



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 tRNA^{Leu}(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 healthy 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)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	20		
Male	7		

Subject analysis sets

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	

Reporting group values	Placebo	50 mg KH176	100 mg KH176
Number of subjects	27	27	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)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	46.0	46.0	46.0
standard deviation	± 10.8	± 10.8	± 10.8
Gender categorical			
Units: Subjects			
Female	20	20	20
Male	7	7	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. 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 (\pm 0.01002)	-0.00084 (\pm 0.009309)	0.002007 (\pm 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 (\pm 0.01200)	-0.00578 (\pm 0.01157)	0.000936 (\pm 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 (\pm 0.01726)	-0.00515 (\pm 0.01644)	0.007884 (\pm 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 (\pm 0.7114)	1.3792 (\pm 0.6845)	0.5316 (\pm 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 (\pm 14.6268)	-18.0998 (\pm 14.0563)	10.6007 (\pm 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 (\pm 0.8360)	-0.1603 (\pm 0.800)	0.7587 (\pm 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 (\pm 0.2459)	-0.2196 (\pm 0.2303)	0.1093 (\pm 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 (\pm 1.6203)	-2.5723 (\pm 1.5259)	-4.5131 (\pm 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 (\pm 0.9988)	-1.7517 (\pm 0.9701)	-2.2450 (\pm 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 (\pm 0.3756)	0.05148 (\pm 0.3490)	-0.1463 (\pm 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 (\pm 0.3647)	-0.1733 (\pm 0.3561)	-0.2147 (\pm 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:	
<p>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).</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	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:	
<p>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).</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	24	26	25	
Units: Units on a scale				
least squares mean (standard error)	0.2829 (\pm 0.5080)	-0.3325 (\pm 0.4913)	0.09058 (\pm 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:	
<p>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:</p> <ul style="list-style-type: none"> • 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 (\pm 0.2349)	-0.3924 (\pm 0.2375)	-0.1116 (\pm 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:	
<p>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:</p> <ul style="list-style-type: none"> • 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 (\pm 5.15)	1.48 (\pm 5.59)	0.05 (\pm 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 (\pm 9.35)	-0.77 (\pm 11.24)	0.57 (\pm 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 (\pm 4.14)	-0.22 (\pm 3.91)	-1.05 (\pm 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 (\pm 3.16)	0.65 (\pm 2.72)	1.55 (\pm 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 (\pm 7.42)	-6.91 (\pm 20.65)	2.05 (\pm 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 (\pm 8.44)	-3.64 (\pm 9.70)	4.60 (\pm 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 (\pm 3.29)	-2.43 (\pm 15.61)	0.70 (\pm 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 (\pm 4.10)	0.48 (\pm 3.33)	0.05 (\pm 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 (\pm 4.46)	-2.87 (\pm 13.98)	-1.30 (\pm 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 (\pm 5.37)	1.05 (\pm 6.16)	-0.85 (\pm 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 (\pm 4.75)	-4.23 (\pm 13.27)	-0.15 (\pm 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 (\pm 3.18)	-3.91 (\pm 14.84)	-1.19 (\pm 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 (\pm 4.38)	1.10 (\pm 3.78)	1.80 (\pm 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 (\pm 5.99)	1.24 (\pm 6.17)	-0.15 (\pm 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 (\pm 1.71)	-0.68 (\pm 1.70)	-0.50 (\pm 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
-----------------	---

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 (\pm 0.6261)	-1.4324 (\pm 0.5844)	0.1638 (\pm 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 occurrences (all)	1 / 25 (4.00%) 1	0 / 27 (0.00%) 0	0 / 26 (0.00%) 0
Eye disorders Eye pruritus alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Eyelid ptosis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Eyelids pruritus alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0	1 / 27 (3.70%) 1 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 1 / 26 (3.85%) 1
Gastrointestinal disorders Abdominal pain upper alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Vomiting alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Abdominal distension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Abdominal pain	2 / 25 (8.00%) 2 0 / 25 (0.00%) 0 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1	1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	2 / 26 (7.69%) 2 3 / 26 (11.54%) 3 2 / 26 (7.69%) 2 1 / 26 (3.85%) 1

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			

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

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): 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): <ul style="list-style-type: none">• Thyroid sonography included as safety assessment preceding the first Treatment Period and at Follow Up visit Requested by German Ethics Committee.• 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.• Exclusion criteria #2: Specification of prior treatment with an Investigational Product Requested by German Health Authority (BfArM).• Exclusion criteria #5: Addition of threshold values for blood pressure, and renal and hepatic laboratory parameters. Requested by German Health Authority (BfArM).• Exclusion criteria #15: Specification of prior and concomitant use of disallowed medications and supplements Requested by German Health Authority (BfArM) and Dutch Ethics Committee.• Pregnancy test included as Follow Up visit assessment Requested by German Health Authority (BfArM).• Section 1.4 'KH176': Assessment of and guidance on phototoxicity potential included. Requested by United Kingdom Health Authority (MHRA).• Section 1.5.4 'KH176 Dose Justification': Specification of the concomitant use of CYP3A4 and PGP inhibitors. Requested by German Health Authority (BfArM).• 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).• Section 4.5.3 'Emergency Procedure for Unblinding': Procedure updated to remove requirement of sponsor contact Requested by United Kingdom Health Authority (MHRA).• 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): <ul style="list-style-type: none">• Inclusion criterion #11: More stringent contraceptive measures for male and female subjects. Requested by German (BfArM) and United Kingdom (MHRA) Health Authorities.• Exclusion criterion #2: Specification of prior treatment with an Investigational Product. Requested by German Health Authority (BfArM).• Exclusion criterion #5: Addition of threshold values for blood pressure, and renal and hepatic laboratory parameters. Requested by German Health Authority (BfArM).• Exclusion criterion #15: Specification of prior and concomitant use of disallowed medications and supplements. Requested by German Health Authority (BfArM) and Dutch Ethics Committee.• Schedule of Assessments: Pregnancy test included as Follow Up visit assessment. Requested by German Health Authority (BfArM).• Section 1.5.4 'KH176 Dose Justification': Specification of the concomitant use of CYP3A4 and PGP inhibitors. Requested by German Health Authority (BfArM).• 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).• Section 6.3.7.2 'Clinical Chemistry': Addition of lipase to clinical chemistry panel Requested by German Health Authority (BfArM).

15 October 2020	<p>Protocol version 3.0 (Local amendment NL): Protocol version 3.0 (UK, Ger), issued 15 October 2020:</p> <ul style="list-style-type: none"> • 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. • 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. • 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. • Section 1.4 'KH176': <ul style="list-style-type: none"> 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. o Summary of additional data on anti-inflammatory properties of KH183, and (the absence of) NMDAR (1A/2B) blocker/antagonism of KH183. o Additional text to further clarify occurrence of (TE)AEs. o Additional text further clarifying the reported dissociative TEAEs. o Additional explanation/specification of 'cardiac electrophysiology'.
19 March 2021	<p>Protocol version 5.0 (Ger, UK):</p> <ul style="list-style-type: none"> • Additional site in Denmark: Dr John Vissing, Rigshospitalet, University of Copenhagen. • Section 3.2.3 'Treatment periods': Visit window increased for D28 (treatment periods 1 to 3): +/- 1 day. • Inclusion criterion #11: additional details and more stringent contraceptive measures 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. • 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. • 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