# Clinical trial results:
# A Phase IIb double-blind, randomised, placebo-controlled, multi-centre, confirmative three-way cross-over study on cognitive function with two doses of KH176 in subjects with a genetically confirmed mitochondrial DNA tRNALeu(UUR) m.3243A>G mutation.

## Summary

| | |
|---|---|
| EudraCT number | 2019-000599-40 |
| Trial protocol | NL GB DE DK |
| Global end of trial date | 24 May 2022 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 October 2023 |
| First version publication date | 15 October 2023 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | KH176-202 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04165239 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Khondrion B.V. |
| Sponsor organisation address | Transistorweg 5C, Nijmegen, Netherlands, 6534 AT |
| Public contact | Gerrit Ruiterkamp, Khondrion B.V., +31 612805425, ruiterkamp@khondrion.com |
| Scientific contact | Gerrit Ruiterkamp, Khondrion B.V., +31 612805425, ruiterkamp@khondrion.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 | 28 November 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 May 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of KH176 during a 4 week treatment period on the attention domain score of cognitive functioning, as assessed by the visual identification test of the Cogstate computerised cognitive testing battery.

Protection of trial subjects:

1. Monitoring incidence and severity of Treatment Emergent Adverse Events
2. Evaluation of changes in findings of physical examination, vital signs and clinical laboratory results

Background therapy:

None

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 January 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | Germany: 8 |
| Worldwide total number of subjects | 27 |
| EEA total number of subjects | 19 |

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) | 27 |

| | |
|---|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study KH176-202 was conducted at 4 Investigational sites (the Netherlands, Germany, the United Kingdom, and Denmark). 50 unique patients were screened and signed informed consent. A total of 23 unique subjects were screening failures and 27 subjects were randomized over 3 treatment sequences.

### Pre-assignment

Screening details:

Males and females aged 18 years or older with a confirmed m.3243A>G mutation and with clinical signs and disease severity of mitochondrial disease as demonstrated by an NMDAS score of >10, including attentional dysfunction, defined as a Cogstate Identification Test (IDN) score of ≥0.5 standard deviations poorer than healty controls

### 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 treatment (sequence) that was assigned to the randomization treatment numbers was blinded to the study team. Treatment blind was maintained by the use of identically packaged active and placebo medications, which fully matched visually, and which could not be distinguished by taste, odor or touch either. Treatments remained blinded until the issuing of a final statement confirming that all data had been collected, verified, and stored in a locked database.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | A-B-C |

Arm description:

All subjects who received bid oral administration in the randomized sequence: placebo, KH176 50 mg, KH176 100 mg

| | |
|---|---|
| Arm type | Randomized sequence |
| Investigational medicinal product name | KH176 |
| Investigational medicinal product code | SUB198953 |
| Other name | sonlicromanol |
| Pharmaceutical forms | Oral solution in bottle |
| Routes of administration | Oral use |

Dosage and administration details:

KH176 is available as a powder for reconstitution, to be reconstituted with physiologic salt. KH176 50 mg or 100 mg will be provided in 20 mL bottles, which can be used to add the physiological salt (10 mL) and consequently drink the oral liquid. Placebo will be a NaCl salt/bitrex powder, to be reconstituted with physiologic salt solution in 20 mL bottles.

| | |
|---|---|
| **Arm title** | B-C-A |

Arm description:

All subjects who received bid oral administration in the randomized sequence: KH176 50 mg, KH176 100 mg, placebo

| | |
|---|---|
| Arm type | Randomized sequence |
| Investigational medicinal product name | KH176 |
| Investigational medicinal product code | SUB198953 |
| Other name | sonlicromanol |
| Pharmaceutical forms | Oral solution in bottle |
| Routes of administration | Oral use |

Dosage and administration details:

KH176 is available as a powder for reconstitution, to be reconstituted with physiologic salt. KH176 50 mg or 100 mg will be provided in 20 mL bottles, which can be used to add the physiological salt (10 mL) and consequently drink the oral liquid. Placebo will be a NaCl salt/bitrex powder, to be reconstituted with physiologic salt solution in 20 mL bottles.

| **Arm title** | C-A-B |
|---|---|

Arm description:

All subjects who received bid oral administration in the randomized sequence: KH176 100 mg, KH176 50 mg, placebo

| | |
|---|---|
| Arm type | Treatment sequence |
| Investigational medicinal product name | KH176 |
| Investigational medicinal product code | SUB198953 |
| Other name | sonlicromanol |
| Pharmaceutical forms | Oral solution in bottle |
| Routes of administration | Oral use |

Dosage and administration details:

KH176 is available as a powder for reconstitution, to be reconstituted with physiologic salt. KH176 50 mg or 100 mg will be provided in 20 mL bottles, which can be used to add the physiological salt (10 mL) and consequently drink the oral liquid. Placebo will be a NaCl salt/bitrex powder, to be reconstituted with physiologic salt solution in 20 mL bottles.

| **Number of subjects in period 1** | A-B-C | B-C-A | C-A-B |
|---|---|---|---|
| Started | 10 | 9 | 8 |
| Completed | 9 | 7 | 8 |
| Not completed | 1 | 2 | 0 |
| Adverse event, non-fatal | 1 | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | A-B-C |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: placebo, KH176 50 mg, KH176 100 mg | |
| Reporting group title | B-C-A |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: KH176 50 mg, KH176 100 mg, placebo | |
| Reporting group title | C-A-B |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: KH176 100 mg, KH176 50 mg, placebo | |

| Reporting group values | A-B-C | B-C-A | C-A-B |
|---|---|---|---|
| Number of subjects | 10 | 9 | 8 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | |
| From 65-84 years | | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 48.0 | 44.8 | 45.0 |
| standard deviation | ± 14.1 | ± 10.7 | ± 6.0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 9 | 4 | 7 |
| Male | 1 | 5 | 1 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 27 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |

| | | | |
|---|---|---|---|
| Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br>- | | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 20<br>7 | | |

| **Subject analysis sets** | |
|---|---|
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description:<br>All subjects who were administered bid oral administration of placebo | |
| Subject analysis set title | 50 mg KH176 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description:<br>All subjects who were administered bid oral administration 50 mg KH176 | |
| Subject analysis set title | 100 mg KH176 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description:<br>All subjects who were administered bid oral administration of 100 mg KH176 | |

| **Reporting group values** | Placebo | 50 mg KH176 | 100 mg KH176 |
|---|---|---|---|
| Number of subjects | 27 | 27 | 27 |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | <br><br>46.0<br>± 10.8 | <br><br>46.0<br>± 10.8 | <br><br>46.0<br>± 10.8 |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 20<br>7 | 20<br>7 | 20<br>7 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | A-B-C |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: placebo, KH176 50 mg, KH176 100 mg | |
| Reporting group title | B-C-A |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: KH176 50 mg, KH176 100 mg, placebo | |
| Reporting group title | C-A-B |
| Reporting group description: | |
| All subjects who received bid oral administration in the randomized sequence: KH176 100 mg, KH176 50 mg, placebo | |
| Subject analysis set title | Placebo |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All subjects who were administered bid oral administration of placebo | |
| Subject analysis set title | 50 mg KH176 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All subjects who were administered bid oral administration 50 mg KH176 | |
| Subject analysis set title | 100 mg KH176 |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All subjects who were administered bid oral administration of 100 mg KH176 | |

### Primary: Changes from baseline at Day 28 in the attention domain score of cognitive functioning: Identification Test (IDN)

| | |
|---|---|
| End point title | Changes from baseline at Day 28 in the attention domain score of cognitive functioning: Identification Test (IDN) |
| End point description: | |
| Visual Identification Test (IDN) of the Cogstate computerized cognitive testing battery was used to evaluate the effect of KH176 during a 4-week treatment period on the attention domain score of cognitive functioning. Changes from baseline (measured at pre-dose Day 1) to end of treatment (Day 28 of each treatment period) in the attention domain score of cognitive functioning are measured.<br>The Identification Test (IDN) is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the centre of the screen is red. The subject responds by pressing the Yes key when the joker card is red and No when it is black. The software measures the speed and accuracy of each response | |
| End point type | Primary |
| End point timeframe: | |
| Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period | |

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: seconds | | | | |
| least squares mean (standard error) | 0.005498 (± 0.01002) | -0.00084 (± 0.009309) | 0.002007 (± 0.009702) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|

Statistical analysis description:

Superiority analysis using a three-period, three treatment cross-over model comparing change from baseline at Day 28 for all treatments. Period effects are investigated using a mixed model (treatment/period: fixed effects, subject: random effect). Treatment effects of active doses vs. placebo are estimated and 95% confidence intervals are calculated using mixed-modelling results incorporating a multiplicity correction for the prim. efficacy parameter doses comparison with placebo (Dunnet's)

| | |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.00634 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03612 |
| upper limit | 0.02345 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01446 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|

Statistical analysis description:

Superiority analysis using a three-period, three treatment cross-over model comparing change from baseline at Day 28 for all treatments. Period effects are investigated using a mixed model (treatment/period: fixed effects, subject: random effect). Treatment effects of active doses vs. placebo are estimated and 95% confidence intervals are calculated using mixed-modelling results incorporating a multiplicity correction for the prim. efficacy parameter doses comparison with placebo (Dunnet's)

| | |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.00349 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03467 |
| upper limit | 0.02769 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01514 |

## Secondary: Changes from baseline at day 28 in the following domains of cognitive functioning: 1. Executive functioning: Groton Maze Learning (GML).

| | |
|---|---|
| End point title | Changes from baseline at day 28 in the following domains of cognitive functioning: 1. Executive functioning: Groton Maze Learning (GML). |

End point description:

Measure of problem solving and reasoning and uses a well-validated maze learning paradigm. The subject is shown a 10 × 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (i.e., 10 × 10). Subjects are required to find the hidden pathway guided by four search rules. These rules are: do not move diagonally, do not move more than one box, do not move back on the pathway, and return to the last correct location after an error. At each step only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession to indicate to the subject that they must return to this location. There are 21 well-matched alternate pathways

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1(baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: sec | | | | |
| least squares mean (standard error) | -3.7912 (± 2.8641) | -2.9229 (± 2.8803) | 1.3719 (± 2.8580) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.8682 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.0173 |
| upper limit | 9.7537 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.3143 |

| | |
|---|---|
| **Statistical analysis title** | Mixed models Treatment diff between C-A |
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 5.1631 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.5638 |
| upper limit | 13.8899 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.2373 |

## Secondary: Changes from baseline at day 28 in the following domains of cognitive functioning: 2. Working memory: One Back Test (ONB)

| | |
|---|---|
| End point title | Changes from baseline at day 28 in the following domains of cognitive functioning: 2. Working memory: One Back Test (ONB) |

End point description:

The One Back test is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the centre of the screen is the same as the card presented immediately previously. The subject responds by pressing the Yes or No key. Because no card has been presented yet on the first study, a correct first response is always No. The software measures the speed and accuracy of each response.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1 baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: sec | | | | |
| least squares mean (standard error) | -0.01867 (± 0.01200) | -0.00578 (± 0.01157) | 0.000936 (± 0.01181) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01288 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02334 |
| upper limit | 0.0491 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01759 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.0196 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01703 |
| upper limit | 0.05623 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.01779 |

**Secondary: Changes from baseline at Day 28 in the following domains of cognitive**

| functioning: 3. Psychomotor function: Detection Test | |
|---|---|
| End point title | Changes from baseline at Day 28 in the following domains of cognitive functioning: 3. Psychomotor function: Detection Test |

End point description:

The Detection Test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the Yes key as soon as the card in the centre of the screen turns face up. The software measures the speed and accuracy of each response.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 25 | 25 | |
| Units: sec | | | | |
| least squares mean (standard error) | -0.03608 (± 0.01726) | -0.00515 (± 0.01644) | 0.007884 (± 0.01664) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.03093 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02398 |
| upper limit | 0.08584 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02666 |

| Statistical analysis title | Copy of Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |

| | |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.04397 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.01216 |
| upper limit | 0.1001 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02725 |

## Secondary: Changes from baseline at day 28 in the following domains of cognitive functioning: 4. Visual learning: One Card Learning Test (OCL)

| | |
|---|---|
| End point title | Changes from baseline at day 28 in the following domains of cognitive functioning: 4. Visual learning: One Card Learning Test (OCL) |

End point description:

The One Card Learning Test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the centre of the screen was seen previously in this test. The subject responds by pressing the Yes or No key. The software measures the speed and accuracy of each response.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: sec | | | | |
| least squares mean (standard error) | -0.00689 (± 0.02298) | 0.01383 (± 0.02200) | -0.02481 (± 0.02239) | |

## Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |

| | |
|---|---|
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.02072 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.03943 |
| upper limit | 0.08086 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.0292 |

| **Statistical analysis title** | Copy of Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.01791 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.07905 |
| upper limit | 0.04323 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.02969 |

## Secondary: Changes from baseline at day 28 in the following domains of cognitive functioning: 5. Verbal learning: International Shopping List (ISL)

| End point title | Changes from baseline at day 28 in the following domains of cognitive functioning: 5. Verbal learning: International Shopping List (ISL) |
|---|---|

End point description:

The International Shopping List test is a measure of verbal learning and uses a well-validated list-learning paradigm. High frequencies, high imagery, concrete nouns (items from a shopping list) are read to the subject by the test supervisor at the rate of one word every two seconds. Once all words have been read, the subject is asked to recall as many of the words as he/she can as quickly as possible. The test supervisor uses a mouse to mark the words recalled by the subject on the computer screen. When the subject can recall no more words, the same list is read a second time. The test supervisor records the words recalled by the subject on this study. This is then repeated a third time. The software measures the number of correct responses as recorded by the test supervisor.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 24 | |
| Units: sec | | | | |
| least squares mean (standard error) | 1.0274 (± 0.7114) | 1.3792 (± 0.6845) | 0.5316 (± 0.7061) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.3519 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6695 |
| upper limit | 2.3732 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.9814 |

| Statistical analysis title | Copy of Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.4958 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.5657 |
| upper limit | 1.5742 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.005 |

| **Secondary: Changes from baseline at day 28 to end of treatment in Test of Attentional Performance (TAP): Alertness with alarm median** | |
|---|---|
| End point title | Changes from baseline at day 28 to end of treatment in Test of Attentional Performance (TAP): Alertness with alarm median |
| End point description: | |
| Test of Attentional Performance (TAP) (Version 2.3.1) is a standardised test to evaluate alertness and mental flexibility. Only the alertness subtest, with reaction time examination under 2 conditions, was used in this study. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period) | |

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: sec | | | | |
| least squares mean (standard error) | -18.3978 (± 14.6268) | -18.0998 (± 14.0563) | 10.6007 (± 14.2719) | |

**Statistical analyses**

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.298 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -34.9794 |
| upper limit | 35.5754 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 17.1288 |

| **Statistical analysis title** | Copy of Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |

| | |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 28.9985 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.5757 |
| upper limit | 64.5727 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 17.2729 |

## Secondary: Changes from baseline at day 28 in Beck Depression Inventory (BDI): Total score

| | |
|---|---|
| End point title | Changes from baseline at day 28 in Beck Depression Inventory (BDI): Total score |

End point description:

The Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory, for measuring the severity of depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Each answer is scored on a scale value of 0 to 3; higher scores indicate more severe depressive symptoms. The total score can thus range from 0 to 63. The BDI can be divided into subscales, ie, BDI-Affective (BDI-A), BDI-Cognitive (BDI-C), and BDI-Somatic (BDI-S). A BDI total score of more than 10 points was considered as affected (Kendall 1987). For BDI-A, BDI-C and BDI-S these cut-off values are >0.9, >1.4, and >4 respectively (Beck 2002).

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 26 | 25 | |
| Units: units on a scale | | | | |
| least squares mean (standard error) | 0.3912 (± 1.0322) | -1.0101 (± 0.9857) | -1.9693 (± 0.9770) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |

| | |
|---|---|
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | -1.4013 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.0581 |
| upper limit | 1.2555 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.29 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | -2.3604 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.9403 |
| upper limit | 0.2195 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.2527 |

## Secondary: Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): Total score

| End point title | Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): Total score |
|---|---|

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a subject-reported outcome measure and comprises 14 items equally divided over the two subscales anxiety (HADS-A) and depression (HADS-D). HADS-A includes items such as tension, worry, fear, panic, difficulties in relaxing, and restlessness, HADS-D includes items predominantly measuring anhedonia (not experiencing joy). Respondents indicate how they currently feel, rated on a 4-point Likert scale ranging from 0 to 3, with higher scores indicating higher severity. The ratings of the 14 items are summed to yield a total score (0 to 42), or for each subscale separately (0 to 21).

| End point type | Secondary |
|---|---|

End point timeframe:

pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 25 | 26 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.4455 (± 0.8360) | -0.1603 (± 0.800) | 0.7587 (± 0.8102) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.6058 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7588 |
| upper limit | 1.5473 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.0454 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.3132 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9088 |
| upper limit | 2.5353 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.0789 |

## Secondary: Changes from baseline at day 28 in the NMDAS score: Section I

| End point title | Changes from baseline at day 28 in the NMDAS score: Section I |
|---|---|

End point description:

The Newcastle Mitochondrial Disease Scale for Adults (NMDAS) is a semi-quantitative clinical rating scale designed specifically for all forms of mitochondrial disease. The rating scale encompasses all aspects of mitochondrial disease by exploring several domains:
• Section I, Current function, consists of vision; hearing; speech; swallowing; handwriting; cutting food and handling utensils; dressing; hygiene; exercise; gait stability.
• Section II, System-specific involvement, (input from the subject and clinical judgment) and encompasses psychiatric; migraine headaches; seizures; stroke-like episodes; encephalopathic episodes; gastro-intestinal symptoms, diabetes mellitus; respiratory weakness; cardiovascular system.
• Section III, Current clinical assessment, is based on the clinician's assessment. It includes visual acuity; ptosis; chronic progressive external ophthalmoplegia; dysphonia/dysarthria; myopathy; cerebellar ataxia; neuropathy; pyramidal; extrapyramidal; cognition

| End point type | Secondary |
|---|---|

End point timeframe:

Pre dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | -0.5221 (± 0.2459) | -0.2196 (± 0.2303) | 0.1093 (± 0.2365) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | 50 mg KH176 v Placebo |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.3025 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3375 |
| upper limit | 0.9424 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3107 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.6314 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.02402 |
| upper limit | 1.2868 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3182 |

## Secondary: Number of headache days

| End point title | Number of headache days |
|---|---|
| End point description: | |
| Subjects report the number of headache days, intensity and duration, and on the use of medication to relieve headache in a diary. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period) | |

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: number | | | | |
| arithmetic mean (standard deviation) | 6.4 (± 6.6) | 5.5 (± 5.5) | 4.9 (± 5.2) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 0.5kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 0.5kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA was assessed according to international standards (air conduction measurements at 0.25, 0.50, 1, 2, 3, 4, 6, and 8 kHz; bone conduction measurements at octave intervals at 0.5, 1, 2 and 4 kHz).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1(baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.23 (± 5.63) | 1.48 (± 4.89) | 0.33 (± 5.10) | |

**Statistical analyses**

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Smell Identification Test (UPSIT)

| End point title | Changes from baseline at Day 28 in the Smell Identification Test (UPSIT) |
|---|---|

End point description:

The 40-item University of Penn Smell Identification Test (UPSIT) is a measurement of the individual's ability to detect odors at a suprathreshold level. The test consists of 4 different 10 page booklets, with a total of 40 questions. On each page, there is a different "scratch and sniff" strip which are embedded with a microencapsulated odorant. There is also a four choice multiple choice question on each page. The scents are released using a pencil. After each scent is released, the subject smells the level and detects the odor from the four choices. There is an answer column on the back of the test booklet, and the test is scored out of 40 items.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | 1.1974 (± 0.6150) | -0.1836 (± 0.5889) | 0.2700 (± 0.5928) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.381 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.1773 |
| upper limit | 0.4153 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8722 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.9274 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.7141 |
| upper limit | 0.8593 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8675 |

## Secondary: Changes from baseline at day 28 in the Cognitive Failure Questionnaire (CFQ): Total score

| End point title | Changes from baseline at day 28 in the Cognitive Failure Questionnaire (CFQ): Total score |
|---|---|

End point description:

The Cognitive Failure Questionnaire is a questionnaire to evaluate subjective cognitive functioning. It monitors the occurrence of daily cognitive errors with respect to memory and attention. The questionnaire has 25 items on daily activities related to attention and memory, that have to be scored on a 5 point scale. The outcome is an overall score over all items and 4 subscales (distraction, distraction in different social environments, names and words, orientation).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 1.0328 (± 1.6203) | -2.5723 (± 1.5259) | -4.5131 (± 1.5474) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -3.6051 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.9481 |
| upper limit | 0.738 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1087 |

| Statistical analysis title | Copy of Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -5.5459 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.893 |
| upper limit | -1.1988 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.1107 |

## Secondary: Changes from baseline at day 28 in the Quality of Life in neurological disorders Short Form (Neuro-QoL-SF): Total Score

| End point title | Changes from baseline at day 28 in the Quality of Life in neurological disorders Short Form (Neuro-QoL-SF): Total Score |
|---|---|

End point description:

The Neuro-QoL (quality in life in neurological disorders) is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological disorders. Each item in the measurement system can be evaluated separately and reference populations are available benchmarking the scores in population in this study at baseline and after treatment. In this study, only the Fatigue Short Form will be applied. The Fatigue Short Form is an 8-item score evaluating the perception of fatigue and its impact in daily life activities. Sensations ranging from tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that decreases one's capacity for physical, functional, social, and mental activities. The Fatigue Short Form is an 8-item self-assessment questionnaire on paper.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | -0.4203 (± 0.9988) | -1.7517 (± 0.9701) | -2.2450 (± 0.9721) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | 50 mg KH176 v Placebo |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.3314 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.8001 |
| upper limit | 1.1374 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.1987 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -1.824 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2513 |
| upper limit | 0.6019 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.1782 |

## Secondary: Changes from baseline at day 28 to end of treatment in Test of Attentional Performance (TAP): Alertness without alarm

| End point title | Changes from baseline at day 28 to end of treatment in Test of Attentional Performance (TAP): Alertness without alarm |
|---|---|

End point description:

Test of Attentional Performance (TAP) (Version 2.3.1) is a standardised test to evaluate alertness and mental flexibility. Only the alertness subtest, with reaction time examination under 2 conditions, was used in this study.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre dose Day 1 (baseline) to end of treatment (Day 28 of each  treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: sec | | | | |
| arithmetic mean (standard deviation) | -10.8555 (± 12.8006) | -7.7724 (± 12.4769) | 1.0216 (± 12.4431) | |

## Statistical analyses

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |

| | |
|---|---|
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 3.083 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -24.1367 |
| upper limit | 30.3028 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 13.2164 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 11.877 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.8221 |
| upper limit | 38.5762 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 12.9636 |

## Secondary: Changes from baseline at day 28 in Beck Depression Inventory (BDI): Affective score

| End point title | Changes from baseline at day 28 in Beck Depression Inventory (BDI): Affective score |
|---|---|

End point description:

The Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory, for measuring the severity of depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Each answer is scored on a scale value of 0 to 3; higher scores indicate more severe depressive symptoms. The total score can thus range from 0 to 63.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.05778 (± 0.3756) | 0.05148 (± 0.3490) | -0.1463 (± 0.3539) | |

**Statistical analyses**

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.00631 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8937 |
| upper limit | 0.8811 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4309 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.2041 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.0885 |
| upper limit | 0.6803 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4294 |

## Secondary: Changes from baseline at day 28 in Beck Depression Inventory: Cognitive score

| End point title | Changes from baseline at day 28 in Beck Depression Inventory: Cognitive score |
|---|---|

End point description:

The Beck Depression Inventory (BDI) is a 21-question multiple-choice self-report inventory, for measuring the severity of depression. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. Each answer is scored on a scale value of 0 to 3; higher scores indicate more severe depressive symptoms. The total score can thus range from 0 to 63. The BDI can be divided into subscales, ie, BDI-Affective (BDI-A), BDI-Cognitive (BDI-C), and BDI-Somatic (BDI-S). A BDI total score of more than 10 points was considered as affected (Kendall 1987). For BDI-A, BDI-C and BDI-S these cut-off values are >0.9, >1.4, and >4 respectively (Beck 2002).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.3031 (± 0.3647) | -0.1733 (± 0.3561) | -0.2147 (± 0.3447) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.4764 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.5136 |
| upper limit | 0.5608 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5036 |

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.5178 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4978 |
| upper limit | 0.4622 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.4758 |

## Secondary: Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): A-score

| End point title | Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): A-score |
|---|---|

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a subject-reported outcome measure and comprises 14 items equally divided over the two subscales anxiety (HADS-A) and depression (HADS-D). HADS-A includes items such as tension, worry, fear, panic, difficulties in relaxing, and restlessness, HADS-D includes items predominantly measuring anhedonia (not experiencing joy). Respondents indicate how they currently feel, rated on a 4-point Likert scale ranging from 0 to 3, with higher scores indicating higher severity. The ratings of the 14 items are summed to yield a total score (0 to 42), or for each subscale separately (0 to 21).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.4172 (± 0.4499) | 0.1361 (± 0.4273) | 0.4344 (± 0.4348) | |

## Statistical analyses

| Statistical analysis title | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.2811 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4067 |
| upper limit | 0.8445 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5465 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.01722 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.1372 |
| upper limit | 1.1716 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5605 |

## Secondary: Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): D-score

| End point title | Changes from Baseline at Day 28 in Hospital Anxiety and Depression Scale (HADS): D-score |
|---|---|

End point description:

The Hospital Anxiety and Depression Scale (HADS) is a subject-reported outcome measure and comprises 14 items equally divided over the two subscales anxiety (HADS-A) and depression (HADS-D). HADS-A includes items such as tension, worry, fear, panic, difficulties in relaxing, and restlessness, HADS-D includes items predominantly measuring anhedonia (not experiencing joy). Respondents indicate how they currently feel, rated on a 4-point Likert scale ranging from 0 to 3, with higher scores indicating higher severity. The ratings of the 14 items are summed to yield a total score (0 to 42), or for each subscale separately (0 to 21).

| End point type | Secondary |
|---|---|

End point timeframe:
Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units on a scale | | | | |
| least squares mean (standard error) | 0.2829 (± 0.5080) | -0.3325 (± 0.4913) | 0.09058 (± 0.4974) | |

**Statistical analyses**

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.6153 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.0039 |
| upper limit | 0.7732 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6742 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.1923 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.6208 |
| upper limit | 1.2363 |

| | |
|---|---|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.6936 |

## Secondary: Changes from Baseline at Day 28 in NMDAS: Section II

| | |
|---|---|
| End point title | Changes from Baseline at Day 28 in NMDAS: Section II |

End point description:

The Newcastle Mitochondrial Disease Scale for Adults (NMDAS) is a semi-quantitative clinical rating scale designed specifically for all forms of mitochondrial disease. The rating scale encompasses all aspects of mitochondrial disease by exploring several domains:
• Section I, Current function, consists of vision; hearing; speech; swallowing; handwriting; cutting food and handling utensils; dressing; hygiene; exercise; gait stability.
• Section II, System-specific involvement, (input from the subject and clinical judgment) and encompasses psychiatric; migraine headaches; seizures; stroke-like episodes; encephalopathic episodes; gastro-intestinal symptoms, diabetes mellitus; respiratory weakness; cardiovascular system.
• Section III, Current clinical assessment, is based on the clinician's assessment. It includes visual acuity; ptosis; chronic progressive external ophthalmoplegia; dysphonia/dysarthria; myopathy; cerebellar ataxia; neuropathy; pyramidal; extrapyramidal; cognition

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | 0.03490 (± 0.2349) | -0.3924 (± 0.2375) | -0.1116 (± 0.2345) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | 50 mg KH176 v Placebo |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.4273 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1525 |
| upper limit | 0.2979 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3521 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.1465 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8538 |
| upper limit | 0.5609 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.3435 |

**Secondary: Changes from Baseline at Day 28 in NMDAS: Section III**

| End point title | Changes from Baseline at Day 28 in NMDAS: Section III |
|---|---|

End point description:

The Newcastle Mitochondrial Disease Scale for Adults (NMDAS) is a semi-quantitative clinical rating scale designed specifically for all forms of mitochondrial disease. The rating scale encompasses all aspects of mitochondrial disease by exploring several domains:
• Section I, Current function, consists of vision; hearing; speech; swallowing; handwriting; cutting food and handling utensils; dressing; hygiene; exercise; gait stability.
• Section II, System-specific involvement, (input from the subject and clinical judgment) and encompasses psychiatric; migraine headaches; seizures; stroke-like episodes; encephalopathic episodes; gastro-intestinal symptoms, diabetes mellitus; respiratory weakness; cardiovascular system.
• Section III, Current clinical assessment, is based on the clinician's assessment. It includes visual acuity; ptosis; chronic progressive external ophthalmoplegia; dysphonia/dysarthria; myopathy; cerebellar ataxia; neuropathy; pyramidal; extrapyramidal; cognition

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | -0.7284 (± 0.4649) | -1.0848 (± 0.4357) | -0.07640 (± 0.4653) | |

**Statistical analyses**

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.3564 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4533 |
| upper limit | 0.7404 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5326 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.652 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4902 |
| upper limit | 1.7941 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5546 |

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 0.25 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 0.25 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.09 (± 7.55) | 2.39 (± 6.27) | 1.38 (± 7.47) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 1 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 1 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype. P

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.50 (± 4.00) | 0.61 (± 3.50) | 1.48 (± 5.19) | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 2kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 2kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | 0.41 (± 4.75) | 0.48 (± 3.23) | -0.24 (± 4.90) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 3 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 3 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -1.59 (± 3.19) | -0.87 (± 4.80) | -0.25 (± 3.35) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 4 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 4 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum

disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.05 (± 5.15) | 1.48 (± 5.59) | 0.05 (± 6.01) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 6 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 6 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 22 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.43 (± 9.35) | -0.77 (± 11.24) | 0.57 (± 8.63) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 8kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Air Conduction at 8kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 22 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | 5.81 (± 21.94) | -3.14 (± 13.46) | 3.62 (± 21.60) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction at 0.5 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction at 0.5 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 24 | 22 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.13 (± 4.16) | 0.58 (± 3.37) | 1.59 (± 3.80) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA):

## Right Ear Air Conduction at 1 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction at 1 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.86 (± 4.14) | -0.22 (± 3.91) | -1.05 (± 3.25) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction at 2 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction at 2 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 23 | 22 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -1.09 (± 3.16) | 0.65 (± 2.72) | 1.55 (± 6.41) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction: 3 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Right Ear Air Conduction: 3 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 24 | 21 | |
| Units: Khz | | | | |
| arithmetic mean (standard deviation) | -1.22 (± 4.37) | -0.58 (± 4.11) | -0.33 (± 4.89) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 4 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 4 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 21 | |
| Units: KhZ | | | | |
| arithmetic mean (standard deviation) | -0.45 (± 2.84) | 0.39 (± 4.54) | -0.57 (± 4.11) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 6 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 6 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Day 1

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 22 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.33 (± 7.42) | -6.91 (± 20.65) | 2.05 (± 10.78) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 8 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Conduction: 8 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 22 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -3.52 (± 8.44) | -3.64 (± 9.70) | 4.60 (± 11.91) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 1 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 1 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 22 | 23 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.23 (± 3.29) | -2.43 (± 15.61) | 0.70 (± 4.64) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 2 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 2 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | 0.05 (± 4.10) | 0.48 (± 3.33) | 0.05 (± 5.21) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction at 0.5 kHz

| End point title | Changes from baseline at day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction at 0.5 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 23 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -1.05 (± 4.46) | -2.87 (± 13.98) | -1.30 (± 6.42) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 4 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Left Ear Bone Conduction: 4 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.62 (± 5.37) | 1.05 (± 6.16) | -0.85 (± 5.74) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 0.5 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 0.5 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 22 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -0.33 (± 4.75) | -4.23 (± 13.27) | -0.15 (± 5.89) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 1 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 1 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 23 | 21 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | 0.33 (± 3.18) | -3.91 (± 14.84) | -1.19 (± 3.98) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 2 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 2 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -1.95 (± 4.38) | 1.10 (± 3.78) | 1.80 (± 6.74) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 4 kHz

| End point title | Changes from baseline at Day 28 in the Pure Tone Audiometry (PTA): Right Ear Bone Conduction: 4 kHz |
|---|---|

End point description:

To identify individual hearing threshold levels and changes due to treatment, PTA will be assessed according to international standards. Hearing loss is a common sign in mitochondrial spectrum

disorders, especially in the MIDD phenotype.

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 20 | 21 | 20 | |
| Units: kHz | | | | |
| arithmetic mean (standard deviation) | -2.70 (± 5.99) | 1.24 (± 6.17) | -0.15 (± 4.85) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from baseline at day 28 in the Cognitive Failure Questionnaire (CFQ): Sub Total score

| End point title | Changes from baseline at day 28 in the Cognitive Failure Questionnaire (CFQ): Sub Total score |
|---|---|

End point description:

The Cognitive Failure Questionnaire is a questionnaire to evaluate subjective cognitive functioning. It monitors the occurrence of daily cognitive errors with respect to memory and attention. The questionnaire has 25 items on daily activities related to attention and memory, that have to be scored on a 5 point scale. The outcome is an overall score over all items and 4 subscales (distraction, distraction in different social environments, names and words, orientation).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 16 | 19 | 18 | |
| Units: Units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.38 (± 1.71) | -0.68 (± 1.70) | -0.50 (± 2.50) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Changes from Baseline at Day 28 in NMDAS: Total score (Sections I-III)

| End point title | Changes from Baseline at Day 28 in NMDAS: Total score |
|---|---|

| | |
|---|---|
| | (Sections I-III) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28) of each treatment period

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 24 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | -1.5529 (± 0.6261) | -1.4324 (± 0.5844) | 0.1638 (± 0.6060) | |

**Statistical analyses**

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | 0.1204 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.4223 |
| upper limit | 1.6632 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7491 |

| **Statistical analysis title** | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 50 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Median difference (net) |
| Point estimate | 1.7167 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.1515 |
| upper limit | 3.2818 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.76 |

## Secondary: Changes from baseline at day 28 in Beck Depression Inventory (BDI): Somatic score

| | |
|---|---|
| End point title | Changes from baseline at day 28 in Beck Depression Inventory (BDI): Somatic score |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 23 | 26 | 25 | |
| Units: Units | | | | |
| least squares mean (standard error) | -0.4626 (± 0.5705) | -0.8977 (± 0.5494) | -1.2662 (± 0.5463) | |

### Statistical analyses

| **Statistical analysis title** | Mixed models Treatment diff between B-A |
|---|---|
| Comparison groups | Placebo v 50 mg KH176 |
| Number of subjects included in analysis | 49 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.4351 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.9651 |
| upper limit | 1.0949 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.7429 |

| Statistical analysis title | Mixed models Treatment diff between C-A |
|---|---|
| Comparison groups | Placebo v 100 mg KH176 |
| Number of subjects included in analysis | 48 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | ≤ 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.8036 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3112 |
| upper limit | 0.704 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.732 |

## Secondary: Average duration of headaches

| End point title | Average duration of headaches |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-dose Day 1 (baseline) to end of treatment (Day 28 of each treatment period)

| End point values | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 18 | 19 | 17 | |
| Units: Hours | | | | |
| arithmetic mean (standard deviation) | 6.59 (± 5.53) | 5.92 (± 3.01) | 4.62 (± 2.41) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Intensity of the headaches

| End point title | Intensity of the headaches |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
Day 1

| **End point values** | Placebo | 50 mg KH176 | 100 mg KH176 | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 18 | 19 | 17 | |
| Units: Units | | | | |
| arithmetic mean (standard deviation) | 4.49 (± 1.74) | 4.58 (± 1.53) | 4.18 (± 1.71) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Adverse Events (collected during total study period (all Treatment Periods including FU; AEs were collected from First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

| Reporting groups | |
|---|---|
| Reporting group title | A: Placebo |
| Reporting group description: | |
| Subjects receiving  bid oral administration placebo | |
| Reporting group title | B: 50 mg KH176 bid |
| Reporting group description: - | |
| Reporting group title | C: 100 mg KH176 bid |
| Reporting group description: - | |

| Serious adverse events | A: Placebo | B: 50 mg KH176 bid | C: 100 mg KH176 bid |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Exercise tolerance decreased | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | A: Placebo | B: 50 mg KH176 bid | C: 100 mg KH176 bid |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 15 / 25 (60.00%) | 14 / 27 (51.85%) | 26 / 26 (100.00%) |
| General disorders and administration site conditions | | | |
| Medical device site reaction | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 25 (12.00%) | 3 / 27 (11.11%) | 3 / 26 (11.54%) |
| occurrences (all) | 3 | 3 | 3 |
| Fatigue | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 27 (3.70%) | 2 / 26 (7.69%) |
| occurrences (all) | 2 | 1 | 2 |
| Chest pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Exercise tolerance decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Gait disturbance | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Reproductive system and breast disorders | | | |
| Intermenstrual bleeding | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Oropharyngeal pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Poor quality sleep | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 2 / 27 (7.41%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Investigations | | | |
| Blood pressure increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Electrocardiogram T wave amplitude decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Glomerular filtration rate decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| SARS-CoV-2 test positive | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye contusion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fall | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Limb injury | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin laceration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sunburn | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Palpitations | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 2 / 26 (7.69%) |
| occurrences (all) | 0 | 1 | 2 |
| Tachycardia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Memory impairment | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 27 (3.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 1 | 1 |
| Disturbance in attention | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 1 | 1 |
| Dizziness | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 1 | 1 |
| Neuralgia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Paraesthesia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Altered state of consciousness | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Balance disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lethargy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Tremor | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| External ear inflammation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoacusis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|---|---|---|
| Vertigo | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Eye pruritus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eyelid ptosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eyelids pruritus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 1 / 27 (3.70%) | 2 / 26 (7.69%) |
| occurrences (all) | 2 | 1 | 2 |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 3 / 26 (11.54%) |
| occurrences (all) | 0 | 1 | 3 |
| Diarrhoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 2 / 26 (7.69%) |
| occurrences (all) | 1 | 0 | 2 |
| Abdominal distension | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Abdominal pain | | | |

| | | | |
|---|---|---|---|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Constipation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastritis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Irritable bowel syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Regurgitation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| COVID-19 | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastroenteritis viral | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Oral herpes | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Post-acute COVID-19 syndrome | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal candidiasis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eczema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperhidrosis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neurodermatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin irritation | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |
| Skin reaction | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Pain in extremity | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 25 (8.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Back pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 0 / 26 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Myalgia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 3 / 27 (11.11%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 3 | 1 |
| lower res | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 1 | 1 |
| Upper respiratory tract infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 25 (4.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 1 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 1 / 27 (3.70%) | 0 / 26 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkalaemia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 25 (0.00%) | 0 / 27 (0.00%) | 1 / 26 (3.85%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 03 December 2019 | Protocol version 1.1 (NL only):<br>Section 1.4 'KH176': updated to include a summary of the results of the assessment of the phototoxicity potential of KH176 (by determining the UV-Vis spectrum for KH176 and its metabolite KH183 in methanol. The assessment showed that KH183 is not considered photoreactive. |
| 23 January 2020 | Protocol version 2.0 (GER, UK):<br>• Thyroid sonography included as safety assessment preceding the first Treatment Period and at Follow Up visit Requested by German Ethics Committee.<br>• Inclusion criteria #11: More stringent contraceptive measures for male and female subjects Requested by German (Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM]) and United Kingdom (MHRA) Health Authorities.<br>• Exclusion criteria #2: Specification of prior treatment with an Investigational Product Requested by German Health Authority (BfArM).<br>• Exclusion criteria #5: Addition of threshold values for blood pressure, and renal and hepatic laboratory parameters. Requested by German Health Authority (BfArM).<br>• Exclusion criteria #15: Specification of prior and concomitant use of disallowed medications and supplements Requested by German Health Authority (BfArM) and Dutch Ethics Committee.<br>• Pregnancy test included as Follow Up visit assessment Requested by German Health Authority (BfArM).<br>• Section 1.4 'KH176': Assessment of and guidance on phototoxicity potential included. Requested by United Kingdom Health Authority (MHRA).<br>• Section 1.5.4 'KH176 Dose Justification': Specification of the concomitant use of CYP3A4 and PGP inhibitors. Requested by German Health Authority (BfArM).<br>• Section 4.3.5 'Premature Termination or Suspension of Study': Specification of criteria for (premature) termination or suspension of study Requested by German Health Authority (BfArM).<br>• Section 4.5.3 'Emergency Procedure for Unblinding': Procedure updated to remove requirement of sponsor contact Requested by United Kingdom Health Authority (MHRA).<br>• Section 6.3.7.2 'Clinical Chemistry': Addition of lipase to clinical chemistry panel Requested by German Health Authority (BfArM). |
| 04 March 2020 | Protocol version 2.0 (Local amendment: NL only):<br>• Inclusion criterion #11: More stringent contraceptive measures for male and female subjects. Requested by German (BfArM) and United Kingdom (MHRA) Health Authorities.<br>• Exclusion criterion #2: Specification of prior treatment with an Investigational Product. Requested by German Health Authority (BfArM).<br>• Exclusion criterion #5: Addition of threshold values for blood pressure, and renal and hepatic laboratory parameters. Requested by German Health Authority (BfArM).<br>• Exclusion criterion #15: Specification of prior and concomitant use of disallowed medications and supplements. Requested by German Health Authority (BfArM) and Dutch Ethics Committee.<br>• Schedule of Assessments: Pregnancy test included as Follow Up visit assessment. Requested by German Health Authority (BfArM).<br>• Section 1.5.4 'KH176 Dose Justification': Specification of the concomitant use of CYP3A4 and PGP inhibitors. Requested by German Health Authority (BfArM).<br>• Section 4.3.5 'Premature Termination or Suspension of the Study': Specification of criteria for (premature) termination or suspension of study. Requested by German Health Authority (BfArM).<br>• Section 6.3.7.2 'Clinical Chemistry': Addition of lipase to clinical chemistry panel Requested by German Health Authority (BfArM). |

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|---|---|
| 15 October 2020 | Protocol version 3.0 (Local amendment NL):<br>Protocol version 3.0 (UK, Ger), issued 15 October 2020:<br>• Exclusion criterion #4: Adapted: Further specification of exclusion criterion.• Exclusion criterion #6: Addition of gender specific QTc exclusion thresholds. Normal values for QTc differ between males and females.<br>• Additional exclusion criterion #15: KH176 is an antagonist of the NMDA1A/2B receptor and for other NMDA (1A/2B) antagonists dissociative effects (leading to abuse potential) and other CNS AEs were reported. Therefore, subjects with a history of abuse potential are excluded and subjects will be cautioned against driving or working in situations where alertness and adequate motor coordination are important when they notice adverse CNS effects.<br>• Exclusion criterion #16e: Adapted; subjects using drugs known to prolong QTc interval who have a normal QTc value will not be excluded. If despite use of potentially QTcprolonging drugs patients have a normal QTc interval, there is no increased risk for torsades de pointes. Also, synergism of two potentially QT-prolonging drugs is not expected: currently, there are no data available suggesting the possibility of a more pronounced QTc prolongation by KH176 if the patient is taking any medication expected to affect cardiac repolarization.<br>• Section 1.4 'KH176':<br>o Summary of additional data from receptor binding assay on NMDAR (1A/2B) blocker/antagonism: in a recent receptor binding assay, KH176 was found to be a NMDAR (1A/2B) blocker/antagonist with an half-maximal inhibitory concentration (IC50) of 7.4 uM.<br>o Summary of additional data on anti-inflammatory properties of KH183, and (the absence of) NMDAR (1A/2B) blocker/antagonism of KH183.<br>o Additional text to further clarify occurrence of (TE)AEs.<br>o Additional text further clarifying the reported dissociative TEAEs.<br>o Additional explanation/specification of 'cardiac electrophysiology'. |
| 19 March 2021 | Protocol version 5.0 (Ger, UK):<br>• Additional site in Denmark: Dr John Vissing, Rigshospitalet, University of Copenhagen.<br>• Section 3.2.3 'Treatment periods': Visit window increased for D28 (treatment periods 1 to 3): +/- 1 day.<br>• Inclusion criterion #11: additional details and more stringent contraceptive measures<br>with regards to hormonal contraception, vasectomy and sexual abstinence. Requested by German Health Authority (BfArM) for the KHENEREXT study and according to the Clinical Trials Facilitation Group recommendations.<br>• Section 4.3.1 'Discontinuation of Study Medication': Clarification of the discontinuation criteria for the case of abnormal ECG and in case a pregnancy is diagnosed (subjects must be discontinued). Requested by German Health Authority (BfArM) for the KHENEREXT study.<br>• Section 4.3.4 'End of Study Definition': Clarification of the end of study definition as Last Patient Last Visit. Requested by German Health Authority (BfArM) for the KHENEREXT study. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported