Clinical trial results:
Effects of Acetyl-DL-Leucine on cerebellar ataxia - a multinational, multicenter, randomized, double-blind, placebo-controlled, 2-way crossover phase III trial (ALCAT)

Summary

EudraCT number	2015-000460-34
Trial protocol	DE AT
Global end of trial date	07 July 2017

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	ALCAT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	LMU Klinikum
Sponsor organisation address	Marchioninistr. 15, Munich, Germany, 81377
Public contact	Studienzentrale der Neurologie, LMU Klinikum Munich, 0049 089440076977, IFB-Studienzentrale@med.uni-muenchen.de
Scientific contact	Department of Neurology and German Center for Vertigo and Balance Disorders (DSGZ), LMU Klinikum Munich, 0049 089440073678, michael.strupp@med.uni-muenchen.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	29 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the ALCAT trial was to determine the efficacy of a symptomatic treatment with Acetyl-DL-Leucine compared to placebo on absolute change from baseline to week 6 in motor function as assessed by the total score of the Scale for the Assessment and Rating of Ataxia (SARA).

Protection of trial subjects:

Only standard diagnostic examinations were used during the trial, no experimental examination were performed. Patients received best clinical treatment with continous monitoring of adverse events and side effects including blood tests.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 January 2016
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	Austria: 10
Country: Number of subjects enrolled	Germany: 98
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	77
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

ALCAT was an investigator-initiated, multicenter, double-blind, randomized, placebo-controlled, 2-treatment 2-period crossover phase 3 clinical trial at 7 university centers in Germany (Munich, Bonn, Essen, Tübingen, Berlin) and Austria (Innsbruck). Recruitment occurred between January 25, 2016, and February 17, 2017

Pre-assignment

Screening details:

Patients were aged at least 18 years and diagnosed with cerebellar ataxia of hereditary (suspected or genetically confirmed) or nonhereditary or unknown type presenting with a total score of at least 3 points on the Scale for the Assessment and Rating of Ataxia (SARA).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo followed by acetyl-DL-leucine (P-A)

Arm description: -

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; subjects took three placebo capsules in the morning; three placebo capsules at noon; and four placebo capsules in the evening in week 3 to 6 (week 1: dose schedule (1-1-1); week 2: dose schedule (2-2-2)).

Arm title	Acetyl-DL-leucine followed by placebo (A-P)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Acetyl-DL-leucine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Acetyl-DL-Leucine 5 g per day (dose schedule: 3-3-4) in week 3 to 6 after a 2-week up-titration (week 1: 1.5 g per day, dose schedule: 1-1-1; week 2: 3 g per day, dose schedule: 2-2-2). Each capsule contained 500 mg Acetyl-DL-Leucine.

Number of subjects in period 1	Placebo followed by acetyl-DL-leucine (P-A)	Acetyl-DL-leucine followed by placebo (A-P)
Started	54	54
Completed	52	50
Not completed	2	4
Adverse event, non-fatal	1	1
hereditary spastic paraplegia diagnosis	1	1
Lack of efficacy	-	2

Period 2	
Period 2 title	Washout period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo followed by acetyl-DL-leucine (P-A)
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Acetyl-DL-leucine followed by placebo (A-P)
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Placebo followed by acetyl-DL-leucine (P-A)	Acetyl-DL-leucine followed by placebo (A-P)
Started	52	50
Completed	50	49
Not completed	2	1
Adverse event, non-fatal	1	1
Lost to follow-up	1	-

Period 3

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo followed by acetyl-DL-leucine (P-A)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Acetyl-DL-leucine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Acetyl-DL-Leucine 5 g per day (dose schedule: 3-3-4) in week 3 to 6 after a 2-week up-titration (week 1: 1.5 g per day, dose schedule: 1-1-1; week 2: 3 g per day, dose schedule: 2-2-2). Each capsule contained 500 mg Acetyl-DL-Leucine.

Arm title	Acetyl-DL-leucine followed by placebo (A-P)

Arm description: -

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; subjects took three placebo capsules in the morning; three placebo capsules at noon; and four placebo capsules in the evening in week 3 to 6 (week 1: dose schedule (1-1-1); week 2: dose schedule (2-2-2)).

Number of subjects in period 3	Placebo followed by acetyl-DL-leucine (P-A)	Acetyl-DL-leucine followed by placebo (A-P)
Started	50	49
Completed	45	48
Not completed	5	1
Adverse event, non-fatal	4	-
Excluded due to Friedreich ataxia diagnosis	1	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo followed by acetyl-DL-leucine (P-A)
Reporting group description: -	
Reporting group title	Acetyl-DL-leucine followed by placebo (A-P)
Reporting group description: -	

Reporting group values	Placebo followed by acetyl-DL-leucine (P-A)	Acetyl-DL-leucine followed by placebo (A-P)	Total
Number of subjects	54	54	108
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53	56.7	
standard deviation	± 14.3	± 14.3	-
Gender categorical Units: Subjects			
Female	25	30	55
Male	29	24	53

End points

End points reporting groups

Reporting group title	Placebo followed by acetyl-DL-leucine (P-A)
Reporting group description: -	
Reporting group title	Acetyl-DL-leucine followed by placebo (A-P)
Reporting group description: -	
Reporting group title	Placebo followed by acetyl-DL-leucine (P-A)
Reporting group description: -	
Reporting group title	Acetyl-DL-leucine followed by placebo (A-P)
Reporting group description: -	
Reporting group title	Placebo followed by acetyl-DL-leucine (P-A)
Reporting group description: -	
Reporting group title	Acetyl-DL-leucine followed by placebo (A-P)
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

105 subjects were Included in the FAS (103 Received placebo treatment, 104 Received acetyl-DL-leucine treatment in the first or the third period; both periods were accounted for in the final analysis). Afterwashout period new baseline was established and all measurements were conducted.

52 In P-A (both time points: 50 for placebo, 41 for acetyl-DL-leucine)
53 In A-P (both time points: 48 for placebo, 49 for acetyl-DL-leucine)

Primary: Change in SARA total score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point title	Change in SARA total score from baseline to Week 6 (Acetyl-DL-leucine - placebo)[1]

End point description:

P value from the mixed model for repeated measures (fixed effects: factor variables for treatment [acetyl-DL-leucine vs placebo], visit and treatment period, and treatment-by-visit interaction; random effects: patient-specific random intercepts). Estimated marginal means (least-squares means) derived from the mixed model, averaged over the levels of period.
The mean absolute change from baseline to week 6 in SARA total scores did not differ significantly between acetyl-DL-leucine and placebo (mean treatment difference: 0.23 points [95%CI, −0.40 to 0.85 points]; P = 0.48).

End point type	Primary

End point timeframe:

6 weeks from baseline

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: System limitation - cannot accurately enter the number of participants enrolled in each treatment arm of this cross-over design.
Full data set of 105 patients was analyzed of which 103 received placebo and 104 received Acetyl-DL-leucine treatment. The principal model was used to derive (marginal) mean absolute changes in SARA total score from (period-dependent) baseline to posttreatment values, and to compare between both treatment conditions (difference in mean absolute change scores at w6.

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.23 (-0.40 to 0.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in SCAFI, total z score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point title	Change in SCAFI, total z score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. In SCAFI z score, no treatment benefit of acetyl-DL-leucine compared with placebo could be found. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the overall SCAFI score was -0.02 points (95%CI, −0.07 to 0.04 points; P = 0.52)
Likewise, we identified a significant period effect, with higher SCAFI z scores in the second period (main effect for mean improvement in index values was 0.12 points [95%CI, 0.06 to 0.17 points; P < 0.001] compared with the first period).

End point type	Secondary

End point timeframe:

6 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	-0.02 (-0.07 to 0.04)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in EQ VAS score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point title	Change in EQ VAS score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference

on acetyl-DL-leucine versus placebo) on the efficacy outcome. There was no evidence for a clinically relevant effect of acetyl-DL-leucine on the subjective health rating EQ visual analogue scale compared with placebo at week 6 with no evidence of a period effect. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the overall self-rated health status was −1.84 points (95%CI, −5.19 to 1.50 points; P = 0.28)

End point type	Secondary

End point timeframe:

6 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	-1.84 (-5.19 to 1.50)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BDI-II, sum score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point title	Change in BDI-II, sum score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the BDI-II sum score was 0.10 points (95%CI, -0.91 to 1.11 points; P = 0.85)
Higher BDI scores (range 0 to 63) indicate greater impairment.

End point type	Secondary

End point timeframe:

6 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.10 (-0.91 to 1.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FSS, mean score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point title	Change in FSS, mean score from baseline to Week 6 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the FSS mean score was 0.06 points (95%CI, -0.17 to 0.30 points; P = 0.61)
Higher FSS scores (range 1 to 7) indicate greater impairment.

End point type	Secondary

End point timeframe:

6 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.06 (-0.17 to 0.30)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SARA total score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point title	Changes in SARA total score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point description:

Contrast of primary interest: difference is the effect of treatment (acetyl-DL-leucine versus placebo) on the efficacy outcome. At week 2, the marginal mean treatment difference in SARA total scores did not differ significantly between acetyl-DL-leucine and placebo (mean treatment difference: 0.43 points [95%CI, −0.18 to 1.05 points]; P = 0.17).

End point type	Secondary

End point timeframe:

2 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.43 (-0.18 to 1.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in SCAFI total z score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point title	Changes in SCAFI total z score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. In SCAFI z score, no treatment benefit of acetyl-DL-leucine compared with placebo could be found. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the overall SCAFI score was 0.03 points (95%CI, −0.02 to 0.08 points; P = 0.26)

End point type	Secondary

End point timeframe:

2 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.03 (-0.02 to 0.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes in EQ VAS score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point title	Changes in EQ VAS score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. There was no evidence for a clinically relevant effect of acetyl-DL-leucine on the subjective health rating EQ visual analogue scale compared

with placebo at week 6 with no evidence of a period effect. At week 2, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the overall self-rated health status was 0.78 points (95%CI, −2.51 to 4.07 points; P = 0.64)

End point type	Secondary
End point timeframe:	
2 weeks from baseline	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.78 (-2.51 to 4.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BDI-II, sum score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point title	Change in BDI-II, sum score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the BDI-II sum score was 0.49 points (95%CI, -0.50 to 1.48 points; P = 0.33).
Higher BDI scores (range 0 to 63) indicate greater impairment.

End point type	Secondary
End point timeframe:	
2 weeks from baseline	

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.49 (-0.50 to 1.48)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FSS, mean score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point title	Change in FSS, mean score from baseline to Week 2 (Acetyl-DL-leucine - placebo)

End point description:

Estimated marginal means derived from the mixed model for repeated measures, averaged over the levels of period. Contrast of primary interest: difference means the effect of treatment (mean difference on acetyl-DL-leucine versus placebo) on the efficacy outcome. At week 6, the marginal mean treatment difference between acetyl-DL-leucine and placebo in the FSS mean score was 0.09 points (95%CI, -0.15 to 0.32 points; P = 0.47).
Higher FSS scores (range 1 to 7) indicate greater impairment.

End point type	Secondary

End point timeframe:

2 weeks from baseline

End point values	Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	105			
Units: points				
least squares mean (confidence interval 95%)	0.09 (-0.15 to 0.32)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Documentation and evaluation of each AE occurred between the start with first study specific intervention up to 30 days after the subject has received the last dose of trial drug.

Adverse event reporting additional description:

A total of 246 AEs (86 patients with at least 1 AE) occurred in similar numbers in both sequence groups (A-P: 42 patients; P-A: 45 patients) with a median of 2 (range 0-10) AEs per patient throughout their individual observation period. Of these 8 were assessed as SAEs (6 on acetyl-DLleucine, 2 on placebo), whereas 191 were mild and 48 moderate.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Placebo followed by Acetyl-DL-leucin

Reporting group description:

Patients were initially screened and assessed for eligibility at the first visit and randomized at the second to 1 of 2 treatment sequences and after the washout period they were given the alternatie therapy. In this group the first therapy they received was placebo and was followed by active treatment [P-A].

Reporting group title	Acetyl-DL-leucin followed by placebo

Reporting group description:

Patients were initially screened and assessed for eligibility at the first visit and randomized at the second to 1 of 2 treatment sequences and after the washout period they were given the alternatie therapy. In this group the first therapy they received was Acetyl-DL-leucine and was followed by placebo treatment [A-P].

Serious adverse events	Placebo followed by Acetyl-DL-leucin	Acetyl-DL-leucin followed by placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 103 (5.83%)	2 / 104 (1.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	2 / 103 (1.94%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic stroke			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (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			

Active suicidal ideation			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin texture abnormal			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Placebo followed by Acetyl-DL-leucin	Acetyl-DL-leucin followed by placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 103 (57.28%)	52 / 104 (50.00%)	
Injury, poisoning and procedural complications			
Bruise from the fall			
subjects affected / exposed	1 / 103 (0.97%)	2 / 104 (1.92%)	
occurrences (all)	1	2	
Cut			

subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Injury			
subjects affected / exposed	4 / 103 (3.88%)	3 / 104 (2.88%)	
occurrences (all)	4	3	
Nervous system disorders			
Additive behavior to study medication			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Concentration disturbance			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Inner restlessness			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Parkinson's disease worsening			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Ataxia worsening			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Vertigo			
subjects affected / exposed	2 / 103 (1.94%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Mixed anxiety-panic disorder			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Ischias			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Deterioration of gait			
subjects affected / exposed	0 / 103 (0.00%)	3 / 104 (2.88%)	
occurrences (all)	0	3	
Increase in pre-existing depressive moods			

subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Tingling paresthesias left hand, distally accentuated			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 103 (3.88%)	3 / 104 (2.88%)	
occurrences (all)	5	3	
Chills			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Daytime sleepiness			
subjects affected / exposed	2 / 103 (1.94%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Deterioration of hand motor skills/coordination			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Difficulty falling asleep			
subjects affected / exposed	2 / 103 (1.94%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Sleep disorder			
subjects affected / exposed	3 / 103 (2.91%)	0 / 104 (0.00%)	
occurrences (all)	3	0	
Dizziness/increase of dizziness			
subjects affected / exposed	5 / 103 (4.85%)	5 / 104 (4.81%)	
occurrences (all)	8	6	
Fall			
subjects affected / exposed	8 / 103 (7.77%)	11 / 104 (10.58%)	
occurrences (all)	12	13	
Headache/Migraine			
subjects affected / exposed	4 / 103 (3.88%)	7 / 104 (6.73%)	
occurrences (all)	5	9	
Increased instability			

subjects affected / exposed	2 / 103 (1.94%)	1 / 104 (0.96%)		
occurrences (all)	2	1		
Increased staggering				
subjects affected / exposed	3 / 103 (2.91%)	0 / 104 (0.00%)		
occurrences (all)	3	0		
Speech disorder				
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)		
occurrences (all)	1	1		
Sensory disturbance increase				
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
Pain in extremity				
subjects affected / exposed	7 / 103 (6.80%)	4 / 104 (3.85%)		
occurrences (all)	7	4		
Numbness				
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
Uncontrolled sallivation				
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)		
occurrences (all)	1	0		
Disturbances of neck muscles after a BOTOX inje				
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Increased clumsiness after the up-titration of the study medication				
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Nocturia				
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)		
occurrences (all)	0	1		
Stabbing chest/breast pain				
subjects affected / exposed	0 / 103 (0.00%)	2 / 104 (1.92%)		
occurrences (all)	0	2		
Thick feet without water retention				

subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Worsening of restless leg syndrome			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
General malaise after taking tablets			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Bilateral hearing aid device supply			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Preexisting mild tinnitus on right side increased significantly			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Eye disorders			
Increase in double vision			
subjects affected / exposed	0 / 103 (0.00%)	3 / 104 (2.88%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Bowel movements drier and harder			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	1 / 103 (0.97%)	2 / 104 (1.92%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	5 / 103 (4.85%)	7 / 104 (6.73%)	
occurrences (all)	6	9	
Dyspepsia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Reflux gastritis			
subjects affected / exposed	5 / 103 (4.85%)	1 / 104 (0.96%)	
occurrences (all)	5	1	
Stomach ache			

subjects affected / exposed	2 / 103 (1.94%)	4 / 104 (3.85%)	
occurrences (all)	3	5	
Nausea			
subjects affected / exposed	2 / 103 (1.94%)	3 / 104 (2.88%)	
occurrences (all)	3	4	
Vomiting			
subjects affected / exposed	1 / 103 (0.97%)	5 / 104 (4.81%)	
occurrences (all)	1	5	
Weight decreased			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Persistent morning sickness			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	2 / 103 (1.94%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	4 / 103 (3.88%)	1 / 104 (0.96%)	
occurrences (all)	4	1	
Sore throat			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Cough			

subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Psoriasis worsening			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 103 (0.00%)	4 / 104 (3.85%)	
occurrences (all)	0	6	
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	2 / 103 (1.94%)	0 / 104 (0.00%)	
occurrences (all)	2	0	
Urinary urge increase			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Renal pain			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 103 (4.85%)	2 / 104 (1.92%)	
occurrences (all)	5	2	
Blockage in hip joint with limitation of movement and pain			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Lumbago			
subjects affected / exposed	2 / 103 (1.94%)	1 / 104 (0.96%)	
occurrences (all)	2	1	
Muscle soreness			
subjects affected / exposed	2 / 103 (1.94%)	0 / 104 (0.00%)	
occurrences (all)	3	0	
Muscle spasms			

subjects affected / exposed	0 / 103 (0.00%)	5 / 104 (4.81%)	
occurrences (all)	0	5	
Jaw blockage with toothache			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Spontaneous cramps in the cave			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Neck pain			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 103 (5.83%)	5 / 104 (4.81%)	
occurrences (all)	6	5	
Herpes labialis infection after a cold			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Tooth inflammation			
subjects affected / exposed	1 / 103 (0.97%)	1 / 104 (0.96%)	
occurrences (all)	1	1	
Suspected sinusitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 103 (0.97%)	0 / 104 (0.00%)	
occurrences (all)	1	0	
Anorexia nervosa			
subjects affected / exposed	0 / 103 (0.00%)	1 / 104 (0.96%)	
occurrences (all)	0	1	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34905009