Clinical trial results:
MD1003 IN ADRENOMYELONEUROPATHY: A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED STUDY

Summary

EudraCT number	2014-000698-38
Trial protocol	ES
Global end of trial date	23 June 2017

Results information

Result version number	v1 (current)
This version publication date	11 November 2020
First version publication date	11 November 2020

Trial information

Trial identification

Sponsor protocol code	MD1003CT2014-01AMN

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MedDay Pharmaceuticals
Sponsor organisation address	24-26 Rue de la Pépinière, Paris, France, 75008
Public contact	Service of Neurology - Bicêtre Hospital, Prof Patrick Aubourg, frederic.sedel@medday-pharma.com
Scientific contact	Service of Neurology - Bicêtre Hospital, Prof Patrick Aubourg, frederic.sedel@medday-pharma.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	16 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of MD1003 (biotin) at 300 mg/day over placebo in the clinical improvement of patients with Adrenomyeloneuropathy

Protection of trial subjects:

The safety of MD1003 was assessed by recording of adverse events (AEs), clinical examinations (vital signs, ECG), and standard maboratory testing (hematology, biochemistry).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 24
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	67
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patients were recruited to the study in 4 sites:
In France: 2 sites - 30 subjects
In Germany: 1 site - 24 subjects
In Spain: 1 site - 13 subjects
The study was conducted between 28 October 2014 and 23 June 2017.

Pre-assignment

Screening details:

A total of 71 subjetcs were screened and 67 subjects were randomized, 23 subjects in the Placebo group and 44 subjects in the MD1003 group.

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:

The double blinding was protected by sealed envelopes that were stored in the pharmacy and the Investigator's office.

Arms

Are arms mutually exclusive?	Yes
Arm title	MD1003

Arm description:

During the first 12-month double-blind placebo-controlled period, 44 subjects recieved 300 mg/day of MD1003.
During the 12-month extension phase, all subjects recieved MD1003 300 mg/day.

Arm type	Experimental
Investigational medicinal product name	MD1003
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

MD1003 consists 100 mg biotin and excipients (lactose, magnesium stearate, croscarmellose sodium, silica). MD1003 was taken orally and swallowed with a glass of water, with or without food, three times a day for a total of 300 mg/day.

Arm title	Placebo

Arm description:

During the first 12-month double-blind placebo-controlled period, 23 recieved 300 mg/day of Placebo.
During the 12-month extension phase, all subjects recieved MD1003 300 mg/day.

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

Dosage and administration details:

Placebo was administered as a capsule consisting of 100 mg lactose powder and other excipients (magnesium stearate, croscarmellose sodium, silica). Placebo was taken orally and swallowed with a

glass of water, with or without food, three times a day for a total of 300 mg/day.

Number of subjects in period 1	MD1003	Placebo
Started	44	23
Completed	43	23
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	67	67	
Age categorical			
The study was conducted only on male subjects.			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	42.6		
standard deviation	± 8.46	-	
Gender categorical			
Units: Subjects			
Male	67	67	

Subject analysis sets

Subject analysis set title	Subjects under MD1003
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects in the MD1003 group took 300 mg/day of MD1003 during 12 months (100mg tid).

Subject analysis set title	Subjects under Placebo
Subject analysis set type	Full analysis

Subject analysis set description:

The subjects in the Placebo group took 300 mg/day of placebo during 12 months (100mg tid).

Reporting group values	Subjects under MD1003	Subjects under Placebo	
Number of subjects	44	23	
Age categorical			
The study was conducted only on male subjects.			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	42.2	43.4	
standard deviation	± 8.80	± 7.89	
Gender categorical			
Units: Subjects			
Male	44	23	

End points

End points reporting groups

Reporting group title	MD1003
Reporting group description:	
During the first 12-month double-blind placebo-controlled period, 44 subjects recieved 300 mg/day of MD1003. During the 12-month extension phase, all subjects recieved MD1003 300 mg/day.	
Reporting group title	Placebo
Reporting group description:	
During the first 12-month double-blind placebo-controlled period, 23 recieved 300 mg/day of Placebo. During the 12-month extension phase, all subjects recieved MD1003 300 mg/day.	
Subject analysis set title	Subjects under MD1003
Subject analysis set type	Full analysis
Subject analysis set description:	
The subjects in the MD1003 group took 300 mg/day of MD1003 during 12 months (100mg tid).	
Subject analysis set title	Subjects under Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
The subjects in the Placebo group took 300 mg/day of placebo during 12 months (100mg tid).	

Primary: The mean change of 2-minute walking test (2MWT) between baseline and Month 12

End point title	The mean change of 2-minute walking test (2MWT) between baseline and Month 12
End point description:	
End point type	Primary
End point timeframe:	
12 months: from baseline to month 12	

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: meter				
arithmetic mean (standard deviation)	-1.25 (± 15.36)	2.27 (± 22.99)		

Statistical analyses

Statistical analysis title	Change from baseline
Comparison groups	Subjects under MD1003 v Subjects under Placebo

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	0.2714
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.44
upper limit	3.84
Variability estimate	Standard error of the mean
Dispersion value	4.33

Secondary: Proportion of subjects with improved 2MWT at least 20% at M9 and M12

End point title	Proportion of subjects with improved 2MWT at least 20% at M9 and M12

End point description:

End point type	Secondary

End point timeframe:

12 months (during double blind phase)

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: meter				
number (confidence interval 100%)	1 (0.0342 to 7.9793)	1 (0.0342 to 7.9793)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with improved TW25 of at least 20% at M9 and M12

End point title	Proportion of subjects with improved TW25 of at least 20% at M9 and M12

End point description:

End point type	Secondary

End point timeframe:

M9 and M12

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: second				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in TW25 between baseline and M12

End point title	Mean change in TW25 between baseline and M12

End point description:

End point type	Secondary

End point timeframe:

During double-blind period (12 months)

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: second				
arithmetic mean (confidence interval 95%)	0.62 (0.14 to 1.10)	0.84 (0.23 to 1.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in TUG between baseline and M12

End point title	Mean change in TUG between baseline and M12

End point description:

End point type	Secondary

End point timeframe:

12 months (from baseline to M12)

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: second				
arithmetic mean (standard deviation)	0.53 (± 2.42)	-0.60 (± 3.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in the EQ-5D between baseline and M12

End point title	Mean change in the EQ-5D between baseline and M12

End point description:

End point type	Secondary

End point timeframe:

Between M0 and M12 of the study period.

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: EQ VAS				
arithmetic mean (standard deviation)	-4.23 (± 11.32)	-4.32 (± 15.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in the Qualiveen between baseline and M12

End point title	Mean change in the Qualiveen between baseline and M12

End point description:

End point type	Secondary

End point timeframe:

From M0 to M12 of the study period.

End point values	Subjects under MD1003	Subjects under Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: Qualiveen score				
arithmetic mean (standard deviation)	0.09 (± 0.69)	0.27 (± 0.59)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 24 months (the whole study)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	MD1003/MD1003
Reporting group description: Subjects recieved MD1003 during the whole study (12 months double-blind period and 12 months open label)	
Reporting group title	Placebo/MD1003
Reporting group description: Subjects recieved placebo during double-blind phase (12 months) and MD1003 during open label phase (12 months).	

Serious adverse events	MD1003/MD1003	Placebo/MD1003	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 44 (15.91%)	9 / 23 (39.13%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Upper limb fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary angioplasty			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shoulder operation			

subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardinal infarction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy of partner			
subjects affected / exposed	1 / 44 (2.27%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	4 / 44 (9.09%)	3 / 23 (13.04%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Thyroid mass			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (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			
Pathological fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	MD1003/MD1003	Placebo/MD1003	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 44 (84.09%)	20 / 23 (86.96%)	
Vascular disorders			
Contusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Coronary angioplasty			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Glaucoma surgery			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Shoulder operation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Wisdom teeth removal			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	13 / 44 (29.55%)	10 / 23 (43.48%)	
occurrences (all)	18	14	
Fatigue			
subjects affected / exposed	1 / 44 (2.27%)	3 / 23 (13.04%)	
occurrences (all)	1	3	
Asthenia			
subjects affected / exposed	3 / 44 (6.82%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Cyst			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hernia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Prostatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
subjects affected / exposed	2 / 44 (4.55%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 44 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	3	
Depression			
subjects affected / exposed	2 / 44 (4.55%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Anxiety			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Depressed mood			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Investigations			
Laboratory test interference			
subjects affected / exposed	8 / 44 (18.18%)	0 / 23 (0.00%)	
occurrences (all)	8	0	
Carotid bruit			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Exposure via father			
subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Ankle fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Foot fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hand fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Vascular graft occlusion			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Wrist fracture			

subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 44 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	5	1	
Somnolence			
subjects affected / exposed	2 / 44 (4.55%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Sciatica			
subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Burning sensation			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Epilepsy			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Ligament sprain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukocytosis			

subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Ear pain			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Keratitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Vertigo positional			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 44 (2.27%)	3 / 23 (13.04%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	2 / 44 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Gastritis			
subjects affected / exposed	2 / 44 (4.55%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Haemorrhoids			

subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Anal incontinence			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 44 (4.55%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Alopecia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			

subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Enuresis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Thyroid mass			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 44 (11.36%)	4 / 23 (17.39%)	
occurrences (all)	5	4	
Arthralgia			
subjects affected / exposed	5 / 44 (11.36%)	5 / 23 (21.74%)	
occurrences (all)	5	5	
Musculoskeletal pain			
subjects affected / exposed	4 / 44 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Bursitis			

subjects affected / exposed	0 / 44 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Joint swelling			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Torticollis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Muscle twitching			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Osteoporosis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pathological fracture			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 44 (6.82%)	3 / 23 (13.04%)	
occurrences (all)	5	3	

urinary tract infection			
subjects affected / exposed	3 / 44 (6.82%)	2 / 23 (8.70%)	
occurrences (all)	6	3	
Gastroenteritis			
subjects affected / exposed	3 / 44 (6.82%)	2 / 23 (8.70%)	
occurrences (all)	4	2	
Sinusitis			
subjects affected / exposed	2 / 44 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	2	4	
Nasopharyngitis			
subjects affected / exposed	4 / 44 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Bronchitis			
subjects affected / exposed	2 / 44 (4.55%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Pharyngitis			
subjects affected / exposed	1 / 44 (2.27%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	0 / 44 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Gastrointestinal infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	2	0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Otitis media			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

Pilonidal cyst			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Soft tissue infection			
subjects affected / exposed	1 / 44 (2.27%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Urosepsis			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 44 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2014	This protocol amendment is only for Spain site. Potential risks on the use of biotin with peptic ulcer and recurrent gastiritis, and skin rash and fever are updated.
21 January 2015	This protocol amendment is only for German site. MOS SF36 quality of life questionnaire from the secondary endpoints evaluation criteria is removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported