



Clinical trial results:

Randomized double-blind, placebo-controlled parallel group study over 12 months to assess the effects of treatment with benfotiamine on morphometric, neurophysiological, and clinical measures in type 2 diabetes patients with mild to moderate symptomatic polyneuropathy - BOND Study

Summary

EudraCT number	2017-003054-16
Trial protocol	DE
Global end of trial date	13 March 2024

Results information

Result version number	v1 (current)
This version publication date	30 August 2025
First version publication date	30 August 2025

Trial information

Trial identification

Sponsor protocol code	DDZ-BOND-2017
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Wörwag Pharma GmbH & co. KG
Sponsor organisation address	Flugfeld-Allee 24, Böblingen, Germany, 71034
Public contact	Head of Global Clinical Research, Wörwag Pharma GmbH & co. KG, 0049 070316204416, claudia.reule@woerwagpharma.com
Scientific contact	Head of Global Clinical Research, Wörwag Pharma GmbH & co. KG, 0049 070316204416, claudia.reule@woerwagpharma.com

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	31 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2024
Global end of trial reached?	Yes
Global end of trial date	13 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of treatment with benfotiamine compared to placebo for 1 year on morphometric, neurophysiological, and clinical measures in type 2 diabetes patients with mild to moderate symptomatic sensorimotor polyneuropathy.

Protection of trial subjects:

The trial was in compliance with the ethical principles outlined in the Declaration of Helsinki and the International Council for Harmonisation's Good Clinical Practice (ICH GCP) guidelines. Additionally, all local regulatory requirements related to participant safety were followed throughout the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Germany: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

FPFV: 18.10.2018

LPLV: 13.03.2024

Recruitment stop due to COVID19 pandemic: 16.03.2020-18.05.2020 and 13.01.2021-01.02.2021

Pre-assignment

Screening details:

Screening of participants was based on the evaluation of the inclusion and exclusion criteria. A total of 122 participants were screened and 64 of them did not meet the inclusion criteria.

Period 1

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

Blinding implementation details:

Blood thiamin levels were not accessible until the end of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

12 months of treatment with placebo

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

Dosage and administration details:

The dosing scheme according to the clinical trial protocol in its latest version is shown in Table 4. This dosing scheme is to be applied by all randomized trial participants. The medication was to be taken as one tablet in the morning (6 am - 10 am), and one tablet in the evening (6 pm - 10 pm) unchewed with enough liquid, on a daily basis.

Arm title	Benfotiamine
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Arm description:

12 months of treatment with benfotiamine

Arm type	Active comparator
Investigational medicinal product name	Milgamma® mono 300
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In the current study, all participants were randomised to receive 600 mg of Benfotiamine or the corresponding dose of placebo. The dosing scheme according to the clinical trial protocol in its latest version is shown in Table 4. This dosing scheme is to be applied by all randomized trial participants. The medication was to be taken as one tablet in the morning (6 am - 10 am), and one tablet in the evening (6 pm - 10 pm) unchewed with enough liquid, on a daily basis.

Number of subjects in period 1	Placebo	Benfotiamine
Started	29	28
Completed	24	22
Not completed	5	6
Adverse Event, serious non-fatal	-	2
Drop Out	5	4

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	57	57	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	26	26	
From 65-84 years	31	31	
85 years and over	0	0	
Age continuous			
Units: years			
median	64		
inter-quartile range (Q1-Q3)	58 to 71	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	47	47	

Subject analysis sets

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

Subject analysis set description:

The ITT Population included all participants having at least one dose of treatment and at least one measurement of the primary endpoint under treatment.

The efficacy evaluation in this report focuses on the results of the ITT analysis. Criteria for "Intention to treat" were fulfilled by 27 in the placebo group. 2 Participants didn't fulfil the ITT criteria because they finished the trial before having a measurement of the primary endpoint under treatment and therefore, were not included into efficacy analysis.

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

Subject analysis set description:

The ITT Population included all participants having at least one dose of treatment and at least one measurement of the primary endpoint under treatment.

The efficacy evaluation in this report focuses on the results of the ITT analysis. Criteria for "Intention to treat" were fulfilled by 24 in the befotiamine grou. Four participants didn't fulfil the ITT criteria because they finished the trial before having a measurement of the primary endpoint under treatment and therefore, were not included into efficacy analysis.

Reporting group values	Placebo	Benfotiamine	
Number of subjects	27	24	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	 13 14	 9 15	
Age continuous Units: years median inter-quartile range (Q1-Q3)	 65 58 to 73	 68.5 62.5 to 71.5	
Gender categorical Units: Subjects			
Female Male	 3 24	 7 17	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: 12 months of treatment with placebo	
Reporting group title	Benfotiamine
Reporting group description: 12 months of treatment with benfotiamine	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population included all participants having at least one dose of treatment and at least one measurement of the primary endpoint under treatment. The efficacy evaluation in this report focuses on the results of the ITT analysis. Criteria for "Intention to treat" were fulfilled by 27 in the placebo group. 2 Participants didn't fulfil the ITT criteria because they finished the trial before having a measurement of the primary endpoint under treatment and therefore, were not included into efficacy analysis.	
Subject analysis set title	Benfotiamine
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT Population included all participants having at least one dose of treatment and at least one measurement of the primary endpoint under treatment. The efficacy evaluation in this report focuses on the results of the ITT analysis. Criteria for "Intention to treat" were fulfilled by 24 in the befotiamine grou. Four participants didn't fulfil the ITT criteria because they finished the trial before having a measurement of the primary endpoint under treatment and therefore, were not included into efficacy analysis.	

Primary: PRIMARY ENDPOINT: CORNEAL NERVE FIBER LENGTH (CNFL)

End point title	PRIMARY ENDPOINT: CORNEAL NERVE FIBER LENGTH (CNFL)
End point description: The primary aim of the trial was to demonstrate that the corneal nerve fiber length (CNFL) can be improved by the regular intake of 600 mg of benfotiamine for 12 months compared to placebo. The CNFL measurement focuses on the total length of all nerve fibers and branches within the area of corneal tissue. CNFL was measured by using laser scanning corneal confocal microscopy (CCM) examination with the HRT III Rostock Cornea module in vivo corneal confocal microscope (Heidelberg Engineering, Heidelberg, Germany). CCM was measured and scored according to a DDZ SOP. Measurement was performed by sub-investigators only and evaluation by study staff. The study staff selected 6 representative images which were entered into the ACCMetrics software for automatic analysis. CNFL have proven to be highly reproducible and to be closely associated with the severity of DSPN. CCM was performed at baseline, after 6 months (visit 5) and after 12 months (visit 7) of treatment.	
End point type	Primary
End point timeframe: Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: mm/mm2				
arithmetic mean (standard deviation)	0.84 (± 3.54)	0.56 (± 3.58)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
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Statistical analysis description:

Differences of baseline to post-treatment changes after 12 months between treatment arms were planned to be analysed by means of analysis of covariance (ANCOVA), where the post-treatment outcome entered the model as the dependent variable and a treatment indicator and the baseline outcome, age, gender, covid-19 information (pre and during covid-19 pandemic) and concomitant medication with gabapentin, pregabalin or duloxetine entered as independent variables.

Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76 ^[1]
Method	ANCOVA

Notes:

[1] - P values: Unadjusted analysis (t Test): 0.314; Adjusted analysis (ANCOVA): 0.806; Adjusted analysis (ANCOVA) after multiple imputation: 0.760

Secondary: CORNEAL NERVE FIBER DENSITY (CNFD)

End point title	CORNEAL NERVE FIBER DENSITY (CNFD)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 12 months of treatment

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: mm/mm ²				
arithmetic mean (standard deviation)	0.50 (± 4.62)	-0.94 (± 4.21)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine2
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.479
Method	ANCOVA

Secondary: CORNEAL NERVE BRANCH DENSITY (CNBD)

End point title	CORNEAL NERVE BRANCH DENSITY (CNBD)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: mm/mm2				
arithmetic mean (standard deviation)	10.40 (± 19.71)	3.22 (± 14.99)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.309
Method	ANCOVA

Secondary: CORNEAL NERVE FIBER TORTUOSITY (CNFT)

End point title	CORNEAL NERVE FIBER TORTUOSITY (CNFT)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.01 ($\pm$ 0.07)	-0.00 ($\pm$ 0.06)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Benfotiamine v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.531
Method	ANCOVA

Secondary: INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD)

End point title	INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: fibers/mm				
arithmetic mean (standard deviation)	-0.70 ($\pm$ 2.78)	-1.30 ($\pm$ 1.99)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.484
Method	ANCOVA

Secondary: ENDOTHELIAL CELL AREA-CLUSTER OF DIFFERENTIATION 31 (CD31)

End point title	ENDOTHELIAL CELL AREA-CLUSTER OF DIFFERENTIATION 31 (CD31)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: %				
arithmetic mean (standard deviation)	-0.09 (± 2.37)	-0.38 (± 1.45)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.775
Method	ANCOVA

Secondary: MITOCHONDRIAL SUPEROXIDE DISMUTASE AREA (SOD2)

End point title	MITOCHONDRIAL SUPEROXIDE DISMUTASE AREA (SOD2)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: %				
arithmetic mean (standard deviation)	-0.35 (± 2.06)	-0.28 (± 0.83)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.792
Method	ANCOVA

Secondary: MOTOR NERVE CONDUCTION VELOCITY (MNCV) SUM SCORE

End point title	MOTOR NERVE CONDUCTION VELOCITY (MNCV) SUM SCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	2.92 (± 14.09)	-2.43 (± 11.53)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	ANCOVA

Secondary: SENSORY NERVE CONDUCTION VELOCITY (SNCV) SUM SCORE

End point title	SENSORY NERVE CONDUCTION VELOCITY (SNCV) SUM SCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	2.87 (± 14.10)	-2.29 (± 11.60)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.919
Method	ANCOVA

Secondary: NERVE CONDUCTION VELOCITY (NCV) SUM SCORE

End point title	NERVE CONDUCTION VELOCITY (NCV) SUM SCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	2.91 ($\pm$ 14.09)	-2.38 ($\pm$ 11.55)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.979
Method	ANCOVA

Secondary: MEAN VALUE VIBRATION PERCEPTION THRESHOLD (VPT) CARPAL

End point title	MEAN VALUE VIBRATION PERCEPTION THRESHOLD (VPT) CARPAL
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: μ m				
arithmetic mean (standard deviation)	-0.09 ($\pm$ 1.00)	0.25 ($\pm$ 1.96)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.526
Method	ANCOVA

Secondary: MEAN VALUE VIBRATION PERCEPTION THRESHOLD (VPT) MALLEOLAR

End point title	MEAN VALUE VIBRATION PERCEPTION THRESHOLD (VPT) MALLEOLAR
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 month of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: μm				
arithmetic mean (standard deviation)	-1.15 ($\pm$ 4.89)	-1.88 ($\pm$ 4.21)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.609
Method	ANCOVA

Secondary: COLD DETECTION THRESHOLD (CDT) THENAR

End point title	COLD DETECTION THRESHOLD (CDT) THENAR
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: °C				
arithmetic mean (standard deviation)	0.16 (± 1.73)	0.04 (± 1.42)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.437
Method	ANCOVA

Secondary: WARMTH DETECTION THRESHOLD (WDT) THENAR

End point title	WARMTH DETECTION THRESHOLD (WDT) THENAR
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: °C				
arithmetic mean (standard deviation)	-0.81 (± 2.25)	-0.04 (± 1.37)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.328
Method	ANCOVA

Secondary: COLD DETECTION THRESHOLD (CDT) FOOT

End point title	COLD DETECTION THRESHOLD (CDT) FOOT
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: °C				
arithmetic mean (standard deviation)	0.21 (± 8.44)	1.26 (± 6.38)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.903
Method	ANCOVA

Secondary: WARMTH DETECTION THRESHOLD (WDT) FOOT

End point title	WARMTH DETECTION THRESHOLD (WDT) FOOT
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: °C				
arithmetic mean (standard deviation)	-0.91 (± 4.83)	0.98 (± 4.55)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.966
Method	ANCOVA

Secondary: SYSTOLIC BLOOD PRESSURE (SBP) IN RESPONSE TO STANDING

End point title	SYSTOLIC BLOOD PRESSURE (SBP) IN RESPONSE TO STANDING
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: mmHg				
arithmetic mean (standard deviation)	-2.33 (± 10.45)	-0.93 (± 9.14)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.274
Method	ANCOVA

Secondary: BAROREFLEX SENSITIVITY POSITIVE SLOPE (BRS+ / +)

End point title	BAROREFLEX SENSITIVITY POSITIVE SLOPE (BRS+ / +)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	6.16 (± 28.39)	3.32 (± 19.11)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	ANCOVA

Secondary: BAROREFLEX SENSITIVITY NEGATIVE SLOPE (BRS- / -)

End point title	BAROREFLEX SENSITIVITY NEGATIVE SLOPE (BRS- / -)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	-1.29 ($\pm$ 12.36)	-0.78 ($\pm$ 8.97)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.947
Method	ANCOVA

Secondary: SEQUENCE ANALYSIS BAROREFLEX SENSITIVITY (BRS-ALLSEQ)

End point title	SEQUENCE ANALYSIS BAROREFLEX SENSITIVITY (BRS-ALLSEQ)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	4.79 ($\pm$ 28.54)	0.60 ($\pm$ 11.49)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.581
Method	ANCOVA

Secondary: LOW FREQUENCY BAROREFLEX SENSITIVITY (BRS-LF)

End point title	LOW FREQUENCY BAROREFLEX SENSITIVITY (BRS-LF)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	4.50 (± 28.59)	1.08 (± 12.22)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.488
Method	ANCOVA

Secondary: HIGH FREQUENCY BAROREFLEX SENSITIVITY (BRS-HF)

End point title	HIGH FREQUENCY BAROREFLEX SENSITIVITY (BRS-HF)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	4.54 (± 28.58)	0.96 (± 12.64)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Benfotiamine v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.926
Method	ANCOVA

Secondary: SPONTANEOUS BAROREFLEX SENSITIVITY ALPHA (BRS-ALPHA)

End point title	SPONTANEOUS BAROREFLEX SENSITIVITY ALPHA (BRS-ALPHA)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	4.52 (± 28.59)	1.02 (± 12.28)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.867
Method	ANCOVA

Secondary: SPONTANEOUS BAROREFLEX SENSITIVITY CROSS-SPECTRAL ANALYSIS (XBRS)

End point title	SPONTANEOUS BAROREFLEX SENSITIVITY CROSS-SPECTRAL ANALYSIS (XBRS)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: ms/mmHg				
arithmetic mean (standard deviation)	0.22 (± 3.78)	0.39 (± 5.30)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.978
Method	ANCOVA

Secondary: STANDARD DEVIATION DERIVED BAROREFLEX SENSITIVITY (BRS-SD)

End point title	STANDARD DEVIATION DERIVED BAROREFLEX SENSITIVITY (BRS-SD)
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	1.52 ($\pm$ 2.87)	1.98 ($\pm$ 3.54)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232
Method	ANCOVA

Secondary: NEUROPAD QUANTITATIVE EVALUATION ROSE

End point title	NEUROPAD QUANTITATIVE EVALUATION ROSE
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: %				
arithmetic mean (standard deviation)	-8.20 ($\pm$ 60.01)	-30.12 ($\pm$ 52.71)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.347
Method	ANCOVA

Secondary: NEUROPAD QUANTITATIVE EVALUATION BLUE

End point title	NEUROPAD QUANTITATIVE EVALUATION BLUE
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: %				
arithmetic mean (standard deviation)	8.24 ($\pm$ 60.02)	30.57 ($\pm$ 52.44)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Benfotiamine v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	ANCOVA

Secondary: ELECTROCHEMICAL SKIN CONDUCTANCE (ESC) HANDS

End point title	ELECTROCHEMICAL SKIN CONDUCTANCE (ESC) HANDS
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: μS				
arithmetic mean (standard deviation)	-3.00 ($\pm$ 16.70)	0.93 ($\pm$ 15.17)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374
Method	ANCOVA

Secondary: ELECTROCHEMICAL SKIN CONDUCTANCE (ESC) FEET

End point title	ELECTROCHEMICAL SKIN CONDUCTANCE (ESC) FEET
End point description:	
End point type	Secondary
End point timeframe:	
Visit 2 (randomization) to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: μS				
arithmetic mean (standard deviation)	-0.98 ($\pm$ 14.44)	-6.68 ($\pm$ 15.70)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.524
Method	ANCOVA

Secondary: NEUROPATHY DISABILITY SCORE (NDS)

End point title	NEUROPATHY DISABILITY SCORE (NDS)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.79 (± 1.56)	0.14 (± 1.73)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	ANCOVA

Secondary: NEUROPATHY IMPAIRMENT SCORE – LOWER LIMBS (NIS-LL)

End point title	NEUROPATHY IMPAIRMENT SCORE – LOWER LIMBS (NIS-LL)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.46 ($\pm$ 2.43)	0.55 ($\pm$ 1.79)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANCOVA

Secondary: MICHIGAN NEUROPATHY SCREENING INSTRUMENT (MNSI) TOTALSCORE

End point title	MICHIGAN NEUROPATHY SCREENING INSTRUMENT (MNSI) TOTALSCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.33 ($\pm$ 1.26)	0.05 ($\pm$ 1.10)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.704
Method	ANCOVA

Secondary: MODIFIED TORONTO CLINICAL NEUROPATHY SCORE (MTCNS) TOTALSCORE

End point title	MODIFIED TORONTO CLINICAL NEUROPATHY SCORE (MTCNS) TOTALSCORE
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 12 months of treatment

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.33 (± 4.34)	0.32 (± 5.16)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.668
Method	ANCOVA

Secondary: NEUROPATHY SYMPTOM SCORE (NSS)

End point title	NEUROPATHY SYMPTOM SCORE (NSS)
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 12 months of treatment

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.33 ($\pm$ 1.49)	-0.59 ($\pm$ 2.54)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	ANCOVA

Secondary: TOTAL SYMPTOM SCORE (TSS) SHANK

End point title	TOTAL SYMPTOM SCORE (TSS) SHANK
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.26 ($\pm$ 2.58)	1.21 ($\pm$ 3.70)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.616
Method	ANCOVA

Secondary: TOTAL SYMPTOM SCORE (TSS) FEET

End point title	TOTAL SYMPTOM SCORE (TSS) FEET
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.14 ($\pm$ 2.61)	0.32 ($\pm$ 4.13)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.465
Method	ANCOVA

Secondary: NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI) SUMSCORE

End point title	NEUROPATHIC PAIN SYMPTOM INVENTORY (NPSI) SUMSCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-3.08 ($\pm$ 13.20)	0.64 ($\pm$ 20.28)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.967
Method	ANCOVA

Secondary: 11-POINT NUMERICAL PAIN RATING SCALE (NRS) PAIN 24H

End point title	11-POINT NUMERICAL PAIN RATING SCALE (NRS) PAIN 24H
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.17 ($\pm$ 1.27)	0.55 ($\pm$ 3.29)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.777
Method	ANCOVA

Secondary: 11-POINT NUMERICAL PAIN RATING SCALE PAIN NIGHT

End point title	11-POINT NUMERICAL PAIN RATING SCALE PAIN NIGHT
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.25 (± 3.07)	0.18 (± 3.83)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Benfotiamine v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.631
Method	ANCOVA

Secondary: 11-POINT NUMERICAL PAIN RATING SCALE (NRS) PAIN DAY

End point title	11-POINT NUMERICAL PAIN RATING SCALE (NRS) PAIN DAY
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.25 ($\pm$ 1.82)	0.77 ($\pm$ 3.16)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.634
Method	ANCOVA

Secondary: BRIEF PAIN INVENTORY (BPI) SEVERITY SCORE

End point title	BRIEF PAIN INVENTORY (BPI) SEVERITY SCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.58 ($\pm$ 2.60)	0.63 ($\pm$ 2.14)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.693
Method	ANCOVA

Secondary: BRIEF PAIN INVENTORY (BPI) INTERFERENCE SCORE

End point title	BRIEF PAIN INVENTORY (BPI) INTERFERENCE SCORE
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 12 months of treatment

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.52 (± 2.65)	-0.12 (± 1.59)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.846
Method	ANCOVA

Secondary: EUROQOL 5 DIMENSIONS, 5 LEVELS QUALITY OF LIFE QUESTIONNAIRE (EQ-5D-5L) EQ INDEX

End point title	EUROQOL 5 DIMENSIONS, 5 LEVELS QUALITY OF LIFE QUESTIONNAIRE (EQ-5D-5L) EQ INDEX
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End point description:

End point type	Secondary
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End point timeframe:

Baseline to 12 months of treatment

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-0.01 ($\pm$ 0.18)	-0.00 ($\pm$ 0.20)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.868
Method	ANCOVA

Secondary: EUROQOL 5 DIMENSIONS, 5 LEVELS QUALITY OF LIFE QUESTIONNAIRE (EQ-5D-5L) EQ VISUAL ANALOG SCALE (EQ VAS)

End point title	EUROQOL 5 DIMENSIONS, 5 LEVELS QUALITY OF LIFE QUESTIONNAIRE (EQ-5D-5L) EQ VISUAL ANALOG SCALE (EQ VAS)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-3.92 ($\pm$ 26.23)	-0.05 ($\pm$ 22.73)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.749
Method	ANCOVA

Secondary: SF-36 PHYSICAL COMPONENT SUMMARY

End point title	SF-36 PHYSICAL COMPONENT SUMMARY
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.18 ($\pm$ 7.03)	-0.82 ($\pm$ 10.69)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.881
Method	ANCOVA

Secondary: SF-36 MENTAL COMPONENT SUMMARY

End point title	SF-36 MENTAL COMPONENT SUMMARY
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	-1.17 ($\pm$ 8.00)	-1.28 ($\pm$ 8.53)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636
Method	ANCOVA

Secondary: PATIENT HEALTH QUESTIONNAIRE (PHQ-9) TOTALSCORE

End point title	PATIENT HEALTH QUESTIONNAIRE (PHQ-9) TOTALSCORE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: -				
arithmetic mean (standard deviation)	0.58 ($\pm$ 2.52)	0.00 ($\pm$ 3.70)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.756
Method	ANCOVA

Secondary: THIAMINE DIPHOSPHATE (TDP)

End point title	THIAMINE DIPHOSPHATE (TDP)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: nMol/l				
arithmetic mean (standard deviation)	40.00 (± 96.24)	191.09 (± 97.36)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	ANCOVA

Notes:

[2] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: <0.0001

Secondary: THIAMINE MONOPHOSPHATE (TMP)

End point title	THIAMINE MONOPHOSPHATE (TMP)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: nMol/l				
arithmetic mean (standard deviation)	0.29 (± 3.43)	8.18 (± 6.78)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[3]
Method	ANCOVA

Notes:

[3] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: <0.0001

Secondary: FREE THIAMINE (FT)

End point title	FREE THIAMINE (FT)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: nMol/l				
arithmetic mean (standard deviation)	16.88 (± 80.80)	326.73 (± 149.59)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	ANCOVA

Notes:

[4] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: <0.0001

Secondary: TRANSKETOLASE ACTIVITY

End point title	TRANSKETOLASE ACTIVITY
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: U/I				
arithmetic mean (standard deviation)	-3.54 (± 13.78)	27.06 (± 50.74)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[5]
Method	ANCOVA

Notes:

[5] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: 0.003

Secondary: THIAMIN PYROPHOSPHAT (TPP) EFFECT

End point title	THIAMIN PYROPHOSPHAT (TPP) EFFECT
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: %				
arithmetic mean (standard deviation)	-0.21 ($\pm$ 10.64)	5.37 ($\pm$ 56.06)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[6]
Method	ANCOVA

Notes:

[6] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: 0.002

Secondary: TOTAL THIAMINE

End point title	TOTAL THIAMINE
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: nMol/l				
arithmetic mean (standard deviation)	40.21 ($\pm$ 95.69)	181.14 ($\pm$ 91.92)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Placebo v Benfotiamine

Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	ANCOVA

Notes:

[7] - P values: Unadjusted analysis (t Test): <0.0001; Adjusted analysis (ANCOVA): <0.0001; Adjusted analysis (ANCOVA) after multiple imputation: <0.0001

Secondary: LANGERHANS CELL DENSITY (CD207)

End point title	LANGERHANS CELL DENSITY (CD207)
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to 12 months of treatment	

End point values	Placebo	Benfotiamine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	24		
Units: cells/mm ²				
arithmetic mean (standard deviation)	-14.70 (± 44.81)	-44.63 (± 113.86)		

Statistical analyses

Statistical analysis title	Changes after 12 months placebo vs. benfotiamine
Comparison groups	Benfotiamine v Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected before, during and after treatment. Only the adverse events during the treatment will be reported in this report.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27

Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Benfotiamine
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Reporting group description: -

Serious adverse events	Placebo	Benfotiamine	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 29 (17.24%)	6 / 28 (21.43%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign duodenal neoplasm			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ductal adenocarcinoma of pancreas alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	
Vascular disorders Peripheral artery occlusion subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 28 (0.00%) 0 / 0 0 / 0	
Surgical and medical procedures Spinal decompression alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 28 (0.00%) 0 / 0 0 / 0	
General disorders and administration site conditions Chest pain alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Respiratory failure alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0 0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0 1 / 28 (3.57%) 0 / 1 0 / 0	

Acute respiratory failure alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	
Investigations Inflammatory marker increased alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	
Injury, poisoning and procedural complications Fall alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 28 (0.00%) 0 / 0 0 / 0	
Fracture alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 29 (3.45%) 0 / 1 0 / 0	0 / 28 (0.00%) 0 / 0 0 / 0	
Postoperative delirium alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	
Cardiac disorders Pericarditis alternative dictionary used: MedDRA 26.1 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Pericardial effusion	0 / 29 (0.00%) 0 / 0 0 / 0	1 / 28 (3.57%) 0 / 1 0 / 0	

alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
alternative dictionary used: MedDRA 26.1.			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer perforation			
alternative dictionary used: MedDRA 26.1			

subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Micturition disorder			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal stenosis			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 26.1			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-serious adverse events	Placebo	Benfotiamine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 29 (93.10%)	27 / 28 (96.43%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine neoplasm			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Hypertensive emergency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
General physical health deterioration			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Oedema peripheral			

subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	5 / 28 (17.86%) 5	
Pain subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 28 (7.14%) 3	
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 28 (0.00%) 0	
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Postmenopausal haemorrhage subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Haematospermia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Respiratory disorder subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Pleural effusion subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Psychiatric disorders			

Sleep disorder subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 28 (3.57%) 1	
Premature ejaculation subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Investigations			
Blood albumin increased subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 28 (7.14%) 2	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 28 (3.57%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Blood glucose increased subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	2 / 28 (7.14%) 2	
Blood iron decreased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Blood pressure abnormal subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Blood pressure decreased subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Blood triglycerides increased			

subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Blood urea increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Carbohydrate antigen 19-9			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	3 / 29 (10.34%)	2 / 28 (7.14%)	
occurrences (all)	3	3	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Glycosylated haemoglobin increased			
subjects affected / exposed	3 / 29 (10.34%)	5 / 28 (17.86%)	
occurrences (all)	3	5	
Lipase increased			
subjects affected / exposed	3 / 29 (10.34%)	4 / 28 (14.29%)	
occurrences (all)	4	4	
Weight decreased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	2	2	
Humerus fracture			

subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Immunisation reaction		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Ligament sprain		
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences (all)	1	1
Mouth injury		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Post procedural haematoma		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Postoperative wound complication		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Reactive gastropathy		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Skin abrasion		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Skin injury		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Skin laceration		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Spinal column injury		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Tendon rupture		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Wound		

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Aortic valve disease mixed			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Coronary artery disease			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 29 (6.90%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Burning sensation			
subjects affected / exposed	0 / 29 (0.00%)	2 / 28 (7.14%)	
occurrences (all)	0	2	
Cerebral microangiopathy			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Headache			
subjects affected / exposed	0 / 29 (0.00%)	3 / 28 (10.71%)	
occurrences (all)	0	3	
Hypoaesthesia			

subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	3 / 28 (10.71%) 4	
Hyporeflexia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Migraine subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 28 (3.57%) 2	
Motor dysfunction subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Neuralgia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	2 / 28 (7.14%) 2	
Paraesthesia subjects affected / exposed occurrences (all)	5 / 29 (17.24%) 6	3 / 28 (10.71%) 4	
Sciatica subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Ear and labyrinth disorders Vertigo positional subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Eye disorders Bilateral cataracts subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Cataract subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 3	2 / 28 (7.14%) 2	
Macular oedema subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Gastrointestinal disorders			

Abdominal pain upper		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Chronic gastritis		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Dental caries		
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)
occurrences (all)	3	0
Diarrhoea		
subjects affected / exposed	5 / 29 (17.24%)	4 / 28 (14.29%)
occurrences (all)	11	13
Diverticulum intestinal		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Dyschezia		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Dyspepsia		
subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)
occurrences (all)	1	1
Flatulence		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Gastric ulcer		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Gastritis		
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)
occurrences (all)	1	0
Gastrooesophageal reflux disease		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)
occurrences (all)	0	1

Hiatus hernia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	3	
Pancreatic disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Pancreatic duct dilatation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Pancreatic failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tooth disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	3 / 29 (10.34%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hepatic cyst			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Biliary dilatation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Hydrocholecystis			

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Skin lesion			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Neurodermatitis			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Hidradenitis			
subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Ingrowing nail			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Dermatitis			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Blister			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Ketonuria			
subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Microalbuminuria			
subjects affected / exposed occurrences (all)	4 / 29 (13.79%) 4	5 / 28 (17.86%) 5	
Proteinuria			

subjects affected / exposed	1 / 29 (3.45%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Renal cyst			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	2	
Urinary retention			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 29 (6.90%)	4 / 28 (14.29%)	
occurrences (all)	2	8	
Back pain			
subjects affected / exposed	2 / 29 (6.90%)	4 / 28 (14.29%)	
occurrences (all)	4	7	
Flank pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 29 (3.45%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	1 / 29 (3.45%)	2 / 28 (7.14%)	
occurrences (all)	1	16	
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Osteitis			

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Osteoarthritis subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 28 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 6	5 / 28 (17.86%) 5	
Tendon pain subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	0 / 28 (0.00%) 0	
COVID-19 subjects affected / exposed occurrences (all)	3 / 29 (10.34%) 3	1 / 28 (3.57%) 1	
Cystitis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 6	
Focal peritonitis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Gastrointestinal infection subjects affected / exposed occurrences (all)	2 / 29 (6.90%) 2	1 / 28 (3.57%) 3	
Gingivitis subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Helicobacter gastritis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	

Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 29 (31.03%) 13	4 / 28 (14.29%) 6	
Pulpitis dental subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Sinusitis subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 28 (7.14%) 2	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 28 (3.57%) 1	
Onychomycosis subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Diabetes mellitus inadequate control subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 1	
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	0 / 28 (0.00%) 0	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 29 (3.45%) 1	1 / 28 (3.57%) 1	
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	1 / 28 (3.57%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 December 2018	Changes in the clinical trial protocol and change in subject compensation
08 May 2019	Changes to the inclusion and exclusion criteria
24 April 2020	Substantial changes in the trial conduct, handling drop-outs/discontinuations and statistical considerations due to COVID-19.
19 May 2020	Substantial amendment to clinical study protocol (Note to File #7 to #12); Submission Note to File #1 to #3
16 February 2021	Approval for resumption of screening visits due to COVID-19 and Amendment to clinical study protocol due to change of deputy investigator and incorporation of COVID-19 note to files.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
16 March 2020	Recruitment stop due to COVID19 pandemic	18 May 2020
13 January 2021	Recruitment stop due to COVID19 pandemic	01 February 2021

Notes:

Limitations and caveats

None reported