IV) No.26. laboratory values out of normal range unless the deviation from normal is judged as not relevant for the clinical trial by the investigator or if the following thresholds have been reached (haemoglobin < 6.2 mmol/l, leukocytes <2500 / µl, platelets < 60000 / µl). For calculation of the eGFR the MDRD formula has been added to chapter 13.5.6.1 "Description of measurements" as follows: The eGFR at screening will be calculated from the creatinine concentration measured in serum according to the following formula : eGFR [mL/min/1.73 m2] = 175 × [Creatinine in Serum (mg/dL)]-1.154 × [Age (years)]-0.203 × (0.742 if female) × (1.212 if African American) 2. According to the Guideline on the evaluation of drugs for the treatment of gastro-oesophageal reflux disease the wash out phase of PPIs was adapted from 3 to 4 weeks prior to screening (exclusion criteria 18) and also 4 weeks prior to baseline visit via re-check of exclusion criteria (exclusion criteria No. 27). 3. According to the final protocol an independent representative of the sponsor will be involved in the DMC. Upon request of the authority preventive measures, which will be taken to avoid accidental transfer of non-blinded data have been added in the protocol.
14 December 2018	1. Upon request by the leading Ethics Committee an exclusion criteria was added in the protocol, which prevents the participation in the clinical trial due to intake of potential stomach damaging medication. Thus, exclusion criteria No. 17 "continuous treatment with nonsteroidal anti-inflammatory drugs (NSAIDs e.g. piroxicam, ketoprofen, diclofenac, acetylsalicylic acid or indomethacin (occasionally treatment with NSAIDs or except for ASS 100 mg daily is permitted, see also chapter 13.4.4.))" was adapted. Furthermore, in chapter 13.4.4 a paragraph regarding permitted medication was added and the original wording adapted. 2. During planning of the trial, it was observed, that the exclusion criterion No. 2 "severe renal impairment (i.e. eGFR1 < 59 mL/min/1.73 m2 determined from serum creatinine during screening)" cannot be assessed on visit 1 as the result of creatinine is not yet available on visit 1. Thus, the exclusion criterion was adapted to "signs of severe renal impairment known from medical history or reported during screening examination". The originally exclusion criterion No. 2 will now be assessed on visit 2 before randomisation and treatment with the IMP will start. Thus, the exclusion criterion "severe renal impairment (i.e. eGFR ≤ 29 mL/min/1.73 m2 determined from serum creatinine during screening) was added as No. 26 determined at baseline visit.. However, the limit was adapted from eGFR of ≤ 59 mL/min/1.73 m2 to ≤ 29 mL/min/1.73 m2 as erroneously 59 mL/min/1.73 m2 represents the upper limit of the classification of moderate renal impairment and not the limit for severe." 3. Furtheremore, documentation in CRF and diary was adapted with regard to date of inclusion, date of randomsiation and information on daily fluid in the administrative period.

04 November 2019	In accordance with the Scientific Advice, patients were included based on a gastric endoscopic examination within the last year prior indicating a Los Angeles classification of grade A or better in endoscopic examination. The participating Principal Investigators informed the sponsor, that this request is not in accordance with the common medical practice since the new version of the German medical guideline "S2k-Leitlinie 021/013 Gastroösophageale Refluxkrankheit" (version dated June 14th, 2014) came into effect. According to this a gastric endoscopic examination should not be performed as long as due to typical symptoms of a reflux disease like heartburn a GERD can be estimated as long as no alarm symptoms like dysphagia and odynophagia, non-intended weight loss of >5% or anaemia, especially in case of information about blood loss in the GI-tract or clinical information with regard to complications such as development of esophageal/epigastric mass, strictures and/or, ulceration exist. Furthermore, investigations of Malfertheiner et al. (ProGERD study) have showed, that in patients with primary symptom of heartburn and non-erosive (NERD), erosive reflux disease (ERD), or LA grades A-D (Los Angeles classification) during the 5 year follow-up period only a few patients with NERD and mild/moderate ERD progressed to severe forms of ERD or Barrett's oesophagus. Most GERD patients remain stable or improve over a 5-year observation period under current routine clinical care and also for patients with oesophagitis, they remained stable or showed improvement. Thus, inclusion criteria No. 04 was adapted and an endoscopic examination witin the last 5 years was accepted for inclusion.
10 March 2020	Dr. Cornelius Koch will resign from his position as Coordinating Investigator of the trial and as Principal Investigator for the site Erfurt by March 31st 2020. Subsequently, Dr. Frank Donath will take over as Coordinating Investigator and Principal Investigator for the site Erfurt.
03 April 2020	As during the trial the public life restrictions due to COVID-19 pandemic came into effect, the study protocol was adapted to allowed a remotely performance of for V2 to V5. Thus, all chapters describing measures to be performed on V2 to V5 have been adapted accordingly.
08 April 2021	According to previous protocol version recruitment was intended to be stopped during the time of the interim analysis. In case the sample size does not suffice the study may be continued after the interim analysis. However, to compensate the significantly delayed recruitment as a result of the Covid-19 pandemic a formal stop of the recruitment was not realised to allow for uninterrupted recruitment procedures in case further subjects are needed. Furthermore, the protocol did not state how potentially occurring overrunning subjects shall be handled biometrically. Thus, with Amendment 06 the procedure is clarified in accordance with the EMA requirements for adaptive designs. Overrunning patients will not have an impact on the planned interim analysis. Overrunning patients - will become part of the populations of the 2nd stage, in case of continuation of the trial, or - these patients will be included in an additional analysis that will be provided based on all randomized patients and will be considered the final analysis, in case of discontinuation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported