

**Clinical trial results:****EFFECTS OF BENFOTIAMINE ON INTRAEPIDERMAL NERVE FIBER DENSITY (IENFD) AND DIABETIC NEUROPATHY IN SUBJECTS WITH SENSORIMOTOR DIABETIC POLYNEUROPATHY: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP PILOT STUDY OVER 12 MONTHS****Summary**

EudraCT number	2013-001058-85
Trial protocol	DE
Global end of trial date	19 October 2015

Results information

Result version number	v2 (current)
This version publication date	30 July 2020
First version publication date	13 December 2016
Version creation reason	<ul style="list-style-type: none">• Correction of full data set During QC check an inconsistency was identified to statistical report. Therefore correction is necessary.
Summary attachment (see zip file)	Development Safety Update Report (2016-06-17 DSUR Benfothiamine.pdf)

Trial information**Trial identification**

Sponsor protocol code	WOE_2013_SB
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01868191
WHO universal trial number (UTN)	U1111-1140-6958

Notes:

Sponsors

Sponsor organisation name	Woerwag Pharma GmbH & Co. KG
Sponsor organisation address	Calwer Strasse 7, Boeblingen, Germany, 71034
Public contact	Investigator , Priv.-Doz. Dr. med. Ovidiu Alin Stirban , stirban@web.de
Scientific contact	Investigator , Priv.-Doz. Dr. med. Ovidiu Alin Stirban , stirban@web.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	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 April 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of the present study was to assess before, as well as after 6 and 12 months following a therapy with benfotiamine the influence of therapy on intraepidermal nerve fiber density (an early marker of nerve damage) in 22 people with type 1 or 2 diabetes mellitus and diabetic sensorimotor polyneuropathy. The trial was prematurely terminated (25-Sept-2015), due to technical problems with analysis of primary end point (skin biopsy). Therefore, secondary endpoints were analysed as observed.

Protection of trial subjects:

The trial was not initiated before the protocol and all other relevant documents according to German GCP Ordinance had been reviewed, and received favourable opinion from the local Independent Ethics Committee (IEC) and approval by the Competent Authority, respectively.

Should a protocol amendment be made that needed IEC favourable opinion and/or authority approval, the changes in the protocol were not to be instituted until the amendment had been reviewed and received favourable opinion by the local IEC, and approval by the Competent Authority. A protocol amendment intended to eliminate an apparent immediate hazard to subjects could have been implemented immediately providing that the regulatory authority and IEC were notified as soon as possible and an approval would have been requested.

The constitution of the IEC met the requirements of ICH GCP and of the participating country. The IEC performed all duties outlined by the requirements of ICH GCP and of the participating country.

Prior to subject participation in the trial, written informed consent was obtained from each subject according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature was personally dated by each signatory and the informed consent and any additional subject information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information was given to each subject.

The subject was informed that his/her personal trial-related data would be used in accordance with the local data protection law. The level of disclosure was also explained to the subject.

The subject was informed that his / her medical records could be examined by authorised monitors or Clinical Quality Assurance auditors appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

Background therapy:

Benfotiamine 300 mg was approved on 23.06.2005 for the treatment or prophylaxis of clinical manifest vitamin B1 deficiency if a dietary supplementation is not effective. Though, benfotiamine is used for many years in the treatment of diabetic and alcoholic polyneuropathies.

Evidence for comparator:

Placebo tablets were provided in a blinded manner by the Sponsor for the 12 months therapy.

Actual start date of recruitment	09 September 2013
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	12
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from the patients of the Diabetes Schwerpunktpraxis Essen (Camillo-Sitte Platz 1, 45136 Essen) and all study-related activities took place there.

Pre-assignment

Screening details:

Participants were screened at visit 1 (baseline) to be able to include 22 patients with T1 or T2DM on a stable regimen of antidiabetic treatment with no possibility of therapy intensification, with DSP, between 18 and 75 years of age, with a BMI between 25 and 45 kg/m², HbA1c ≤9.5 % .

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Benfotiamine V1

Arm description:

Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months

Arm type	Experimental
Investigational medicinal product name	Benfotiamine 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

visit 1 to visit 4 (3 months): 2x 1 tablet with 300 mg Benfotiamin (total daily dose: 600mg)

visit 4 to visit 7 (9 months): 1x1 tablet with 300 mg Benfotiamin (total daily dose: 300mg)

Arm title	Placebo V1
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Arm description:

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:

visit 1 to visit 4 (3 months): 2x 1 tablet placebo

visit 4 to visit 7 (9 months): 1x1 tablet placebo

Number of subjects in period 1	Benfotiamine V1	Placebo V1
Started	11	11
Completed	11	11

Period 2

Period 2 title	visit 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benfotiamine V4

Arm description:

Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months

Arm type	Experimental
Investigational medicinal product name	Benfotiamine 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

visit 1 to visit 4 (3 months): 2x 1 tablet with 300 mg Benfotiamin (total daily dose: 600mg)

visit 4 to visit 7 (9 months): 1x1 tablet with 300 mg Benfotiamin (total daily dose: 300mg)

Arm title	Placebo V4
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Arm description:

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:

visit 1 to visit 4 (3 months): 2x 1 tablet placebo

visit 4 to visit 7 (9 months): 1x1 tablet placebo

Number of subjects in period 2	Benfotiamine V4	Placebo V4
Started	11	11
Completed	11	10
Not completed	0	1
Adverse event, non-fatal	-	1

Period 3

Period 3 title	visit 5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benfotiamine V5

Arm description:

Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the 9 months

Arm type	Experimental
Investigational medicinal product name	Benfotiamine 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

visit 1 to visit 4 (3 months): 2x 1 tablet with 300 mg Benfotiamin (total daily dose: 600mg)

visit 4 to visit 7 (9 months): 1x1 tablet with 300 mg Benfotiamin (total daily dose: 300mg)

Arm title	Placebo V5
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Arm description:

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:

visit 1 to visit 4 (3 months): 2x 1 tablet placebo

visit 4 to visit 7 (9 months): 1x1 tablet placebo

Number of subjects in period 3	Benfotiamine V5	Placebo V5
Started	11	10
Completed	11	10

Period 4

Period 4 title	Visit 7
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benfotiamine V7

Arm description:

Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months

Arm type	Experimental
Investigational medicinal product name	Benfotiamine 300 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

visit 1 to visit 4 (3 months): 2x 1 tablet with 300 mg Benfotiamin (total daily dose: 600mg)

visit 4 to visit 7 (9 months): 1x1 tablet with 300 mg Benfotiamin (total daily dose: 300mg)

Arm title	Placebo V7
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Arm description:

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:

visit 1 to visit 4 (3 months): 2x 1 tablet placebo

visit 4 to visit 7 (9 months): 1x1 tablet placebo

Number of subjects in period 4	Benfotiamine V7	Placebo V7
Started	11	10
Completed	7	7
Not completed	4	3
Adverse event, serious fatal	1	-
prematurely termination of the trial	3	3

Baseline characteristics

Reporting groups

Reporting group title	Benfotiamine V1
Reporting group description: Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months	
Reporting group title	Placebo V1
Reporting group description: Placebo	

Reporting group values	Benfotiamine V1	Placebo V1	Total
Number of subjects	11	11	22
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)	6	6	12
From 65-84 years	5	5	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.82	62.36	
standard deviation	± 7.04	± 10.73	-
Gender categorical Units: Subjects			
Female	5	4	9
Male	6	7	13
Body Mass Index Units: kg/m2			
arithmetic mean	33.98	35.00	
standard deviation	± 6.17	± 5.63	-

End points

End points reporting groups

Reporting group title	Benfotiamine V1
Reporting group description: Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months	
Reporting group title	Placebo V1
Reporting group description: Placebo	
Reporting group title	Benfotiamine V4
Reporting group description: Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months	
Reporting group title	Placebo V4
Reporting group description: Placebo	
Reporting group title	Benfotiamine V5
Reporting group description: Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the 9 months	
Reporting group title	Placebo V5
Reporting group description: Placebo	
Reporting group title	Benfotiamine V7
Reporting group description: Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for 9 months	
Reporting group title	Placebo V7
Reporting group description: Placebo	

Primary: Intraepidermal nerve fiber density

End point title	Intraepidermal nerve fiber density ^[1]
End point description: This Endpoint was not analyzed as due to technical problems no values could be detected in skin biopsy samples. This was the reason for premature termination of the trial. No data are available, at all.	
End point type	Primary
End point timeframe: Visit 2 (baseline), visit 5 (6 months), visit 7 (12 months)	

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: This Endpoint was not analyzed as due to technical problems no values could be detected in skin biopsy samples. This was the reason for premature termination of the trial. There are no data available at all.

End point values	Benfotiamine V1	Placebo V1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[2]	0 ^[3]		
Units: fibres/ mm				
arithmetic mean (standard deviation)	()	()		

Notes:

[2] - This Endpoint was not analyzed as due to technical problems no values could be detected in biopsies

[3] - This Endpoint was not analyzed as due to technical problems no values could be detected in biopsies

Statistical analyses

No statistical analyses for this end point

Secondary: MNSI questionnaire

End point title	MNSI questionnaire
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End point description:

End point type	Secondary
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End point timeframe:

Baseline (visit 1), visit 4 (3 months), visit 5 (6 months) visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: Points				
arithmetic mean (standard deviation)	9.09 (± 2.12)	8.27 (± 2.28)	8.09 (± 3.27)	8.0 (± 2.79)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: Points				
arithmetic mean (standard deviation)	7.45 (± 2.91)	8.5 (± 2.51)	6.0 (± 2.94)	8.0 (± 3.06)

Statistical analyses

No statistical analyses for this end point

Secondary: MNSI examination

End point title	MNSI examination
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End point description:

End point type	Secondary
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End point timeframe:

visit 1 (baseline), visit 4 (3 months), visit 5 (6 months) visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: points				
arithmetic mean (standard deviation)	3.41 (± 1.43)	3.32 (± 1.66)	3.27 (± 2.09)	3.60 (± 1.90)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: points				
arithmetic mean (standard deviation)	3.14 (± 2.16)	3.10 (± 1.31)	2.21 (± 1.52)	3.00 (± 1.91)

Statistical analyses

No statistical analyses for this end point

Secondary: mTCNS

End point title mTCNS

End point description:

End point type Secondary

End point timeframe:

visit 1 (baseline), visit 4 (3 months), visit 5 (6 months) visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: points				
arithmetic mean (standard deviation)	7.55 (± 3.36)	6.64 (± 1.63)	6.18 (± 2.96)	5.70 (± 1.16)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: points				
arithmetic mean (standard deviation)	5.55 (± 3.17)	5.00 (± 2.05)	4.71 (± 2.98)	5.71 (± 1.50)

Statistical analyses

No statistical analyses for this end point

Secondary: Advanced glycation end products

End point title Advanced glycation end products

End point description:

End point type Secondary

End point timeframe:

Visit 2 (baseline for this parameter), visit 4 (3 months) visit 5 (6 months), visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: Autofluorescence				
arithmetic mean (standard deviation)	2.81 (± 0.44)	2.95 (± 0.95)	2.85 (± 0.49)	3.02 (± 0.85)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: Autofluorescence				
arithmetic mean (standard deviation)	2.96 (± 0.53)	3.03 (± 1.07)	2.89 (± 0.34)	3.44 (± 1.15)

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life (Neuro-QoL)

End point title Quality of Life (Neuro-QoL)

End point description:

End point type Secondary

End point timeframe:

visit 1 (baseline), visit 4 (3 months), visit 5 (6 months), visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: points				
arithmetic mean (standard deviation)	35.18 (± 5.71)	35.64 (± 4.03)	34.82 (± 5.36)	36.10 (± 3.96)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: points				
arithmetic mean (standard deviation)	33.91 (± 5.22)	32.90 (± 7.69)	32.57 (± 5.35)	29.14 (± 9.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Thiamine-Di-Phosphate (Vitamin B1)

End point title	Thiamine-Di-Phosphate (Vitamin B1)
End point description:	
End point type	Secondary
End point timeframe:	visit 1 (baseline) visit 4 (3 months) visit 5 (6 months) visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	10	11	10
Units: microgramm/ l				
arithmetic mean (standard deviation)	70.83 (± 34.86)	65.58 (± 12.51)	168.82 (± 23.42)	64.10 (± 10.16)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	9	7	7
Units: microgramm/ l				

arithmetic mean (standard deviation)	162.80 (\pm 20.63)	65.06 (\pm 15.24)	155.53 (\pm 40.66)	59.77 (\pm 14.17)
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Statistical analyses

No statistical analyses for this end point

Other pre-specified: Numerical Rating Scale - Pain

End point title	Numerical Rating Scale - Pain
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End point description:

End point type	Other pre-specified
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End point timeframe:

Visit 1 (baseline) visit 4 (3 months) Visit 5 (6 months) visit 7 (12 months)

End point values	Benfotiamine V1	Placebo V1	Benfotiamine V4	Placebo V4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	11	11	10
Units: points				
arithmetic mean (standard deviation)	4.45 (\pm 1.51)	4.27 (\pm 2.35)	4.0 (\pm 1.94)	3.40 (\pm 2.51)

End point values	Benfotiamine V5	Placebo V5	Benfotiamine V7	Placebo V7
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	10	7	7
Units: points				
arithmetic mean (standard deviation)	3.23 (\pm 2.48)	4.10 (\pm 1.29)	3.29 (\pm 2.50)	2.36 (\pm 2.21)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from inclusion (visit 1) until end of the trial

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Benfotiamine
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Benfotiamine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 11 (27.27%)	2 / 11 (18.18%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Investigations			
Angiocardigram	Additional description: Event. Elective coronary angiography		
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Coronary artery restenosis	Additional description: Related Event: Early in-stent thrombosis after percutaneous myocardial revascularisation		
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris	Additional description: Related Event: Early in-stent thrombosis after percutaneous myocardial revascularisation		
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident	Additional description: Stroke		

subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (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: 5 %

Non-serious adverse events	Benfotiamine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	4 / 11 (36.36%)	
Investigations			
Blood glucose abnormal			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	

Vascular disorders Hypertension subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 11 (0.00%) 0	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 2	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	
General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1	
Respiratory, thoracic and mediastinal disorders Dyspnoea exertional subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 11 (9.09%) 1	
Skin and subcutaneous tissue disorders Diabetic foot subjects affected / exposed occurrences (all) Dermatitis contact subjects affected / exposed occurrences (all) Psoriasis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 0 / 11 (0.00%) 0	0 / 11 (0.00%) 0 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1	
Musculoskeletal and connective tissue			

disorders			
Pain in extremity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2014	Investigator change

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
25 September 2015	Prematurely termination of the trial, as primary endpoint (skin biopsy) could not be analysed, due to technical reasons.	-

Notes:

Limitations and caveats

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

Small number of patients (pilot study); premature termination of the study, both limiting the interpretation of the trial. Furthermore neuropathic symptoms were not an entry criterion, therefore symptom intensity/severity was relatively low.

Notes: