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	07 September 2015

Results information

Result version number	v1
This version publication date	13 December 2016
First version publication date	13 December 2016
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

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	Priv.-Doz. Dr. med. Ovidiu Alin Stirban, Himmelgeister Landstrasse 174 40589 Duesseldorf, Germany , 0049 2191465140, stirban@web.de
Scientific contact	Priv.-Doz. Dr. med. Ovidiu Alin Stirban , Himmelgeister Landstrasse 174 40589 Duesseldorf, Germany , 0049 2191465140, 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 1901/2006 apply to this trial?	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	07 September 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 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.

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.

Should a protocol amendment become necessary, the subject

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.

Clinical trials have been performed with benfotiamine for the treatment of diabetic polyneuropathy, alcoholic polyneuropathy, alleviation of endothelial dysfunction in subjects with type 2 diabetes or in healthy smokers and treatment of diabetic nephropathy. Study durations were up to 2 years at a dose of 300 mg/day and the highest doses were 1050 mg for 3 days and 900 mg/day administered for 12 weeks.

Evidence for comparator:

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

Actual start date of recruitment	30 April 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)	16
From 65 to 84 years	6
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:

It was planned that 22 participants with T1DM 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 % will be randomized, ensuring 18 completers (at least 9 in each group) at 6 months.

Period 1

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

Blinding implementation details:

The medication was provided in a blinded manner by the Sponsor for the 12 months therapy, along with emergency envelops for unblinding single participants.

Tablets packaged:
Benfotiamin 300 mg: 1 tablet
Placebo : 1 tablet

Approximately 13.5 months (12.5-15 months), including 5 ambulatory and 3

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the rest of the study duration

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:

The recommended daily dose for the treatment of neuropathies is 300 mg, but doses as high as 900 mg/day have been given for 3 months and doses of 300 mg/day for 2 years. Therefore it was decided to administer 600 mg/day for 3 months and decrease the dose to 300 mg/day for the next 9 months. Study medication was administered in a blinded manner. The first administration was undertaken by subjects on an outpatient basis in the morning of day 2 after being instructed with regard to the procedure and receiving the medication at Visit 2 (day 1), Visit 3 (day 91±7) for the next at least 100 days (3 months + 1 week) and at Visit 5 (day 181±7) for the next 6 months and 1 week. The medication was taken as one tablet in the morning and one in the evening (before meals) until Visit 3 (600 mg/day) and one tablet in the morning afterwards (300 mg/day).

Arm title	Group 2

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:

Placebo (identical appearance to benfotiamine)

Number of subjects in period 1	Group 1	Group 2
Started	11	11
Completed	11	11

Baseline characteristics

Reporting groups

Reporting group title	Duration of study participation

Reporting group description: -

Reporting group values	Duration of study participation	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
22 participants with T1DM or T2DM on a stable regimen of antidiabetic treatment with no possibility of therapy intensification, with DSP, between 18 and 75 years of age were enrolled.			
Units: years			
arithmetic mean	62.09		
standard deviation	± 8.86	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	12	12	
Body Mass Index Units: kg/m2			
arithmetic mean	34.49		
standard deviation	± 5.78	-	

End points

End points reporting groups	
Reporting group title	Group 1
Reporting group description:	
Benfotiamine 600 mg/day for 3 months followed by benfotiamine 300 mg/day for the rest of the study duration	
Reporting group title	Group 2
Reporting group description:	
Placebo	

Primary: Primary	
End point title	Primary
End point description:	
Change from baseline in IENFD after 6 months of benfotiamine treatment compared to placebo. Change from baseline in IENFD after 12 months of benfotiamine treatment compared to placebo.	
End point type	Primary
End point timeframe:	
Study participation	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Fibers/mm	11	11		

Statistical analyses

Statistical analysis title	Double blinded
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Mean difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	2

Secondary: Secondary Pharmacodynamic

End point title	Secondary Pharmacodynamic

End point description:

Change from baseline in MNSI questionnaire after 6 months of benfotiamine treatment compared to placebo.
Change from baseline in MNSI examination after 6 months of benfotiamine treatment compared to placebo
Change from baseline in MNSI questionnaire after 12 months of benfotiamine treatment compared to placebo.
Change from baseline in MNSI examination after 12 months of benfotiamine treatment compared to placebo.

End point type	Secondary

End point timeframe:

Study participation

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Points				
arithmetic mean (standard deviation)	2 (± 1)	2 (± 1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Pharmacokinetic

End point title	Secondary Pharmacokinetic

End point description:

Change from baseline in plasma thiamine concentration after 6 months of benfotiamine treatment compared to placebo
Change from baseline in plasma thiamine concentration after 12 months of benfotiamine treatment compared to placebo

End point type	Secondary

End point timeframe:

Study participation

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: mg/dl				
number (not applicable)	11	11		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Safety

End point title	Safety

End point description:

Adverse events
Laboratory safety variables
Physical examination
Vital signs

End point type	Other pre-specified

End point timeframe:

Study participation

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Number of AEs	11	11		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator was to submit all SUSARs that occur during the period of observation (from the time the informed consent form is signed until the Follow-up visit), to the Sponsor within 24 hours. The Sponsor was to report within 15 days electronically.

Adverse event reporting additional description:

7 days after initial report from the investigator and the follow up report will be submitted maximum 8 days later via the notification form. Life threatening SUSARs or such that led to death were to be reported within 7 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	Adverse Events

Reporting group description:

AEs were collected from the subject enrolment until the last visit. Concomitant illnesses, which existed prior to entry into the clinical study, were not considered AEs unless they increased in frequency or severity, or worsen in nature during the treatment period. Medical occurrences prior to randomisation but after obtaining informed consent were recorded on the Medical History/Current Medical Conditions CRF.
The cannula inserted in a forearm vein for the collection of blood samples could have lead to superficial irritation of the vein. This was appropriately treated by the study staff and not reported as an AE in the clinical study report.
Skin biopsy could have led to bleeding, local infections, and wound healing or sensitivity disturbances. These will be recorder as AEs.
An AE that meets serious criteria should be recorded both on the AE Report Form and on the Serious Adverse Event Report Form.

Serious adverse events	Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
In-stent coronary artery restensosis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident prophylaxis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Sudden cardiac death			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea paroxysmal nocturnal			
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 16 (56.25%)		
Investigations			
Non-serious AEs			
subjects affected / exposed	9 / 16 (56.25%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported