



Clinical trial results:

An Open-label, non-Comparative Study to Evaluate the Steady-State Pharmacokinetics, Safety, and Efficacy of Mexiletine in Adolescents and Children with Myotonic Disorders

Summary

EudraCT number	2019-003757-28
Trial protocol	FR
Global end of trial date	13 June 2024

Results information

Result version number	v1 (current)
This version publication date	25 December 2024
First version publication date	25 December 2024

Trial information

Trial identification

Sponsor protocol code	MEX-NM-301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04624750
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lupin Europe GmbH
Sponsor organisation address	Hanauer Landstraße 139-143, Frankfurt, Germany, 60314
Public contact	Senior Regulatory Affairs Manager, Lupin Healthcare (UK) Ltd. , +44 1565751378, EU-RA@lupin.com
Scientific contact	Senior Regulatory Affairs Manager, Lupin Healthcare (UK) Ltd. , +44 1565751378, EU-RA@lupin.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-002012-PIP01-16
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	10 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2024
Global end of trial reached?	Yes
Global end of trial date	13 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary

- To evaluate the safety of mexiletine in adolescents (aged 12 to <18 years) and children (aged 6 to <12 years) for the treatment of myotonia
- To evaluate the efficacy of mexiletine for the treatment of myotonia

Secondary

- To evaluate the efficacy of mexiletine for the treatment of myotonia as assessed by patient-reported outcomes
- To evaluate efficacy and tolerability of mexiletine as measured by Clinical Global Impression (CGI) scale indices
- To determine changes in health-related quality-of-life as measured by the PedsQL Quality of Life and Neuromuscular module.
- To determine the steady-state pharmacokinetics (PK) of mexiletine in children (6 to <12 years) and adolescents (aged 12 to <18 years)
- To assess the acceptability of the capsule formulation.
- Palatability of alternative administration (capsule content with milk/juice or sprinkled on food) by 5-point facial hedonic

Protection of trial subjects:

The nature and purpose of the study was fully explained to each patient (or their legally responsible guardian). Before each patient was enrolled into the study, informed consent was obtained from the patient (or his/ her legally authorized representative) according to the most current applicable regulatory and legal requirements. The consent was obtained on the IEC approved and most recent version of consent form in language best comprehended by the patient.

This study was conducted in compliance with the protocol and with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), the World Medical Association Declaration of Helsinki (2013) and in compliance to the specific local regulatory requirements wherever applicable and required. The study was conducted according to Good Clinical Practice (GCP) principles as required by Directive 2001/20/EC, as amended.

Subject Confidentiality requirements as stated in the Data Protection legislation

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	22 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 12
Worldwide total number of subjects	12
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)	5
Adolescents (12-17 years)	7
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 2 sites in France.

Pre-assignment

Screening details:

The study comprised a screening period of 30 days. A total of 12 subjects were enrolled in the study treatment.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Patients aged 12 to < 18 years.

Arm type	Experimental
Investigational medicinal product name	Namuscla (mexiletine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Namuscla (mexiletine) was started as a once-a-day (QD) treatment regimen (weeks 1 to 2), and the dose was escalated every 2 weeks as per investigator judgement (twice daily; BID at Day 14, and thrice daily; TID at Day 28) as per body weight of the patient.

Dose selection was based on body weight.

Arm title	Cohort 2
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Arm description:

Patients aged 6 to < 12 years.

Arm type	Experimental
Investigational medicinal product name	Namuscla (mexiletine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Namuscla (mexiletine) was started as a once-a-day (QD) treatment regimen (weeks 1 to 2), and the dose was escalated every 2 weeks as per investigator judgement (twice daily; BID at Day 14, and thrice daily; TID at Day 28) as per body weight of the patient.

Dose selection was based on body weight.

Number of subjects in period 1	Cohort 1	Cohort 2
Started	7	5
Completed	7	5

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Patients aged 12 to < 18 years.

Arm type	Experimental
Investigational medicinal product name	Namuscla (mexiletine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Namuscla (mexiletine) was started as a once-a-day (QD) treatment regimen (weeks 1 to 2), and the dose was escalated every 2 weeks as per investigator judgement (twice daily; BID at Day 14, and thrice daily; TID at Day 28) as per body weight of the patient.

Dose selection was based on body weight.

Arm title	Cohort 2
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Arm description:

Patients aged 6 to < 12 years.

Arm type	Experimental
Investigational medicinal product name	Namuscla (mexiletine)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Namuscla (mexiletine) was started as a once-a-day (QD) treatment regimen (weeks 1 to 2), and the dose was escalated every 2 weeks as per investigator judgement (twice daily; BID at Day 14, and thrice daily; TID at Day 28) as per body weight of the patient.

Dose selection was based on body weight.

Number of subjects in period 2	Cohort 1	Cohort 2
Started	7	5
Completed	7	5

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Patients aged 12 to < 18 years.

Reporting group title	Cohort 2
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Reporting group description:

Patients aged 6 to < 12 years.

Reporting group values	Cohort 1	Cohort 2	Total
Number of subjects	7	5	12
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	5	5
Adolescents (12-17 years)	7	0	7
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	13.4	8.2	
full range (min-max)	12 to 16	6 to 10	-
Gender categorical			
Units: Subjects			
Female	4	3	7
Male	3	2	5

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Patients aged 12 to < 18 years.	
Reporting group title	Cohort 2
Reporting group description: Patients aged 6 to < 12 years.	
Reporting group title	Cohort 1
Reporting group description: Patients aged 12 to < 18 years.	
Reporting group title	Cohort 2
Reporting group description: Patients aged 6 to < 12 years.	

Primary: Frequency of adverse events

End point title	Frequency of adverse events ^[1]
End point description:	

End point type	Primary
End point timeframe: Throughout the study while on treatment with Namuscla	

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 statistical analyses for this end point

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: %	86	20		

Statistical analyses

No statistical analyses for this end point

Primary: Number and frequency of serious adverse events

End point title	Number and frequency of serious adverse events ^[2]
End point description:	

A SAE is defined as, any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (defined as a participant at immediate risk of death at the time of the event). It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity.
- Is a congenital anomaly/ birth defect.
- Consists of any other medically important condition.

End point type	Primary
End point timeframe:	
Throughout the study while on treatment with Namuscla	
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 statistical analyses for this end point	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: number of subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of adverse events of special interest (AESI)

End point title	Incidence of adverse events of special interest (AESI) ^[3]
End point description:	

End point type	Primary
End point timeframe:	
Throughout the study while on treatment with Namuscla	
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 statistical analyses for this end point	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: number of subjects	7	5		

Statistical analyses

No statistical analyses for this end point

Primary: Mean change in Visual Analogue Scale (VAS) score for muscle stiffness from baseline to days 56

End point title	Mean change in Visual Analogue Scale (VAS) score for muscle stiffness from baseline to days 56 ^[4]
End point description:	

This endpoint is a secondary measure in the study and a primary measure of efficacy, specifically addressing myotonia severity, and complementing the main focus of the study which was on safety. Efficacy of Namuscla treatment on the clinical outcomes.
Change from baseline - Intent to Treat population (ITT)

End point type	Primary
End point timeframe:	
From baseline to Days 14, 28, 42 and 56	
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 statistical analyses for this end point	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-53.7 (± 19.62)	-21.7 (± 27.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean change in Faces (FAS) score for muscle stiffness from baseline to days 56

End point title	Mean change in Faces (FAS) score for muscle stiffness from baseline to days 56 ^[5]
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End point description:

This endpoint is a secondary measure in the study and a primary measure of efficacy, specifically addressing myotonia severity, and complementing the main focus of the study which was on safety. Efficacy of Namuscla treatment on the clinical outcomes.
Change from baseline - Intent to Treat population (ITT)

End point type	Primary
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End point timeframe:

From baseline to Days 14, 28, 42 and 56

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 statistical analyses for this end point

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[6]			
Units: unit(s)				
arithmetic mean (standard deviation)	-3 (± 1.41)			

Notes:

[6] - FAS scale only utilized in children aged 6 to 8 yo.

Statistical analyses

No statistical analyses for this end point

Primary: Change in the score of handgrip myotonia from baseline to Days 56

End point title	Change in the score of handgrip myotonia from baseline to Days 56 ^[7]
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End point description:

This endpoint is a secondary measure in the study and a primary measure of efficacy, specifically addressing myotonia severity, and complementing the main focus of the study which was on safety. The score of hand grip is quantitatively measured using a commercially available grip dynamometer and computerised capture system in standardised conditions.

Change from baseline - Intent to Treat population (ITT)

End point type	Primary
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End point timeframe:

From baseline to Days 14, 28, 42 and 56

Notes:

[7] - 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 statistical analyses for this end point

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.06 (± 0.10)	-0.11 (± 0.21)		

Statistical analyses

No statistical analyses for this end point

Primary: Changes in ECG assessments from baseline to day 56

End point title	Changes in ECG assessments from baseline to day 56 ^[8]
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End point description:

Safety population - results in milliseconds

End point type	Primary
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End point timeframe:

From baseline to day 56

Notes:

[8] - 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 statistical analyses for this end point

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: second				
arithmetic mean (standard deviation)				
HR	11.0 (± 10.75)	8.0 (± 18.11)		
PR	3.7 (± 6.29)	-1.6 (± 9.89)		
RR	-56.6 (± 196.78)	-79.4 (± 181.23)		
QRS	0.6 (± 7.74)	7.2 (± 9.04)		
QTc	-1.7 (± 14.21)	8.4 (± 24.05)		

Statistical analyses

No statistical analyses for this end point

Primary: Number of adverse events (AEs)

End point title	Number of adverse events (AEs) ^[9]
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End point description:

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign, symptom or disease (including intercurrent illness), deterioration of a pre-existing illness, accident, any suspected drug reaction, or a clinically relevant change of laboratory values temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product and/or study treatment.

A treatment emergent AE (TEAE) will be defined as an AE that begins or that worsens in severity after at least one dose of study drug has been administered.

End point type	Primary
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End point timeframe:

Throughout the study while on treatment with Namuscla

Notes:

[9] - 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 statistical analyses for this end point

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: number of subjects with TEAEs	6	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in VAS score for muscle pain from baseline to Days 56

End point title	Mean change in VAS score for muscle pain from baseline to Days 56
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End point description:

Change from baseline - Intent to Treat population (ITT)

End point type	Secondary
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End point timeframe:

From baseline to Days 14, 28, 42 and 56.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-13.6 (± 18.32)	4.3 (± 19.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in VAS for weakness and fatigue from baseline to Days 56

End point title	Mean change in VAS for weakness and fatigue from baseline to Days 56
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End point description:

Change from baseline - Intent to Treat population (ITT)

End point type	Secondary
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End point timeframe:

From baseline to Days 14, 28, 42 and 56.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-21.0 (± 22.91)	-17.0 (± 41.81)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Faces score for muscle pain from baseline to Days 56

End point title	Mean change in Faces score for muscle pain from baseline to Days 56
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End point description:

Change from baseline - Intent to Treat population (ITT)

End point type	Secondary
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End point timeframe:

From baseline to Days 14, 28, 42 and 56

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[10]			
Units: unit(s)				
arithmetic mean (standard deviation)	-1 (± 1.41)			

Notes:

[10] - FAS scale only utilized in children aged to 6 to 8 yo.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Faces score for weakness and fatigue from baseline to Days 56

End point title	Mean change in Faces score for weakness and fatigue from baseline to Days 56
End point description: Change from baseline - Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe: From baseline to Days 14, 28, 42 and 56	

End point values	Cohort 2			
Subject group type	Reporting group			
Number of subjects analysed	2 ^[11]			
Units: unit(s)				
arithmetic mean (standard deviation)	2 (± 0)			

Notes:

[11] - FAS scale only utilized in children aged 6 to 8 yo.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in time to open the eyes after forced eye closure from baseline to Days 56

End point title	Mean change in time to open the eyes after forced eye closure from baseline to Days 56
End point description: This end point is measured on a stopwatch when eyelid myotonia is present. Change from baseline - Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe: From baseline to Days 14, 28, 42 and 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: second				
arithmetic mean (standard deviation)	0 (\pm 0)	2.2 (\pm 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in the right hand flexor muscles from baseline to Days 56

End point title	Change in the right hand flexor muscles from baseline to Days 56
End point description:	
Change from baseline - Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe:	
From baseline to Days 14, 28, 42 and 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-0.23 (\pm 1.3)	-0.42 (\pm 1.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in time to perform Timed-up and go (TUG) test from baseline to Days 56

End point title	Mean change in time to perform Timed-up and go (TUG) test from baseline to Days 56
End point description:	
Change from baseline - Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe:	
From baseline to Days 14, 28, 42 and 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: second				
arithmetic mean (standard deviation)	-0.45 (\pm 2.7)	0.2 (\pm 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to Day 56 in Paediatric Quality of Life (PedsQL) score

End point title	Mean change from baseline to Day 56 in Paediatric Quality of Life (PedsQL) score
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End point description:

Changes in health-related quality-of-life as measured by the PedsQLTM Quality of Life (version 4.0) and Neuromuscular modules (version 3.0). These multidimensional scales assess the frequency of health problems using generic and disease-specific approaches, respectively.

Change from baseline - Intent to Treat population (ITT)

End point type	Secondary
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End point timeframe:

From baseline to Days 56.

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	11.7 (\pm 12.92)	14.4 (\pm 10.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI) scores (efficacy and tolerability) evaluated by the patient, a parent or proxy and by the investigator at Day 56

End point title	Clinical Global Impression (CGI) scores (efficacy and tolerability) evaluated by the patient, a parent or proxy and by the investigator at Day 56
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End point description:

Only CGI scores of "very efficient" or "good" are reported. Unit represents number of subjects with CGI score of "very efficient" or "good".

Intent to Treat population (ITT)

End point type	Secondary
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End point timeframe:

Only Day 56

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: number of subjects	7	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline to Day 56 in Myotonia Behaviour Scale (MBS) scores

End point title	Mean change from baseline to Day 56 in Myotonia Behaviour Scale (MBS) scores
End point description:	
Change from baseline - Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe:	
From baseline to Day 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)	-1.7 (\pm 1.11)	-0.2 (\pm 0.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability of the capsule formulation with respect to the swallowability determined at Day 56

End point title	Acceptability of the capsule formulation with respect to the swallowability determined at Day 56
End point description:	
It will be assessed by interviewing patients and their caregivers on Day 56, using a scale ranging from 1 (extremely easy) to 7 (extremely difficult) to evaluate swallowability	
Intent to Treat population (ITT)	
End point type	Secondary
End point timeframe:	
Only at Day 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	5		
Units: unit(s)				
arithmetic mean (standard deviation)	1.5 (± 0.71)	3.4 (± 1.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical laboratory evaluations from baseline to day 56

End point title	Clinical laboratory evaluations from baseline to day 56
End point description:	
Safety population.	
Each clinical laboratory results have a different units.	
When mean and SD are equal to 0, it means that clinical laboratory results were not evaluable.	
End point type	Secondary
End point timeframe:	
From baseline to day 56	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	5		
Units: unit(s)				
arithmetic mean (standard deviation)				
Haemoglobin (g/dL)	13.63 (± 0.7999)	12.92 (± 0.545)		
Haematocrit (%)	1.56 (± 1.832)	2.12 (± 1.785)		
RBC count (x 10 ¹² /L)	0.123 (± 0.2771)	0.096 (± 0.2489)		
Platelet count (x 10 ⁹ /L)	-38.3 (± 56.07)	-19.6 (± 35.71)		
Total WBC count (x 10 ⁹ /L)	-1.389 (± 2.2600)	-0.206 (± 1.0433)		
Neutrophils (x 10 ⁹ /L)	-0.870 (± 1.7789)	-0.260 (± 1.2357)		
Lymphocytes (x 10 ⁹ /L)	-0.535 (± 0.6379)	-0.068 (± 5.5753)		
Eosinophils (x 10 ⁹ /L)	0.007 (± 0.1052)	0.146 (± 0.1212)		
Monocytes (x 10 ⁹ /L)	-0.052 (± 0.1671)	-0.016 (± 0.0619)		
Basophils (x 10 ⁹ /L)	-0.007 (± 0.0082)	0.006 (± 0.0182)		
Erythrocyte sedimentation rate (mm/h)	-12.5 (± 22.69)	0.4 (± 2.51)		

Total proteins (g/L)	-1.8 (± 4.31)	2.4 (± 6.19)		
Albumin (g/L)	2.28 (± 3.979)	1.30 (± 5.430)		
Globulin (g/L)	-4.12 (± 4.979)	1.10 (± 2.633)		
Total bilirubin (µmol/L)	0.1 (± 3.02)	-1.8 (± 1.30)		
Direct bilirubin (µmol/L)	0.0 (± 1.41)	0 (± 0)		
Alkaline phosphatase (U/L)	42.8 (± 45.34)	59.3 (± 30.37)		
Asparate aminotransferase AST/SGOT (U/L)	-1.7 (± 8.42)	-9.6 (± 17.52)		
Alanine aminotransferase ALT/SGPT (U/L)	0.0 (± 7.23)	-7.0 (± 15.52)		
eGRF (mL/min/1.73 m ²)	-17.458 (± 18.2044)	0 (± 0)		
Gamma-glutamyltransferase (U/L)	-2.4 (± 2.76)	2.4 (± 2.61)		
Uric acid (µmol/L)	16.8 (± 29.44)	12.8 (± 11.43)		
Blood urea (mmol/L)	-0.27 (± 0.758)	0.60 (± 0.300)		
Creatinine (µmol/L)	5.0 (± 5.26)	1.8 (± 1.92)		
Estimated creatinine clearance (mL/min)	-8.020 (± 20.4433)	-6.285 (± 4.0517)		
Creatinine kinase (U/L)	35.8 (± 81.83)	-307.0 (± 455.04)		
Sodium (mmol/L)	-0.3 (± 1.70)	1.0 (± 0)		
Potassium (mmol/L)	0.171 (± 0.5057)	0.140 (± 0.3647)		
Magnesium (mmol/L)	-0.025 (± 0.0638)	0 (± 0)		
Chloride (mmol/L)	0.3 (± 2.50)	0.4 (± 2.70)		
Calcium (mmol/L)	0.045 (± 0.0481)	-0.022 (± 0.1272)		
Phosphate (mmol/L)	0.097 (± 0.1008)	0.127 (± 0.0643)		
Random plasma glucose (mmol/L)	-0.09 (± 0.607)	0.02 (± 0.432)		
Total cholesterol (non fasting) (mmol/L)	-0.026 (± 0.3286)	0.020 (± 0.6380)		
Triglycerides (non fasting) (mmol/L)	-0.266 (± 0.3742)	-0.018 (± 0.1994)		
Lactate deshydrogenase LDH (U/L)	18.0 (± 103.87)	1.3 (± 37.07)		
CRP positive/negative (mg/L)	-8.96 (± 17.484)	0.85 (± 1.700)		
Aldolase test (U/L)	0 (± 0)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Steady-state pharmacokinetic

End point title	Steady-state pharmacokinetic
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End point description:

PK population.

C_{max}-ss (peak concentrations during the dosing interval at steady-state) and AUC₀-tau (area under the concentration time curve for one dosing interval at steady-state) are determined in µg/L.

If mean is equal to 0, it means results were not evaluable. The average arithmetic is presented.

Results are presented by total daily dose :

- 186 (62 mg 1 capsule 3 times per day)
- 248 (2 capsules of 62 mg twice a day)
- 249 (83 mg 1 capsule 3 times per day)
- 334 (167 mg 1 capsule twice a day)
- 372 (2 capsules of 62 mg 3 times a day)
- 501 (167 mg 1 capsule 3 times per day)

End point type	Secondary
End point timeframe:	
At day 42	

End point values	Cohort 1	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2 ^[12]	3 ^[13]		
Units: unit(s)				
number (not applicable)				
186_Cmax-ss	450.4280	905.3437		
186_AUC0-tau	2350.9735	6409.2805		
248_Cmax-ss	951.4285	0		
248_AUC0-tau	5325.9102	0		
249_Cmax-ss	0	975.4105		
249_AUC0-tau	0	4816.7661		
334_Cmax-ss	790.2660	0		
334_AUC0-tau	0	0		
372_Cmax-ss	1103.5750	0		
372_AUC0-tau	7017.0355	0		
501_Cmax-ss	1398.8395	0		
501_AUC0-tau	8558.2376	0		

Notes:

[12] - PK results have been determined for 2 subjects in the total daily dose 248 & 501 ; 1 for 186 & 362.

[13] - PK results have been determined for 3 subjects in the total daily dose 186 ; 2 for 249.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Patients aged 12 to < 18 years.

Reporting group title	Cohort 2
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Reporting group description:

Patients aged 6 to < 12 years.

Serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1	Cohort 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	1 / 5 (20.00%)	
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Amenorrhoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 5 (20.00%) 1	
Injury, poisoning and procedural complications Ligament sprain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2 1 / 7 (14.29%) 1	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting	3 / 7 (42.86%) 3 3 / 7 (42.86%) 4 1 / 7 (14.29%) 1	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 5 (0.00%) 0	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	0 / 5 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported