Clinical trial results:
A phase IIa study to investigate safety, Pharmacokinetics, and efficacy of odiparcil in patients 16 years and above with mucopolysaccharidosis (MPS) type VI.

Summary

EudraCT number	2017-002158-35
Trial protocol	GB DE FR PT
Global end of trial date	22 October 2019

Results information

Result version number	v1 (current)
This version publication date	16 August 2020
First version publication date	16 August 2020

Trial information

Trial identification

Sponsor protocol code	IVA_01_ODI_HMPS_17_002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03370653
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inventiva S.A.
Sponsor organisation address	50 rue de Dijon, Daix, France, 21121
Public contact	Mireille Tallandier, Inventiva S.A, +33 380 447 500, mireille.tallandier@inventivapharma.com
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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	22 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 October 2019
Global end of trial reached?	Yes
Global end of trial date	22 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the safety and efficacy of two doses of odiparcil in MPS VI patients and to provide evidence to enable the selection of the relevant dose of odiparcil for phase III study.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

In the ERT cohort, ERT (Enzyme Replacement Therapy) is background therapy.

Evidence for comparator:

In the double blinded period, placebo is the comparator.

Actual start date of recruitment	30 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Portugal: 3
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	3
Adults (18-64 years)	17
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment of patients started in December 2017 in the UK and last patient was recruited in May 2019 in France.

Pre-assignment

Screening details:

Main inclusion criteria: Male or female aged ≥16 years, with confirmed diagnosis of MPS VI
For ERT cohort: patients under ERT for at least 6 months. For Non-ERT cohort: patients not receiving ERT due to discontinuation of ERT for more than 3 months, allergy to ERT, hematopoietic stem cell transplant or naïve to ERT.

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Data analyst, Carer, Assessor, Subject, Investigator, Monitor

Blinding implementation details:

One of the 4 arms is an open-label arm with odiparcil 1000mg/day only.

Arms

Are arms mutually exclusive?	Yes
Arm title	ERT cohort - placebo

Arm description:

Patients receiving ERT, randomized to receive placebo

Arm type	Placebo
Investigational medicinal product name	Placebo odiparcil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo of 250mg tablet of odiparcil

Arm title	ERT cohort - 500mg odiparcil

Arm description:

Patients receiving ERT, randomized to 500mg odiparcil/day.

Arm type	Experimental
Investigational medicinal product name	Odiparcil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One tablet of 250mg odiparcil to be taken orally twice a day

Arm title	ERT cohort - 1000mg odiparcil

Arm description:

Patients receiving ERT, randomized to 1000 mg/day of odiparcil

Arm type	Experimental

Investigational medicinal product name	Odiparcil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets of 250mg odiparcil to be taken orally twice a day.

Arm title	Non-ERT cohort - 1000mg odiparcil

Arm description:

Patients not receiving ERT, open label arm with 1000 mg/day of odiparcil.

Arm type	Experimental
Investigational medicinal product name	Odiparcil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 tablets of 250mg odiparcil to be taken orally twice a day.

Number of subjects in period 1	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil
Started	5	5	5
Completed	4	3	3
Not completed	1	2	2
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	-	2	2

Number of subjects in period 1	Non-ERT cohort - 1000mg odiparcil
Started	5
Completed	3
Not completed	2
Adverse event, serious fatal	-
Adverse event, non-fatal	2

Period 2

Period 2 title	Follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes

Arm title	ERT cohort - placebo
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ERT cohort - 500mg odiparcil
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	ERT cohort - 1000mg odiparcil
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Non-ERT cohort
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil
Started	4	3	3
Completed	4	3	3

Number of subjects in period 2	Non-ERT cohort
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	ERT cohort - placebo
Reporting group description:	
Patients receiving ERT, randomized to receive placebo	
Reporting group title	ERT cohort - 500mg odiparcil
Reporting group description:	
Patients receiving ERT, randomized to 500mg odiparcil/day.	
Reporting group title	ERT cohort - 1000mg odiparcil
Reporting group description:	
Patients receiving ERT, randomized to 1000 mg/day of odiparcil	
Reporting group title	Non-ERT cohort - 1000mg odiparcil
Reporting group description:	
Patients not receiving ERT, open label arm with 1000 mg/day of odiparcil.	

Reporting group values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil
Number of subjects	5	5	5
Age categorical			
Patients 16 years old and above			
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	0	0
Adolescents (12-17 years)	2	0	1
Adults (18-64 years)	3	5	4
From 65-84 years	0	0	0
85 years and over	0	0	0
Adolescents	0	0	0
Gender categorical Units: Subjects			
Female	2	3	2
Male	3	2	3

Reporting group values	Non-ERT cohort - 1000mg odiparcil	Total	
Number of subjects	5	20	
Age categorical			
Patients 16 years old and above			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	

Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	3	
Adults (18-64 years)	5	17	
From 65-84 years	0	0	
85 years and over	0	0	
Adolescents	0	0	
Gender categorical Units: Subjects			
Female	2	9	
Male	3	11	

Subject analysis sets

Subject analysis set title	Full analysis set population
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) population included all randomised patients in double-blind cohort or included in open-label cohort, receiving at least one dose of study treatment.

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients receiving at least one dose of study treatment.

Subject analysis set title	Patients completing the study
Subject analysis set type	Per protocol

Subject analysis set description:

Patients from the Full Analysis Set having completed the Week 26 visit.

Subject analysis set title	Preliminary Assessment Period Subjects
Subject analysis set type	Sub-group analysis

Subject analysis set description:

2 patients receiving ERT were included in the PSA period, an open-label escalating dose part of the study. Both patients received odiparcil 500mg per day for 7 days, then odiparcil 1000mg per day for 7 days. Both patients were then included in the Core study, which is the baseline for the analysis.

Reporting group values	Full analysis set population	Safety population	Patients completing the study
Number of subjects	20	20	13
Age categorical			
Patients 16 years old and above			
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	0	0
Adolescents (12-17 years)	3	3	3
Adults (18-64 years)	17	17	10
From 65-84 years	0	0	0
85 years and over	0	0	0
Adolescents	0	0	0

Gender categorical Units: Subjects			
Female	9	9	4
Male	11	11	9

Reporting group values	Preliminary Assessment Period Subjects		
Number of subjects	2		
Age categorical			
Patients 16 years old and above			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	2		
From 65-84 years	0		
85 years and over	0		
Adolescents	0		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	ERT cohort - placebo
Reporting group description:	
Patients receiving ERT, randomized to receive placebo	
Reporting group title	ERT cohort - 500mg odiparcil
Reporting group description:	
Patients receiving ERT, randomized to 500mg odiparcil/day.	
Reporting group title	ERT cohort - 1000mg odiparcil
Reporting group description:	
Patients receiving ERT, randomized to 1000 mg/day of odiparcil	
Reporting group title	Non-ERT cohort - 1000mg odiparcil
Reporting group description:	
Patients not receiving ERT, open label arm with 1000 mg/day of odiparcil.	
Reporting group title	ERT cohort - placebo
Reporting group description: -	
Reporting group title	ERT cohort - 500mg odiparcil
Reporting group description: -	
Reporting group title	ERT cohort - 1000mg odiparcil
Reporting group description: -	
Reporting group title	Non-ERT cohort
Reporting group description: -	
Subject analysis set title	Full analysis set population
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) population included all randomised patients in double-blind cohort or included in open-label cohort, receiving at least one dose of study treatment.	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients receiving at least one dose of study treatment.	
Subject analysis set title	Patients completing the study
Subject analysis set type	Per protocol
Subject analysis set description:	
Patients from the Full Analysis Set having completed the Week 26 visit.	
Subject analysis set title	Preliminary Assessment Period Subjects
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
2 patients receiving ERT were included in the PSA period, an open-label escalating dose part of the study. Both patients received odiparcil 500mg per day for 7 days, then odiparcil 1000mg per day for 7 days. Both patients were then included in the Core study, which is the baseline for the analysis.	

Primary: Total distance walk: absolute change in 6-Minute Walk test from reference

End point title	Total distance walk: absolute change in 6-Minute Walk test from reference[1]
End point description:	
The 6-minute walk test (6MWT) measures the distance that a person can walk quickly in six minutes and it was performed as a measure of endurance.	
End point type	Primary
End point timeframe:	
From V0 to V7	

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: meter				
arithmetic mean (standard deviation)	-39.88 (± 58.14)	8.00 (± 15.72)	-35.00 (± 34.77)	5.17 (± 21.13)

Statistical analyses

No statistical analyses for this end point

Primary: Time to complete the test dominant hand: 9-Hole Peg Test absolute change from reference

End point title	Time to complete the test dominant hand: 9-Hole Peg Test absolute change from reference[2]

End point description:

This test is a measure of dexterity.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	2	2
Units: second				
median (inter-quartile range (Q1-Q3))	-2.48 (-6.66 to 72.89)	-2.05 (-2.55 to 2.00)	-0.43 (-1.50 to 0.65)	24.2 (-3.00 to 51.40)

Statistical analyses

No statistical analyses for this end point

Primary: Shoulder-Range Of Motion on left shoulder: absolute change from reference

End point title	Shoulder-Range Of Motion on left shoulder: absolute change from reference[3]

End point description:

Range of Motion of the shoulder: both active and passive measurements of the shoulder (flexion, extension, abduction, croos-body-addution), executed with a goniometer by a single operator per site. Defined as sum of passive abduction and flexion.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: degree				
arithmetic mean (standard deviation)	15.00 (± 44.49)	4.67 (± 9.50)	-26.50 (± 48.51)	12.67 (± 24.96)

Statistical analyses

No statistical analyses for this end point

Primary: Shoulder-Range Of Motion on right shoulder: absolute change from reference

End point title	Shoulder-Range Of Motion on right shoulder: absolute change from reference[4]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: degree				
arithmetic mean (standard deviation)	4.38 (± 33.06)	-1.83 (± 25.18)	-15.67 (± 16.51)	11.83 (± 33.36)

Statistical analyses

No statistical analyses for this end point

Primary: BPI Pain right now: absolute change from reference

End point title	BPI Pain right now: absolute change from reference[5]

End point description:

The Brief Pain Inventory (BPI) - Short Form (BPI-sf) is a 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patients were asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: unit(s)				
arithmetic mean (standard deviation)	-0.75 (± 1.66)	-0.50 (± 0.50)	0.67 (± 2.02)	-3.00 (± 0.87)

Statistical analyses

No statistical analyses for this end point

Primary: BPI pain interference: absolute change from reference

End point title	BPI pain interference: absolute change from reference[6]

End point description:

The Brief Pain Inventory (BPI) - Short Form (BPI-sf) is a 9-item self-administered questionnaire used to

evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patients were asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: unit(s)				
arithmetic mean (standard deviation)	-1.84 (± 1.12)	-0.60 (± 0.27)	1.19 (± 3.94)	-1.52 (± 2.04)

Statistical analyses

No statistical analyses for this end point

Primary: Forced Vital Capacity: relative change from reference

End point title	Forced Vital Capacity: relative change from reference[7]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	2
Units: litre(s)				
arithmetic mean (standard deviation)	-5.62 (± 9.03)	2.39 (± 2.58)	5.14 (± 3.50)	9.41 (± 13.30)

Statistical analyses

No statistical analyses for this end point

Primary: Left Carotida Intima-Media Thickness: absolute change from baseline

End point title	Left Carotida Intima-Media Thickness: absolute change from baseline[8]

End point description:

Carotida intima-media thickness (CIMT) measure with ultrasound is widely used and well validated imaging technic to assess arteriosclerosis.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	0.02 (-0.09 to 0.04)	0.03 (-0.02 to 0.04)	0.00 (-0.14 to 0.06)	-0.07 (-0.10 to 0.12)

Statistical analyses

No statistical analyses for this end point

Primary: Righy Carotida Intima-Media Tickness: absolute change from baseline

End point title	Righy Carotida Intima-Media Tickness: absolute change from baseline[9]

End point description:

Carotid intima-media thickness (CIMT) measure with ultrasound is widely used and well validated imaging technic to assess arteriosclerosis.

End point type	Primary

End point timeframe:

V0 to V7

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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	0.01 (-0.03 to 0.02)	0.03 (0.03 to 0.06)	-0.05 (-0.23 to 0.07)	0.01 (-0.04 to 0.13)

Statistical analyses

No statistical analyses for this end point

Primary: Visual acuity on left eye: absolute change from baseline

End point title	Visual acuity on left eye: absolute change from baseline[10]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[10] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	2	2
Units: LogMar				
arithmetic mean (standard deviation)	-0.07 (± 0.06)	0.10 (± 0.10)	0.00 (± 0.00)	0.00 (± 0.00)

Statistical analyses

No statistical analyses for this end point

Primary: Visual acuity on right eye: absolute change from baseline

End point title	Visual acuity on right eye: absolute change from baseline[11]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[11] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	2
Units: LogMar				
arithmetic mean (standard deviation)	0.04 (± 0.18)	0.15 (± 0.07)	0.20 (± 0.28)	0.00 (± 0.14)

Statistical analyses

No statistical analyses for this end point

Primary: Corneal opacification measure on left eye: absolute change from baseline

End point title	Corneal opacification measure on left eye: absolute change from baseline[12]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[12] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	1	2
Units: number				
arithmetic mean (standard deviation)	-7.67 (± 3.56)	-1.02 (± 14.15)	-4.99 (± 0.00)	-2.15 (± 3.04)

Statistical analyses

No statistical analyses for this end point

Primary: Corneal opacification measure on right eye: absolute change from baseline

End point title	Corneal opacification measure on right eye: absolute change from baseline[13]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[13] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	2	2	3
Units: number				
arithmetic mean (standard deviation)	-2.61 (± 5.54)	-5.55 (± 11.31)	-10.04 (± 3.72)	-9.25 (± 14.08)

Statistical analyses

No statistical analyses for this end point

Primary: Zarit caregiver burden interview results at visit 7:Global score: absolute change from reference

End point title	Zarit caregiver burden interview results at visit 7:Global score: absolute change from reference[14]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[14] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	2	3	3
Units: unit(s)				
arithmetic mean (standard deviation)	-4.83 (± 0.76)	-2.25 (± 2.47)	-2.00 (± 2.18)	5.17 (± 11.25)

Statistical analyses

No statistical analyses for this end point

Primary: Fatigue severity scale results at visit 7: Global score: absolute change from reference

End point title	Fatigue severity scale results at visit 7: Global score: absolute change from reference[15]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[15] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: unit(s)				
arithmetic mean (standard deviation)	-5.50 (± 7.88)	-2.50 (± 6.06)	-0.67 (± 3.06)	-3.17 (± 17.48)

Statistical analyses

No statistical analyses for this end point

Primary: EQ-5D-5L results at visit 7: Global Health

End point title	EQ-5D-5L results at visit 7: Global Health[16]

End point description:

End point type	Primary

End point timeframe:

V0 to V7

Notes:

[16] - 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: Because of the very low number of patients, it was expected to have difficulties to detect significant differences using usual statistical tests, but only signals of effect / trends. P-values (Fisher's exact or Chi-square tests) of the difference were provided in the CSR for information purposes but are not part of this report.

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: unit(s)				
arithmetic mean (standard deviation)	70.50 (± 18.65)	63.33 (± 5.77)	53.33 (± 17.56)	66.67 (± 15.28)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of 6-Minute Walk Test made by the external representatives of the Trial Steering Committee

End point title	Evaluation of 6-Minute Walk Test made by the external representatives of the Trial Steering Committee

End point description:

This test measures the distance that a person can walk in 6 minutes.
Evaluation made by the TSC external representatives that was based on relative change of 6MWT between visit 7 (week 26) and reference

End point type	Post-hoc

End point timeframe:

vo to v7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: na				
Improved	1	1	0	0
Stable/Slightly improved	0	0	0	0

Stable	1	2	0	2
Slightly worsened/Stable	1	0	0	0
Worsened	1	0	3	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of 9-Hole Peg Test for the dominant hand made by the external representatives of the Trial Steering Committee

End point title	Evaluation of 9-Hole Peg Test for the dominant hand made by the external representatives of the Trial Steering Committee
End point description: This test is a measure of dexterity.	
End point type	Post-hoc
End point timeframe: V0 to V7	

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	3	2	0	0
Stable/Slightly improved	0	0	0	1
Stable	0	0	1	0
Slightly worsened/Stable	0	0	1	0
Worsened	1	1	0	1
Not assessable	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of Shoulder Range Of Motion made by the external representative of the Trial Steering Committee

End point title	Evaluation of Shoulder Range Of Motion made by the external representative of the Trial Steering Committee
End point description:	
End point type	Post-hoc
End point timeframe: V0 to V7	

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	2	0	0	2
Stable/Slightly improved	0	1	0	0
Stable	0	1	1	0
Slighlty worsened/Stable	1	1	1	0
Worsened	1	0	1	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of pain made by the external representatives of the Trial Steering Committee

End point title	Evaluation of pain made by the external representatives of the Trial Steering Committee

End point description:

Pain from BPI questionnaire, intensity and interference, was assessed by the TSC external representatives on a case-by-case basis. Results were presented to the TSC external representatives as absolute change.

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	2	0	0	2
Stable/Slighlty improved	0	1	1	1
Stable	2	2	1	0
Slightly worsened/Stable	0	0	0	0
Worsened	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of Forced Vital Capacity made by the external representatives of the Trial Steering Committee

End point title	Evaluation of Forced Vital Capacity made by the external representatives of the Trial Steering Committee

End point description:

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	0	0	0	1
Stable/Slightly improved	0	1	2	0
Stable	2	2	1	1
Slightly worsened/Stable	1	0	0	0
Worsened	1	0	0	0
Not assessable	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of Carotid Intima-Media Thickness made by the cardiovascular expert

End point title	Evaluation of Carotid Intima-Media Thickness made by the cardiovascular expert

End point description:

Carotid intima-media thickness (CIMT) measure with ultrasound is widely used and well validated imaging technic to assess arteriosclerosis.

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	1	0	1	0
Slightly improved/Stable	0	0	0	1
Stable	2	2	1	1
Stable/Slightly worsened	1	1	1	1
Worsened	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of cardiac parameters made by the cardiovascular expert

End point title	Evaluation of cardiac parameters made by the cardiovascular expert

End point description:

The echocardiogram parameters reviewed by the expert were intraventricular septal thickness at end diastole, left ventricular end-diastolic diameter and posterior wall thickness at end diastole.

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	0	0	1	0
Stable/Slightly improved	1	2	1	0
Stable	3	0	0	1
Slightly worsened/Stable	0	1	1	1
Worsened	0	0	0	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of audiology parameters made by the audiology expert

End point title	Evaluation of audiology parameters made by the audiology

	expert

End point description:

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	0	0	0	0
Stable/Slightly improved	0	0	0	0
Stable	4	2	3	2
Slightly worsened/Stable	0	0	0	0
Worsened	0	0	0	0
Not assessable	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Post-hoc: Evaluation of ophthalmology assessment made by the ophthalmology experts

End point title	Evaluation of ophthalmology assessment made by the ophthalmology experts

End point description:

End point type	Post-hoc

End point timeframe:

V0 to V7

End point values	ERT cohort - placebo	ERT cohort - 500mg odiparcil	ERT cohort - 1000mg odiparcil	Non-ERT cohort - 1000mg odiparcil
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	3	3
Units: NA				
Improved	0	1	1	0
Slightly improved/Stable	1	0	0	0
Stable	3	0	2	2
Stable/Slightly worsened	0	1	0	0

Worsened	0	0	0	0
Not assessable	0	1	0	1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: December 2017 to October 2019	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	ERT cohort: ERT + Placebo
Reporting group description: -	
Reporting group title	ERT cohort: ERT + odiparcil 500mg/day
Reporting group description: -	
Reporting group title	ERT cohort: ERT + odiparcil 1000mg/day
Reporting group description: -	
Reporting group title	Non-ERT cohort: odiparcil 1000mg/day
Reporting group description: -	
Reporting group title	PSA period: odiparcil 500mg or 1000mg/day
Reporting group description: -	

Serious adverse events	ERT cohort: ERT + Placebo	ERT cohort: ERT + odiparcil 500mg/day	ERT cohort: ERT + odiparcil 1000mg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	2 / 5 (40.00%)	3 / 5 (60.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Vascular disorders			
Venous occlusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Non-ERT cohort: odiparcil 1000mg/day	PSA period: odiparcil 500mg or 1000mg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Venous occlusion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			

subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ERT cohort: ERT + Placebo	ERT cohort: ERT + odiparcil 500mg/day	ERT cohort: ERT + odiparcil 1000mg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	5 / 5 (100.00%)	5 / 5 (100.00%)
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tooth extraction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	2 / 5 (40.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	3	0	1
Cough			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nasal congestion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Investigations			
Protein urine present			
subjects affected / exposed	0 / 5 (0.00%)	2 / 5 (40.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Activated partial thromboplastin time prolonged			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	2
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Body temperature decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Coagulation test abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Transaminases increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Laboratory test interference			

subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
International normalised ratio abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Oxygen saturation decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neck injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tracheostomy malfunction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Post-traumatic pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1

Nervous system disorders			
Headache			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Migraine with aura			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Presyncope			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Iron deficiency anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Middle ear adhesions			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Otorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tympanic membrane perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders			

Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Dental caries			
subjects affected / exposed	2 / 5 (40.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haemorrhoids			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Eczema			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Miliaria			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Crystalluria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hydronephrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Micturition urgency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Influenza			

subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Bronchitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastrointestinal viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	2
Laryngitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Tooth abscess			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tracheobronchitis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Iron deficiency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Non-ERT cohort: odiparcil 1000mg/day	PSA period: odiparcil 500mg or 1000mg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	1 / 2 (50.00%)	
Surgical and medical procedures			
Central venous catheter removal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tooth extraction			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oedema peripheral			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			

subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Sleep apnoea syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Investigations			
Protein urine present			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Activated partial thromboplastin time prolonged			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	
occurrences (all)	3	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Body temperature decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Coagulation test abnormal			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Laboratory test interference			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
International normalised ratio abnormal			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Fall			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Limb injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Neck injury			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Tracheostomy malfunction			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Post-traumatic pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	

Dizziness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Migraine			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Migraine with aura			
subjects affected / exposed	0 / 5 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Middle ear adhesions			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Otorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tympanic membrane perforation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Vertigo			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			

Dental caries			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 5 (40.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Eczema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Miliaria			

subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Crystalluria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Hydronephrosis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Micturition urgency			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			

subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Bronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Folliculitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Laryngitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Tooth abscess			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Tracheobronchitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 2 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 2 (50.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Vitamin D deficiency			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 5 (20.00%)	0 / 2 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2017	- Specification of highly effective contraception in accordance with Clinical Trial Facilitation Group document for clarification of contraception in inclusion criteria #7 and in footer related to exclusion criteria #13 and #14 - Addition of EudraCT Number on study treatment labels UK only.
20 February 2018	- Revision of inclusion criteria for patients not treated with ERT - Specifications added to exclusion criteria # 9 and #10 for patients included in PSA. - Revision of calendar - Changes in study design : both patients receiving ERT and patients not receiving ERT were able to participate in PSA - Addition of sample collections for the analysis of bone markers 25-Hydroxy-Vitamin D and TRACP 5b - Clarification of the list of criteria for permanent treatment discontinuation (section 7.1.3) - Revision of definitions for AE causality rate, action taken and outcome in accordance with CDISC standards UK only.
30 May 2018	- Shortening of follow-up period to 4 weeks - Specification of definition for women with childbearing potential - Revision of inclusion criterion #7 to specify a double method of contraception is required - Justification for inclusion of patients below 18 years of age. France only.
12 June 2018	- Change of randomisation methodology due to the addition of new investigational sites. - Exclusion of patients below 18 years of age - Revision of inclusion criterion #4 to clarify that uGAG criterion is based on historical data - Addition of a new PD evaluation: TGA following scientific advice meeting wih Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) Germany only.
20 July 2018	- Specification of definition for women with childbearing potential (UK) - Revision of inclusion criterion #4 to clarify that uGAG criteria was based on historical data (France and UK) - Revision of inclusion criterion #7 to specify a double method of contraception is required (UK) - Justification for inclusion of patients below 18 years of age (UK) - Shortening of follow-up period to 4 weeks (UK) - Harmonisation of label description (France and UK) - Addition of investigational sites in France and Portugal (UK) - Addition of investigational sites in Portugal (France) - Change in randomisation methodology (France and UK) - Clarification of study treatment dispensation during PSA period (France and UK) - Addition of a new pharmacodynamics evaluation: TGA (France and UK)

10 December 2018	- Revision of exclusion criterion #2 to clarify severe respiratory insufficiency and to add severe renal insufficiency PT only.
18 June 2019	- Section 4.1 Study design: revision of patient number from 24 to 20 (and throughout the document) due to unavailability of new patients for recruitment - Section 5.2 Exclusion criteria: clarification of exclusion criterion #10 with Investigator's judgment addition for aPTT and TT values - Section 5.4 Strategies for recruitment and retention: clarification - Section 6.2.2 IMP packaging and labelling: update of label template - Section 9.7 Guidelines for management of specific coagulation abnormalities: additional coagulation tests - Section 9.11.2 Laboratory Tests: clarification of the scope of the unscheduled laboratory tests - Section 9.11.5 Proteinuria: new section - Section 10.6 Ophthalmology assessments: clarification of non-compulsory assessments - Update of monitoring and data management service provider (CRO), update of Sponsor's representatives

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

23 May 2019	For the 2 SUSARs Proteinuria (Investigator's description "laboratory test interference (proteinuria)"), the relationship to the IMP was considered by the Investigator as possibly related but assessed by the Sponsor as not related for Proteinuria and definitely related for Laboratory test interference. These 2 SUSARs constituted a New Fact that was appropriately reported to all involved CAs and IECs of the participating countries. Following the receipt on 16 May 2019 of those 2 SUSARs Proteinuria, an ad hoc DSMB meeting was held on 20 May 2019 during which the Sponsor communicated the clinical findings to DSMB members and study Investigators, and reminded them of the pre-clinical findings, during the open session. As a conclusion of this previous development program: •No AE Proteinuria was reported across phase 1 studies and •In the vast majority of subjects, there was no urinary abnormal laboratory values in phase 2 studies. All available clinical and biological study data were reviewed by the DSMB during the closed session. A second ad hoc DSMB meeting was held in a closed session on 22 May 2019 and the DSMB recommendations were received on 23 May 2019 and were as follows: •Continuation in the core study with modifications and/or additional expert review: Request additional expert review to understand the mechanistic basis for proteinuria, potential long term consequences and the methodology undertaken for measurement of proteinuria Discuss with the Investigators and DSMB the expert opinion, and the potential for unblinding on trials outcomes •Temporary suspension of study enrolment (submitted as an USM to all CAs and IECs of the participating countries on 24 May 2019) On 27 Oct. 2019, DSMB issued an addendum to the 03 Jul 2019 recommendations with details on methods leading to laboratory interference, and on the cases of SUSARs Proteinuria:It is the opinion of the DSMB that the proteinuria reported as SUSAR has been adequately investigated.	-

Notes:

Limitations and caveats

None reported