



Clinical trial results:

A Phase IIb open-label, multi-centre, extension study to explore the long-term safety and efficacy of KH176 in subjects with a genetically confirmed mitochondrial DNA tRNA^{Leu}(UUR) m.3243A>G mutation who have completed study KH176-202.

Summary

EudraCT number	2020-000832-23
Trial protocol	NL DK
Global end of trial date	08 August 2023

Results information

Result version number	v1 (current)
This version publication date	06 December 2024
First version publication date	06 December 2024

Trial information

Trial identification

Sponsor protocol code	KH176-203
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04604548
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Khondrion B.V.
Sponsor organisation address	Transistorweg 5C, Nijmegen, Netherlands, 6534 AT
Public contact	G. Ruiterkamp, M. Sc., Khondrion B.V., +31 612805425, ruiterkamp@khondrion.com
Scientific contact	Jan M.A. Smeitink, MD, PhD, MAE, Khondrion B.V., +31 24 763 5000 Option 1, info@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	01 November 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 August 2023
Global end of trial reached?	Yes
Global end of trial date	08 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety of sonlicromanol (KH176) during an 18-months treatment period, including:

1. The tolerability and safety of sonlicromanol 100 mg BID following 18 months of oral administration
2. Electrocardiogram (ECG) intervals, rhythm and morphology

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The Informed Consent Forms were signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

The Data Safety Monitoring Committee (DSMB) safeguarded the interests of the study subjects, assessed the accumulating safety data of the interventions during the study, and reviewed the study's progress including accruing data of recruitment and data quality.

Background therapy:

Use of (multi)vitamins, co-enzyme Q10, Vitamin E, riboflavin and anti-oxidant supplements (including, but not limited to idebenone/EPI-743, mitoQ or alternative names of similar products) is not allowed from 4 weeks prior to the first dosing until follow up, unless stable for at least one month prior to first dosing and remaining stable throughout the study. Any medication negatively influencing mitochondrial functioning (including but not limited to valproic acid, glitazones, statins, anti-virals, amiodarone, and NSAIDs) is prohibited from 4 weeks prior to the first dosing until follow up, unless stable for at least one month prior to first dosing and remaining stable throughout the study.

Strong CYP3A4 inhibitors (all 'conazoles-anti-fungals', certain HIV antivirals, grapefruit) and Cytochrome P450 3A4 inducers, including certain HIV antivirals, carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort, pioglitazone, troglitazone are not allowed from 4 weeks prior to the first dosing until follow up.

Any medication known to affect cardiac repolarisation, unless QTc interval at screening is normal during stable treatment for a period of two weeks, or 5 half-lives of the medication and its major metabolite(s), whichever period is the shortest: all anti-psychotics, several anti-depressants: e.g. anti-emetics: domperidone, granisetron, ondansetron.

Evidence for comparator:

Not Applicable

Actual start date of recruitment	01 September 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	15
EEA total number of subjects	12

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)	15
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study KH176-202 was initially conducted at 4 Investigational sites (the Netherlands, Germany, the United Kingdom, and Denmark).

Subjects having fulfilled all inclusion and exclusion criteria and completed the full treatment period of study KH176-202 were enrolled in study KH176-203.

Pre-assignment

Screening details:

18 of 24 subjects who completed Study KH176-202 were screened. 3 subjects were screening failures, 15 subjects were eligible to participate. 11 of the 15 subjects completed the Wk 52 visit, 4 subjects discontinued prior to Wk52: 3 subjects due to withdrawal of consent by subject (2 in the UK and 1 in Germany) and 1 subject due to study terminated.

Period 1

Period 1 title	Baseline to End of Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	100 mg BID sonlicromanol
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Arm description:

Oral administration of sonlicromanol 100 mg BID

Arm type	Experimental
Investigational medicinal product name	sonlicromanol
Investigational medicinal product code	SUB198953
Other name	KH176
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

KH176 is available as a powder for reconstitution, to be reconstituted with tapwater. KH176 50 mg or 100 mg will be provided in 20 mL bottles, which can be used to add the tapwater and consequently drink the oral liquid.

Number of subjects in period 1	100 mg BID sonlicromanol
Started	15
Completed	8
Not completed	7
Consent withdrawn by subject	3
Study Termination by Sponsor	4

Baseline characteristics

Reporting groups

Reporting group title	Baseline to End of Treatment
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Reporting group description:

Subjects with a genetically confirmed mitochondrial deoxyribonucleic acid (DNA) transfer ribonucleic acid (tRNA)^{Leu(UUR)} m.3243A>G mutation who completed study KH176-202. In the KH176-203 study subjects will be receiving sonlicromanol 100 mg BID or sonlicromanol 50 mg BID (as determined by the investigator based on safety / tolerability considerations) for a period of 18 months , thereby ensuring treatment continuation with sonlicromanol after study KH176-202.

Reporting group values	Baseline to End of Treatment	Total	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	0	0	
Age continuous			
Units: years			
arithmetic mean	47.9		
standard deviation	± 5.9	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	5	5	
Country			
Units: Subjects			
Netherlands	7	7	
Germany	3	3	
United Kingdom	3	3	
Denmark	2	2	
Diagnosis			
Units: Subjects			
MELAS	2	2	
MIDD	12	12	
Mixed Phenotype	1	1	
Race			
Units: Subjects			
Black	0	0	
American Native Or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian Or Other Pacific Islander	0	0	
White	15	15	
Height			
Units: Centimeters			
arithmetic mean	168.4		
standard deviation	± 8.6	-	
Body Mass Index (BMI)			
Units: kg/m2			

arithmetic mean	23.12		
standard deviation	± 4.64	-	
Weight			
Units: kilogram(s)			
arithmetic mean	65.29		
standard deviation	± 12.21	-	

End points

End points reporting groups

Reporting group title	100 mg BID sonlicromanol
Reporting group description: Oral administration of sonlicromanol 100 mg BID	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: The Full-Analysis Set (FAS) consists of all subjects who received study medication in this study and who had at least one on-treatment efficacy assessment after first drug intake.	

Primary: Number of Treatment-Emergent Adverse Events (TEAEs) and Serious Treatment-Emergent Adverse Events (SAEs)

End point title	Number of Treatment-Emergent Adverse Events (TEAEs) and Serious Treatment-Emergent Adverse Events (SAEs) ^[1]
End point description: The All-Subjects-Treated/Safety population: includes all subjects who received at least one dose of study medication (sonlicromanol) in this study. A treatment emergent adverse event (TEAE) is defined as an adverse event when the date of onset or when an existing condition increased during the use of the study medication up to 14 days after the last study medication or when an existing condition increased in severity relative to pretreatment state An AE is considered related if the causality to the study medication is classified as either 'Definite', 'Probable', or 'Possible'. Otherwise, it will be considered unrelated.	
End point type	Primary
End point timeframe: Baseline (Day 1) to end of study (Week 78)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	15			
Units: (S)AEs				
Number of Subjects with any TEAE	13	13		
Number of subjects with any related TEAE	8	8		
Number of subjects with any severe TEAE	2	2		
Number of subjects with any serious TEAE	2	2		
Number of subjects with TEAE leading to study disc	0	0		
Number of subjects with TEAE leading to death	0	0		

Statistical analyses

Primary: Changes from baseline to End of Treatment (Week 52) in safety laboratory parameters: biochemistry

End point title	Changes from baseline to End of Treatment (Week 52) in safety laboratory parameters: biochemistry ^[2]
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End point description:

End point type	Primary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Percentage				
arithmetic mean (standard deviation)				
Albumin (g/L)	1.46 (± 6.63)			
Alkaline Phosphatase (ukat/L)	-3.097 (± 9.284)			
Alanine Aminotransferase (ukat/L)	13.652 (± 33.867)			
Amylase (ukat/L)	14.256 (± 47.449)			
Aspartate Aminotransferase (ukat/L)	-2.231 (± 23.799)			
Creatine Kinase (ukat/L)	1.08 (± 42.22)			
Bilirubin (umol/L)	32.03 (± 57.19)			
Calcium Corrected for Albumin (mmol/L)	1.26 (± 4.58)			
Cholesterol (mmol/L)	3.415 (± 8.530)			
Chloride (mmol/L)	0.00 (± 1.93)			
Creatinine (umol/L)	-1.43 (± 8.83)			
C Reactive Protein (mg/L)	-17.21 (± 33.98)			
Gamma Glutamyl Transferase (ukat/L)	3.283 (± 21.057)			
Glucose (mmol/L)	-6.93 (± 24.19)			
Hemoglobin A1C (mmol/mol)	0.26 (± 7.55)			
HDL Cholesterol (mmol/L)	-3.508 (± 27.800)			
Potassium (mmol/L)	-1.527 (± 9.504)			
Lactic Acid (mmol/L)	-2.765 (± 25.622)			
LDL Cholesterol (mmol/L)	0.651 (± 11.137)			
Lipase (ukat/L)	-2.561 (± 24.959)			

Phosphate (mmol/L)	-7.724 (± 23.423)			
Protein (g/L)	-0.14 (± 5.48)			
Sodium (mmol/L)	-0.52 (± 1.51)			
Thyroxine Free (pmol/L)	6.353 (± 9.323)			
Triglycerides (mmol/L)	6.034 (± 29.586)			
Thyrotropin (mIU/L)	48.542 (± 57.525)			
Urate (mmol/L)	-2.4 (± 7.3)			
Urea (mmol/L)	-1.306 (± 20.270)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes from baseline to End of Treatment (Week 52) in safety laboratory parameters: haematology

End point title	Changes from baseline to End of Treatment (Week 52) in safety laboratory parameters: haematology ^[3]
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End point description:

End point type	Primary
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End point timeframe:

Baseline (Day 1) to End of Treatment (week 52)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage				
arithmetic mean (standard deviation)				
Basophils (10 ⁹ /L)	2.035 (± 40.101)			
Eosinophils (10 ⁹ /L)	-7.586 (± 39.332)			
Ery. Mean Corpuscular HGB Concentration (mmol/L)	-1.080 (± 2.875)			
Ery. Mean Corpuscular Hemoglobin (fmol)	0.4164 (± 3.0922)			
Ery. Mean Corpuscular Volume (fL)	1.46 (± 2.16)			
Erythrocytes (10 ¹² /L)	1.738 (± 5.438)			
Hematocrit (fraction of 1)	2.9755 (± 4.5619)			
Hemoglobin (mmol/L)	1.751 (± 4.515)			

Leukocytes (10 ⁹ /L)	-4.472 (± 12.752)			
Lymphocytes (10 ⁹ /L)	-1.98 (± 17.01)			
Monocytes (10 ⁹ /L)	-1.70 (± 16.27)			
Neutrophils (10 ⁹ /L)	-1.860 (± 22.953)			
Thrombocytes (10 ⁹ /L)	2.4 (± 7.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes from baseline to End of Treatment (Week 52) in ECG parameters

End point title	Changes from baseline to End of Treatment (Week 52) in ECG parameters ^[4]
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End point description:

End point type	Primary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage				
arithmetic mean (standard error)				
QT Interval Aggregate	0.5 (± 6.3)			
QTc Interval Framingham correction	0.9 (± 2.6)			
QTcB Interval Aggregate	1.0 (± 3.4)			
QTcF Interval Aggregate	0.8 (± 2.6)			
RR Interval Aggregate	-0.2 (± 15.7)			
PR Interval Aggregate	-5.4 (± 7.4)			
ECG Mean Heart Rate	2.3 (± 16.2)			
QRS Duration Aggregate	1.3 (± 6.4)			
QRS Axis	3.8 (± 481.9)			
T Wave Amplitude Single Beat	-5.2 (± 21.2)			
Tpeak-Tend Interval Aggregate	14.4 (± 29.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes from baseline to End of Treatment (Week 52) in Vital signs

End point title	Changes from baseline to End of Treatment (Week 52) in Vital signs ^[5]
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End point description:

End point type	Primary
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End point timeframe:

Baseline (Day 1) to End of Treatment (week 52)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Percentage				
arithmetic mean (standard deviation)				
Systolic Blood Pressure (mmHg)	2.25 (± 8.99)			
Diastolic Blood Pressure (mmHg)	-1.16 (± 10.73)			
Heart Rate (beats/min)	-2.08 (± 9.22)			
Weight (kg)	-0.80 (± 2.94)			
Body Mass Index (kg/m2)	-0.80 (± 2.94)			

Statistical analyses

No statistical analyses for this end point

Primary: Changes from baseline to End of Treatment (Week 52) in Thyroid parameters

End point title	Changes from baseline to End of Treatment (Week 52) in Thyroid parameters ^[6]
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End point description:

End point type	Primary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical analysis was planned; only descriptive data were reported for this endpoint.

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Percentage				
arithmetic mean (standard deviation)				
Left Lob: Anterior - Posterior	0.3 (± 0.1)			
Left Lob: Craniocaudal	1 (± 0)			
Left Lob: Transverse	-0.4 (± 0.1)			
Right Lob: Anterior-Posterior	-0.3 (± 0.1)			
Right Lob: Craniocaudal	1 (± 0)			
Right Lob: Transverse	-0.9 (± 0.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the attention domain of cognitive functioning: Identification Test (IDN)

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the attention domain of cognitive functioning: Identification Test (IDN)
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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	Secondary
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End point timeframe:

Baseline (Day 1) to End of treatment Week 52

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
median (standard deviation)	0.2766 (± 0.5552)	0.2766 (± 0.5552)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2456
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2023
upper limit	0.6936

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the executive functioning domain of cognitive functioning: Groton Maze Learning (GML).

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the executive functioning domain of cognitive functioning: Groton Maze Learning (GML).
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End point description:

Executive functioning: GML (number of errors learning the same hidden pathway across the consecutive learning trails [Total Errors], lower is better). The GML test is a measure of problem solving and reasoning and uses a maze learning paradigm. The subject was 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 referred to the box array. Subjects were required to find the hidden pathway guided by 4 search rules: do not move diagonally, more than 1 box, move back on the pathway, and return to the last correct location after an error. At each step, only the most recently selected box was shown. Feedback was given with visual and auditory cues. The head of path, or the last correct location, flashed with a green check when 2 errors were made in succession to indicate to the subject that they had to return to this location. There were 21 well-matched alternate pathways available

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	0.1210 (± 0.6361)	0.1210 (± 0.6361)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description: Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1049
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1432
upper limit	0.362

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: One Back Test (ONB) - speed of performance

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: One Back Test (ONB) - speed of performance
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End point description:

Working memory: ONB (speed of performance; mean of the log10 transformed reaction times for correct responses [Reaction Time], lower is better)

The One Back Test (ONB) 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 was asked whether the card displayed in the center of the screen was the same as the card presented immediately previously. The subject responded by pressing the Yes or No key. The software measured the speed and accuracy of each response.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.2383 (± 0.4763)	0.2383 (± 0.4763)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2255
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0867
upper limit	0.5376

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: One Back Test (ONB) – accuracy of performance

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: One Back Test (ONB) – accuracy of performance
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End point description:

Working memory: ONB (accuracy of performance; arcsine square root of proportion corrects [Accuracy], higher is better)

The One Back Test (ONB) 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 was asked whether the card displayed in the center of the screen was the same as the card presented immediately previously. The subject responded by pressing the Yes or No key. Because no card had been presented yet on the first study, a correct first response was always No. The software measured the speed and accuracy of each response.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.2216 ($\pm$ 1.3847)	0.2216 ($\pm$ 1.3847)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2858
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5103
upper limit	1.0818

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: Detection Test (DET) – speed of performance

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the working memory domain of cognitive functioning: Detection Test (DET) – speed of performance
End point description:	
Psychomotor function: DET (speed of performance; mean of the log10 transformed reaction times for correct responses [Reaction Time], lower is better) The Detection Test (DET) 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 was asked to press the Yes key as soon as the card in the center of the screen turned face up. The software measured the speed and accuracy of each response.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.0698 ($\pm$ 1.1579)	-0.0698 ($\pm$ 1.1579)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.0636
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5897
upper limit	0.4626

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the visual learning domain of cognitive functioning: Visual learning: One Card Learning Test (OCL)

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the visual learning domain of cognitive functioning: Visual learning: One Card Learning Test (OCL)
End point description:	
Visual learning: One Card Learning Test (OCL) Test (accuracy of performance; arcsine square root of proportion corrects [Accuracy], higher is better)	
The One Card Learning (OCL) 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 was asked whether the card displayed in the center of the screen was seen previously in this test. The subject responded by pressing the Yes or No key. The software measured the speed and accuracy of each response.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.2266 ($\pm$ 0.9625)	0.2266 ($\pm$ 0.9625)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2286
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3165
upper limit	0.7736

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the verbal learning domain of cognitive functioning: International Shopping List (ISL)

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the verbal learning domain of cognitive functioning: International Shopping List (ISL)
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End point description:

Verbal learning: ISL (number of correct responses remembering the word list on 3 consecutive trials [Total Correct], higher is better)

The International Shopping List Test (ISL) is a measure of verbal learning and uses a well-validated list-learning paradigm. High frequencies, high imagery, and concrete nouns (items from a shopping list) were read to the subject by the test supervisor at the rate of 1 word every 2 seconds. Once all words had been read, the subject was asked to recall as many of the words as he/she could as quickly as possible. The test supervisor used a mouse to mark the words recalled by the subject on the computer screen. When the subject could recall no more words, the same list was read a second time. The test supervisor recorded the words recalled by the subject on this study. This was then repeated a third time. The software measured the number of correct responses as recorded by the test supervisor.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	-0.3582 ($\pm$ 0.6255)	-0.3582 ($\pm$ 0.6255)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.3538
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.779
upper limit	0.0715

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Attention Domain Composites of cognitive functioning: DET and IDN

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Attention Domain Composites of cognitive functioning: DET and IDN
End point description:	
Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met. Only computed if z-scores are available for both tests (DET and IDN).	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.1034 ($\pm$ 0.7955)	0.1034 ($\pm$ 0.7955)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.0951
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.312
upper limit	0.5023

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Executive Function Composite of cognitive functioning: ONB (speed), GML

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Executive Function Composite of cognitive functioning: ONB (speed), GML
End point description:	
Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met. Only computed if z-scores are available for both tests (ONB (speed), GML	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	0.1872 ($\pm$ 0.3994)	0.1872 ($\pm$ 0.3994)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.1874
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0291
upper limit	0.4039

Secondary: Changes from baseline (measured at Day 1) to End of Treatment (Week 52) in the Global Composite of cognitive functioning: DET, IDN, OCL, ONB (speed), ISL, GML

End point title	Changes from baseline (measured at Day 1) to End of Treatment (Week 52) in the Global Composite of cognitive functioning: DET, IDN, OCL, ONB (speed), ISL, GML
End point description:	
Global Composite Score: DET, IDN, OCL, ONB (speed), ISL, GML. Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met.	
Only computed if z-scores are available for DET, IDN, OCL, ONB (speed), ISL, GML: only computed if z-scores are available for a minimum of three tests with representation from all three domain composites listed above.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.0035 ($\pm$ 0.4821)	0.0035 ($\pm$ 0.4821)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.0176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2139
upper limit	0.2491

Secondary: Changes from baseline measured at Day 1 to End of Treatment Week 52 of Attentional Performance (TAP): Alertness with alarm median

End point title	Changes from baseline measured at Day 1 to End of Treatment Week 52 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:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	56.6 (± 59.5)	56.6 (± 59.5)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-72.6
upper limit	-33.4

Secondary: Changes from baseline at measured at Day 1 to End of Treatment in Beck Depression Inventory (BDI): Total score

End point title	Changes from baseline at measured at Day 1 to End of Treatment 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. For BDI-A, BDI-C and BDI-S these cut-off values are >0.9, >1.4, and >4 respectively.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-4.5 (± 6.8)	-4.5 (± 6.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	-0.8

Secondary: Changes from baseline at measured at Day 1 to End of Treatment in Beck Depression Inventory (BDI): Affective scale

End point title	Changes from baseline at measured at Day 1 to End of Treatment in Beck Depression Inventory (BDI): Affective scale
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. For BDI-A, BDI-C and BDI-S these cut-off values are >0.9, >1.4, and >4 respectively.	
End point type	Secondary
End point timeframe:	
Baeline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.5 (± 1.8)	-0.5 (± 1.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	0.5

Secondary: Changes from baseline (measured at pre-dose Day 1) to End of Treatment in (Week 52) in the Beck Depression Inventory (BDI): Somatic scale

End point title	Changes from baseline (measured at pre-dose Day 1) to End of Treatment in (Week 52) in the Beck Depression Inventory (BDI): Somatic scale
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. For BDI-A, BDI-C and BDI-S these cut-off values are >0.9, >1.4, and >4 respectively.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-3.2 (± 4.0)	-3.2 (± 4.0)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %

Secondary: Changes from baseline measured at Day 1 to End of Treatment in Hospital Anxiety and Depression Scale (HADS): Total score

End point title	Changes from baseline measured at Day 1 to End of Treatment 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:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-1.6 (± 7.1)	-1.6 (± 7.1)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	1.9

Secondary: Changes from baseline measured at Day 1 to End of Treatment in Hospital Anxiety and Depression Scale (HADS): Anxiety score

End point title	Changes from baseline measured at Day 1 to End of Treatment in Hospital Anxiety and Depression Scale (HADS): Anxiety 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:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.9 (± 4.1)	-0.9 (± 4.1)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	1

Secondary: Change from baseline measured at Day 1 to End of Treatment in Hospital Anxiety and Depression Scale (HADS): Depression score

End point title	Change from baseline measured at Day 1 to End of Treatment in Hospital Anxiety and Depression Scale (HADS): Depression 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:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.7 (± 3.8)	-0.7 (± 3.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.3

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section 1

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section 1
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End point description:

Section I, Current function, consists of vision; hearing; speech; swallowing; handwriting; cutting food and handling utensils; dressing; hygiene; exercise; and gait stability. Each item is scored according to the subject (or caregiver) and is not based upon the physician's judgment.

Each question/item in the NMDAS has a possible score from 0 to 5. Each of the first 3 section scores are calculated by simply summing the scores obtained for each question in that section, with a higher score indicating more severe disease. Thus, scores can range from 0 to 50 for Sections I and III, from 0 to 45 for Section II, and from 0 to 145 for Sections I through III.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) To End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-1.4 (± 2.3)	-1.4 (± 2.3)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	0

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section II

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section II
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End point description:

Section II, System-specific involvement, is based on both 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. Each question/item in the NMDAS has a possible score from 0 to 5. Each of the first 3 section scores are calculated by simply summing the scores obtained for each question in that section, with a higher score indicating more severe disease. Thus, scores can range from 0 to 50 for Sections I and III, from 0 to 45 for Section II, and from 0 to 145 for Sections I through III.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.8 (± 1.3)	-0.8 (± 1.3)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	-0.1

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section III

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section III
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End point description:

Section III, Current clinical assessment, is entirely based on the clinician's assessment. It includes visual acuity; ptosis; CPEO; dysphonia/dysarthria; myopathy; cerebellar ataxia; neuropathy; pyramidal; extrapyramidal; cognition (measured by an adult reading test, Symbol Search (SS), and Speed of Comprehension Test [SOCT]).

Each question/item in the NMDAS has a possible score from 0 to 5. Each of the first 3 section scores are calculated by simply summing the scores obtained for each question in that section, with a higher score indicating more severe disease. Thus, scores can range from 0 to 50 for Sections I and III, from 0 to 45 for Section II, and from 0 to 145 for Sections I through III.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard error)	0.6 ($\pm$ 1.4)	0.6 ($\pm$ 1.4)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$\leq$ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Physical functioning

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Physical functioning
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	5.7 ($\pm$ 7.9)	5.7 ($\pm$ 7.9)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$\leq$ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.8
upper limit	9.5

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Role limitations due to physical problems

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Role limitations due to physical problems
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	9.2 ($\pm$ 8.0)	9.2 ($\pm$ 8.0)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.6
upper limit	13

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Bodily pain

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Bodily pain
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	6.6 ($\pm$ 5.8)	6.6 ($\pm$ 5.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	10.5

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: General health perceptions

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: General health perceptions
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	3.8 ($\pm$ 6.2)	3.8 ($\pm$ 6.2)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	6.7

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Vitality

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Vitality
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	7.2 ($\pm$ 11.7)	7.2 ($\pm$ 11.7)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	11.7

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Social functioning

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Social functioning
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-7.3 (± 7.8)	-7.3 (± 7.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-7.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12
upper limit	-2.7

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: role limitations due to emotional problems

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: role limitations due to emotional problems
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End point description:

Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	2.4 (± 9.4)	2.4 (± 9.4)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	6.9

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Mental health

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Mental health
End point description:	
Section IV, Quality of Life, is assessed by the subject (or caregiver) using the SF-12. The SF-12 is a standard, extensively validated questionnaire which comes complete with its own administration and scoring manual. There should be no input from the clinician or health professional as this survey assesses the subject's own opinion of their health status. The SF-12 is the abridged practical version of the SF-36. The instrument contains 8 subscales: physical functioning (2 items), role limitations due to physical problems (2 items), bodily pain (1 item), general health perceptions (1 item), vitality (1 item), social functioning (1 item), role limitations due to emotional problems (2 items) and mental health (2 items). Scores are such that a higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	3.6 ($\pm$ 10.0)	3.6 ($\pm$ 10.0)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	8.8

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV (SF-12): Physical Component Score (PCS)

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV (SF-12): Physical Component Score (PCS)
End point description:	
Section IV, Quality of Life, is assessed using the SF-12. The instrument contains 8 subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems) and mental health. The scoring yields 2 summary measures: Physical Component Summary (PCS) and the Mental Component Summary (MCS); 2 factors have been interpreted as physical and mental components of health status. Three scales (physical functioning, role limitations due to physical restrictions, and bodily pain) correlate with the physical component and contribute most to the scoring of the PCS measure. The mental component correlates with the mental health, role limitations due to emotional issues, and social functioning scales, which contribute most to the scoring of the MCS measure. A higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.	
End point type	Secondary

End point timeframe:

Baseline to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	7.7 ($\pm$ 5.4)	7.7 ($\pm$ 5.4)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.4
upper limit	10.2

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV (SF-12) Mental Component Score (MCS)

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV (SF-12) Mental Component Score (MCS)
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End point description:

Section IV, Quality of Life, is assessed using the SF-12. The instrument contains 8 subscales: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems) and mental health. The scoring yields 2 summary measures: Physical Component Summary (PCS) and the Mental Component Summary (MCS); 2 factors have been interpreted as physical and mental components of health status. Three scales (physical functioning, role limitations due to physical restrictions, and bodily pain) correlate with the physical component and contribute most to the scoring of the PCS measure. The mental component correlates with the mental health, role limitations due to emotional issues, and social functioning scales, which contribute most to the scoring of the MCS measure. A higher score indicates a better health state. Raw scores for each subscale are transformed to 0 to 100 scale scores.

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.6 (± 8.0)	-0.6 (± 8.0)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	3.5

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Short Form 6 Dimension [SF-6D]

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Newcastle Mitochondrial Disease Adult Scale (NMDAS): Section IV: Short Form 6 Dimension [SF-6D]
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End point description:

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.0 (± 0.1)	0.0 (± 0.1)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1

Secondary: Changes from baseline measured at Day 1 to End of Treatment (Week 52) in the Smell Identification Test (UPSIT)

End point title	Changes from baseline measured at Day 1 to End of Treatment (Week 52) 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:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.7 (± 2.6)	0.7 (± 2.6)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	3.7

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Cognitive Failure Questionnaire (CFQ): Total score

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) in the Cognitive Failure Questionnaire (CFQ): Total score
End point description:	
The CFQ 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 must be scored on a 5-point scale. CFQ scores can range from 0 to 100. The higher the score, the more cognitive failure is indicated.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-4.6 (± 7.4)	-4.6 (± 7.4)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	0.7

Secondary: Change from baseline measured at Day 1 to End of Treatment (Week 52) Neuro-Quality-of-Life Fatigue Short Form (NQF-SF) Total score

End point title	Change from baseline measured at Day 1 to End of Treatment (Week 52) Neuro-Quality-of-Life Fatigue Short Form (NQF-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.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-6.29 (± 5.53)	-6.29 (± 5.53)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.21
upper limit	-2.8

Secondary: Changes from baseline measured at pre-dose (Day 1) to End of Treatment (week 52) in the Five times Sit-to-Stand Test (5XSTS)

End point title	Changes from baseline measured at pre-dose (Day 1) to End of Treatment (week 52) in the Five times Sit-to-Stand Test (5XSTS)
End point description:	
The Five-time Sit-to-Stand (5xSTS) Test is a performance-based measure to assess the body functions needed to accomplish sit-to-stand transitions (e.g., lower limb strength, balance, and trunk control). The 5xSTS measures the amount of time it takes for a patient to sit and stand five times in succession with arms folded across their chest.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-1.21 (± 2.13)	-1.21 (± 2.13)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.12

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): Total score

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): Total score
End point description:	
The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a comprehensive, unidimensional, brief 14-item balance scale to measure important aspects of dynamic balance control in adults. The Mini-BESTest contains items covering a broad spectrum of performance tasks, including transitions and anticipatory postural adjustments (anticipatory); postural responses to perturbation (reactive postural); sensory orientation while standing on a compliant or inclined base of support (sensory orientation); and dynamic stability in gait (dynamic gait). Each item is rated on a 3-point ordinal scale (0=severe to 2=normal) with 2 representing no impairment in balance and 0 representing severe impairment of balance.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Z-score				
arithmetic mean (standard deviation)	0.0873 ($\pm$ 0.0509)			

Statistical analyses

No statistical analyses for this end point

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Handgrip Strength HS): Left

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Handgrip Strength HS): Left
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End point description:

Handgrip strength (HS) is an important clinical outcome measure in assessing upper extremity deficit. Grip strength was measured using a hand-held dynamometer. HS is assessed to quantify impairment level and to evaluate treatment response.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	2.65 ($\pm$ 3.45)	2.65 ($\pm$ 3.45)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	$\leq$ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	2.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	5.44

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Handgrip Strength Test (HS): Right

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Handgrip Strength Test (HS): Right
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End point description:

Handgrip strength (HS) is an important clinical outcome measure in assessing upper extremity deficit. Grip strength was measured using a hand-held dynamometer. HS is assessed to quantify impairment level and to evaluate treatment response.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.14 (± 3.94)	-0.14 (± 3.94)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.79
upper limit	3.07

Secondary: Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Total score

End point title	Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Total score
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End point description:

The Short-Form McGill Pain Questionnaire (SF-MPQ) is an easy to administer self-rating scale which has been developed to assess the severity, affective, and evaluative dimensions of pain measuring the different qualities of the subjective pain experience. The main component of the SF-MPQ enables calculation of the pain rating index consisting of 15 pain descriptors. The Pain Rating Index has 2 subscales: the sensory subscale consisting of 11 adjectives describing the sensory qualities of the patient's pain, and the affective subscale with 4 adjectives describing the affective qualities of the patient's pain. Both subscales are rated on an intensity scale as 0=none, 1=mild, 2=moderate, or 3=severe. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS) to record the patient's PPI, anchored with no pain (0 mm) (0 mm) and worst possible pain (1

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	-5.7 (± 5.6)	-5.7 (± 5.6)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	0.4

Secondary: Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Sensory Dimension score

End point title	Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Sensory Dimension score
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End point description:

The Short-Form McGill Pain Questionnaire (SF-MPQ) is an easy to administer self-rating scale which has been developed to assess the severity, affective, and evaluative dimensions of pain measuring the different qualities of the subjective pain experience. The main component of the SF-MPQ enables calculation of the pain rating index consisting of 15 pain descriptors. The Pain Rating Index has 2 subscales: the sensory subscale consisting of 11 adjectives describing the sensory qualities of the patient's pain, and the affective subscale with 4 adjectives describing the affective qualities of the patient's pain. Both subscales are rated on an intensity scale as 0=none, 1=mild, 2=moderate, or 3=severe. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS) to record the patient's PPI, anchored with no pain (0 mm) (0 mm) and worst possible pain (1)

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	8	8		
Units: Z-score				
arithmetic mean (standard deviation)	-5.1 (± 4.8)	-5.1 (± 4.8)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	-0.2

Secondary: Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Affective Dimension score

End point title	Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Affective Dimension score
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End point description:

The Short-Form McGill Pain Questionnaire (SF-MPQ) is an easy to administer self-rating scale which has been developed to assess the severity, affective, and evaluative dimensions of pain measuring the different qualities of the subjective pain experience. The main component of the SF-MPQ enables calculation of the pain rating index consisting of 15 pain descriptors. The Pain Rating Index has 2 subscales: the sensory subscale consisting of 11 adjectives describing the sensory qualities of the patient's pain, and the affective subscale with 4 adjectives describing the affective qualities of the patient's pain. Both subscales are rated on an intensity scale as 0=none, 1=mild, 2=moderate, or 3=severe. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS) to record the patient's PPI, anchored with no pain (0 mm) (0 mm) and worst possible pain (1

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.6 (± 2.6)	-0.6 (± 2.6)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	1.1

Secondary: Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Present Pain Inventory (PPI)

End point title	Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Present Pain Inventory (PPI)
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End point description:

The Short-Form McGill Pain Questionnaire (SF-MPQ) is an easy to administer self-rating scale which has been developed to assess the severity, affective, and evaluative dimensions of pain measuring the different qualities of the subjective pain experience. The main component of the SF-MPQ enables calculation of the pain rating index consisting of 15 pain descriptors. The Pain Rating Index has 2 subscales: the sensory subscale consisting of 11 adjectives describing the sensory qualities of the patient's pain, and the affective subscale with 4 adjectives describing the affective qualities of the patient's pain. Both subscales are rated on an intensity scale as 0=none, 1=mild, 2=moderate, or 3=severe. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS) to record the patient's PPI, anchored with no pain (0 mm) (0 mm) and worst possible pain (1)

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-0.9 (± 1.4)	-0.9 (± 1.4)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.2

Secondary: Change from baseline at measured at Day 1 to End of Treatment in the

Short-Form McGill Pain Questionnaire (SF-MPQ): Visual Analogue Scale (VAS)

End point title	Change from baseline at measured at Day 1 to End of Treatment in the Short-Form McGill Pain Questionnaire (SF-MPQ): Visual Analogue Scale (VAS)
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End point description:

The Short-Form McGill Pain Questionnaire (SF-MPQ) is an easy to administer self-rating scale which has been developed to assess the severity, affective, and evaluative dimensions of pain measuring the different qualities of the subjective pain experience. The main component of the SF-MPQ enables calculation of the pain rating index consisting of 15 pain descriptors. The Pain Rating Index has 2 subscales: the sensory subscale consisting of 11 adjectives describing the sensory qualities of the patient's pain, and the affective subscale with 4 adjectives describing the affective qualities of the patient's pain. Both subscales are rated on an intensity scale as 0=none, 1=mild, 2=moderate, or 3=severe. The SF-MPQ also includes the Present Pain Intensity (PPI) index and a visual analog scale (VAS) to record the patient's PPI, anchored with no pain (0 mm) (0 mm) and worst possible pain (1)

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-21.5 (± 13.3)	-21.5 (± 13.3)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.1
upper limit	-9.9

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week

52) in the RAND SF-36: Energy/fatigue

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Energy/fatigue
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	18.6 (± 23.5)	18.6 (± 23.5)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	28.5

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week

52) in the RAND SF-36: Emotional well-being

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Emotional well-being
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	5.8 (± 12.6)	5.8 (± 12.6)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	13.8

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: General health

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: General health
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	7.0 ($\pm$ 8.6)	7.0 ($\pm$ 8.6)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	6.9
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8
upper limit	13

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Health change

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Health change
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	27.3 (± 30.5)	27.3 (± 30.5)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	25
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	41.1

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Pain

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Pain
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-

Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	18.9 ($\pm$ 20.0)	18.9 ($\pm$ 20.0)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.4
upper limit	28.6

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Physical functioning

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Physical functioning
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role

limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	11.8 (± 15.2)	11.8 (± 15.2)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	11.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.6
upper limit	19

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Role functioning/emotional

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Role functioning/emotional
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role

limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	-6.1 ($\pm$ 32.7)	-6.1 ($\pm$ 32.7)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.2
upper limit	12

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Role functioning/physical

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Role functioning/physical
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role

limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	38.6 (± 42.2)	38.6 (± 42.2)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	36.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	13.7
upper limit	59.2

Secondary: Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Social functioning

End point title	Change from baseline at measured at Day 1 to End of Treatment (Week 52) in the RAND SF-36: Social functioning
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End point description:

The RAND SF-36 is a 36-item generic, extensively validated, multidimensional self-reported Health-Related Quality of Life (HRQoL) questionnaire. The SF-36 yields an 8-scale profile of functional health and well-being, physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning,

energy/fatigue, and general health perceptions. It also includes a single item that provides an indication of perceived change in health. This item asks about the general health compared to one year past, and is not included in any of the 8 dimensions. Likert scales and yes/no options are used to assess function and well-being on this 36-item questionnaire. To score the SF-36, scales are standardized with a scoring algorithm to obtain a score ranging from 0 to 100. Higher scores on all subscales represent better health and functioning. The SF-36 also includes a single item that assesses perc

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: Z-score				
arithmetic mean (standard deviation)	21.1 ($\pm$ 21.3)	21.1 ($\pm$ 21.3)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	10.1
upper limit	31.7

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Attention Domain Composites of cognitive functioning: DET, IDN, and ONB (speed):

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Attention Domain Composites of cognitive functioning: DET, IDN, and ONB (speed):
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End point description:

Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met. Only computed if z-scores are available for all three tests.

DET, IDN, and ONB (speed): only computed if z-scores are available for all three tests

End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-scores				
arithmetic mean (standard deviation)	0.1484 ($\pm$ 0.6261)	0.1484 ($\pm$ 0.6261)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	0.1104
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2305
upper limit	0.4514

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Learning/Working Memory Composite of cognitive functioning: OCL and ONB (accuracy)

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Learning/Working Memory Composite of cognitive functioning: OCL and ONB (accuracy)
End point description:	
Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met. Only computed if z-scores are available for both tests: OCL and ONB (accuracy)	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-scores				
arithmetic mean (standard deviation)	0.2241 ($\pm$ 0.8794)	0.2241 ($\pm$ 0.8794)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.2522
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2989
upper limit	0.8032

Secondary: Changes from baseline at measured at Day 1 to End of Treatment in Beck Depression Inventory (BDI): Cognitive scale

End point title	Changes from baseline at measured at Day 1 to End of Treatment in Beck Depression Inventory (BDI): Cognitive scale
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. For BDI-A, BDI-C and BDI-S these cut-off values are >0.9 , >1.4 , and >4 respectively.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-scores				
arithmetic mean (standard deviation)	-0.7 (± 1.3)	-0.7 (± 1.3)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	0.4

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Global Composite of cognitive functioning: DET, IDN, OCL, ONB (speed), ISL, GML

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Global Composite of cognitive functioning: DET, IDN, OCL, ONB (speed), ISL, GML
End point description:	
Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Global Composite of cognitive functioning: DET, IDN, OCL, ONB (speed), ISL, GML:	
Composite scores will be calculated by taking the equally weighted average of the available z-scores if the required number of z-scores available is met. Only computed if z-scores are available for both tests. Only computed if z-scores are available for a minimum of three tests with representation from all three domain composites listed above.	
End point type	Secondary
End point timeframe:	
Baseline 9Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	11	11		
Units: Z-score				
arithmetic mean (standard deviation)	0.0035 ($\pm$ 0.4821)	0.0035 ($\pm$ 0.4821)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.0176
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2139
upper limit	0.2491

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): anticipatory

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): anticipatory
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End point description:

The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a comprehensive, unidimensional, brief 14-item balance scale to measure important aspects of dynamic balance control in adults. The Mini-BESTest contains items covering a broad spectrum of performance tasks, including transitions and anticipatory postural adjustments (anticipatory); postural responses to perturbation (reactive postural); sensory orientation while standing on a compliant or inclined base of support (sensory orientation); and dynamic stability in gait (dynamic gait). Each item is rated on a 3-point ordinal scale (0=severe to 2=normal) with 2 representing no impairment in balance and 0 representing severe impairment of balance.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: Z-score				
arithmetic mean (standard deviation)	0.1111 ($\pm$ 0.1863)	0.1111 ($\pm$ 0.1863)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.0975
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.011
upper limit	0.2059

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): dynamic gait

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): dynamic gait
End point description:	
The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a comprehensive, unidimensional, brief 14-item balance scale to measure important aspects of dynamic balance control in adults. The Mini-BESTest contains items covering a broad spectrum of performance tasks, including transitions and anticipatory postural adjustments (anticipatory); postural responses to perturbation (reactive postural); sensory orientation while standing on a compliant or inclined base of support (sensory orientation); and dynamic stability in gait (dynamic gait). Each item is rated on a 3-point ordinal scale (0=severe to 2=normal) with 2 representing no impairment in balance and 0 representing severe impairment of balance.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: Z-score				
arithmetic mean (standard deviation)	0.09 (± 0.13)	0.09 (± 0.13)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.16

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): reactive postural

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): reactive postural
End point description:	
The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a comprehensive, unidimensional, brief 14-item balance scale to measure important aspects of dynamic balance control in adults. The Mini-BESTest contains items covering a broad spectrum of performance tasks, including transitions and anticipatory postural adjustments (anticipatory); postural responses to perturbation (reactive postural); sensory orientation while standing on a compliant or inclined base of support (sensory orientation); and dynamic stability in gait (dynamic gait). Each item is rated on a 3-point ordinal scale (0=severe to 2=normal) with 2 representing no impairment in balance and 0 representing severe impairment of balance.	
End point type	Secondary
End point timeframe:	
Baseline (Day 1) to End of Treatment (Week 52)	

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: Z-score				
arithmetic mean (standard deviation)	0.1296 ($\pm$ 0.2324)	0.1296 ($\pm$ 0.2324)		

Statistical analyses

Statistical analysis title	Mixed models Treatment diff between B-A
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Statistical analysis description:

Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.

Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.001
upper limit	0.249

Secondary: Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): sensory orientation

End point title	Changes from baseline (measured at Day 1) at End of Treatment (Week 52) in the Mini-Balance Evaluation Systems Test (MiniBESTest): sensory orientation
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End point description:

The Mini-Balance Evaluation Systems Test (Mini-BESTest) is a comprehensive, unidimensional, brief 14-item balance scale to measure important aspects of dynamic balance control in adults. The Mini-BESTest contains items covering a broad spectrum of performance tasks, including transitions and anticipatory postural adjustments (anticipatory); postural responses to perturbation (reactive postural); sensory orientation while standing on a compliant or inclined base of support (sensory orientation); and dynamic stability in gait (dynamic gait). Each item is rated on a 3-point ordinal scale (0=severe to 2=normal) with 2 representing no impairment in balance and 0 representing severe impairment of balance.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to End of Treatment (Week 52)

End point values	100 mg BID sonlicromanol	FAS		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	9	9		
Units: Z-score				
arithmetic mean (standard deviation)	0.0185 (± 0.1547)	0.0185 (± 0.1547)		

Statistical analyses

Statistical analysis title	Repeated measures analysis of covariance (ANCOVA)
Statistical analysis description:	
Statistical analysis are performed on the change from baseline values at Week 52 using repeated measures analysis of covariance (ANCOVA) model including visit as a fixed effect and baseline value as a covariate.	
Comparison groups	100 mg BID sonlicromanol v FAS
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.0223
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0584
upper limit	0.103

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment Emergent Adverse Events are being reported from Day 1 of study treatment up to and including Follow up; AEs are considered treatment emergent when the date of onset is during the use of the study drug up to 14 days after the last study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	100 mg sonlicromanol (KH176) bid
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Reporting group description: -

Serious adverse events	100 mg sonlicromanol (KH176) bid		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Bladder calculus removal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Internal limiting membrane peeling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical procedure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transurethral prostatectomy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	100 mg sonlicromanol (KH176) bid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 15 (86.67%)		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Surgical and medical procedures			
Bladder calculus removal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cochlea implant			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Internal limiting membrane peeling			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Medical procedure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Transurethral prostatectomy subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
General disorders and administration site conditions			
Facial pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pyrexia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Swelling subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vaccination site discomfort subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Reproductive system and breast disorders			
Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Menstruation irregular subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Rhinorrhoea			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood glucose fluctuation subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Electrocardiogram T wave inversion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Epicondylitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye injury subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Fall subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Foot fracture subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Ligament sprain			

subjects affected / exposed occurrences (all) Palate injury subjects affected / exposed occurrences (all) Skin injury subjects affected / exposed occurrences (all) Wound subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Congenital, familial and genetic disorders Talipes subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Nervous system disorders Dizziness postural subjects affected / exposed occurrences (all) Dysaesthesia subjects affected / exposed occurrences (all) Migraine subjects affected / exposed occurrences (all) Multiple sclerosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 2 / 15 (13.33%) 2 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Ear and labyrinth disorders Ear discomfort subjects affected / exposed occurrences (all) Ear pain subjects affected / exposed occurrences (all) Eustachian tube disorder	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vertigo positional			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			
Retinal degeneration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Retinal detachment			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Abdominal discomfort			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tooth ache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pigmentation disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Urge incontinence			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Endocrine disorders Adrenocortical insufficiency acute subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint range of motion decreased subjects affected / exposed occurrences (all) Muscle fatigue subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 4 3 / 15 (20.00%) 3 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Upper respiratory tract infection	8 / 15 (53.33%) 8 4 / 15 (26.67%) 4		

subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Post viral fatigue syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
folate			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2021	Protocol version 2.0 Ger/UK, issued on 27 May 2021: • Section 1.5.2 'Study design' (and synopsis): added text replacing previous text "Primary safety data and secondary efficacy (endpoint) data will be monitored and reviewed every three months by an independent Data Safety Monitoring Board (DSMB) to evaluate potential risks and benefits. The DSMB will provide recommendations to the Sponsor regarding the study conduct." • Inclusion criterion #3 has been adapted by adding the following excerpt: '...with evidence of potential benefit in at least one treatment period in the KH176-202 study.' • Section 1.5.2. 'Study design': text on data review has been replaced by "Primary safety data and secondary efficacy (endpoint) data will be monitored and reviewed every three months by an independent Data Safety Monitoring Board (DSMB) to evaluate potential risks and benefits. Based on the observed benefit/risk the DSMB will provide recommendations regarding future trial conduct to the Sponsor." • Section 1.5.5. 'Benefit/risk': added text "Safety and efficacy data (and consequently Benefit/Risk) will be monitored and reviewed every three months by an independent Data Safety Monitoring Board (DSMB). The DSMB will review and assess the safety and efficacy data as described in section 6.5. and will provide recommendations regarding the study based on the observed benefit-to-risk balance. In view of the safety precautions taken and the periodic review of the accruing benefit/risk information throughout the study by the DSMB, the potential benefits of participating in this trial are considered to outweigh the risks, and therefore the benefit-risk of the trial is considered to be positive." • Section 3.1. 'Overview': revised/added text "Primary safety data and secondary efficacy (endpoint) data will be monitored and reviewed every three months by an independent Data Safety Monitoring Board (DSMB) to evaluate potential risks and benefits (see section 6.5)."
26 November 2021	Protocol version 2.0 NL, issued on 26 November 2021: • Section 1.5.2 'Study design' (and synopsis): updated to include "Primary safety data and secondary efficacy (endpoint) data will be monitored and reviewed periodically, and/or on request of the Sponsor or regulatory authorities by an independent Data Safety Monitoring Board (DSMB) to evaluate potential risks and benefits. DSMB meetings in which the accumulating safety and efficacy data will be reviewed are organized at three monthly intervals, the timing of the first DSMB meeting depending on recruitment rate and accruing data, eg, when data collected in the first treatment period (week 13) are available for a subset of subjects. When the DSMB requests to receive urgent safety information, AE listings and of Medical Monitoring Reports (MMR) will be submitted. The DSMB will provide recommendations to the Sponsor regarding the study conduct. If during the study any severe Serious Adverse Events (SAEs) and Serious Unexpected Suspected Adverse Reaction (SUSARs) are reported, the DSMB will be informed immediately."

26 November 2021	Protocol version 3.0 Ger/UK/DK, issued on 26 November 2021: Section 1.5.2 'Study design' (and synopsis): updated to include "Primary safety data and secondary efficacy (endpoint) data will be monitored and reviewed periodically, and/or on request of the Sponsor or regulatory authorities by an independent Data Safety Monitoring Board (DSMB) to evaluate potential risks and benefits. DSMB meetings in which the accumulating safety and efficacy data will be reviewed are organized at three monthly intervals, the timing of the first DSMB meeting depending on recruitment rate and accruing data, eg, when data collected in the first treatment period (week 13) are available for a subset of subjects. When the DSMB requests to receive urgent safety information, AE listings and of Medical Monitoring Reports (MMR) will be submitted. The DSMB will provide recommendations to the Sponsor regarding the study conduct. If during the study any severe Serious Adverse Events (SAEs) and Serious Unexpected Suspected Adverse Reaction (SUSARs) are reported, the DSMB will be informed immediately."
06 September 2022	Protocol version 4.0 Ger/UK/DK, issued on 06 September 2022: - General change throughout the document: Extension of treatment period of 12 months to 18 months. - Sponsor will not initiate a (generic) compassionate use program; however, each study participant who has experienced benefit from the study medication application will be offered access to the study medication via an individual 'Named Patient Supply' application by the principal investigator.
21 September 2022	Protocol version 3.0 NL, issued on 21 September 2022: - General change throughout the document: Extension of treatment period of 12 months to 18 months. For this purpose, 2 additional study visits have been added and an additional objective has been added: "To assess the longer-term safety and efficacy of sonlicromanol during an additional 6-months treatment period for a total study treatment duration of 18-months by measuring the same safety and efficacy parameters as the primary and secondary objectives in the 12-months study". - Each study participant who has experienced benefit from the study medication application will be offered access to the study medication via an individual 'Named Patient Supply' application by the principal investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported