# 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<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 53 | 56.7 | |
| standard deviation | ± 14.3 | ± 14.3 | - |
| Gender categorical<br>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