Clinical trial results:
A Phase 2, 12-Week, Randomized, Double-Blind, Placebo-Controlled Study of DS-1211b in Individuals With PseudoXanthoma Elasticum

Summary

EudraCT number	2022-000676-19
Trial protocol	NL
Global end of trial date	21 November 2023

Results information

Result version number	v1 (current)
This version publication date	07 December 2024
First version publication date	07 December 2024

Trial information

Trial identification

Sponsor protocol code	DS1211-A-U201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05569252
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Road , Basking Ridge, United States, 07920
Public contact	Contact for Clinical Trial Information, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo_us@daiichisankyo.com
Scientific contact	Contact for Clinical Trial Information, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo_us@daiichisankyo.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this trial were to assess the safety and tolerability of DS-1211b compared with placebo in patients with PXE and to assess the dose response by assessing the treatment changes in PD endpoints.

Protection of trial subjects:

The study protocol, patient information and consent form, the Investigator Brochure, any patient written instructions given to the patient, available safety information, patient recruitment procedures (eg, advertisements), information about payments and compensation available to the patients, and documentation evidencing the Investigator’s qualifications were submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonization (ICH) consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2022
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 States: 51
Country: Number of subjects enrolled	Netherlands: 14
Worldwide total number of subjects	65
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 65 participants who met all inclusion criteria and no exclusion criteria were enrolled in the study in the United States and in the Netherlands.

Pre-assignment

Screening details:

Eligible study participants were randomized in a 1:1:1:1 ratio into 4 treatment groups.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	DS-1211b low dose

Arm description:

Participants who were randomized to receive DS-1211 tablets once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	DS-1211b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-1211b tablet administered once daily in the morning either in the fasted state or with a meal.

Arm title	DS-1211b middle dose

Arm description:

Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	DS-1211b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-1211b tablet administered once daily in the morning either in the fasted state or with a meal.

Arm title	DS-1211b high dose

Arm description:

Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	DS-1211b
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

DS-1211b tablet administered once daily in the morning either in the fasted state or with a meal.

Arm title	Placebo

Arm description:

Participants who were randomized to receive placebo tablets once daily for 12 weeks.

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

Dosage and administration details:

Placebo tablet administered once daily in the morning either in the fasted state or with a meal.

Number of subjects in period 1	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose
Started	16	16	16
Completed	15	16	16
Not completed	1	0	0
Adverse event (central vision loss)	1	-	-

Number of subjects in period 1	Placebo
Started	17
Completed	17
Not completed	0
Adverse event (central vision loss)	-

Baseline characteristics

Reporting groups	
Reporting group title	DS-1211b low dose
Reporting group description:	
Participants who were randomized to receive DS-1211 tablets once daily for 12 weeks.	
Reporting group title	DS-1211b middle dose
Reporting group description:	
Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.	
Reporting group title	DS-1211b high dose
Reporting group description:	
Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants who were randomized to receive placebo tablets once daily for 12 weeks.	

Reporting group values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose
Number of subjects	16	16	16
Age categorical Units: Subjects			
≥18 years and <64 years	14	14	14
≥64 years	2	2	2
Age continuous Units: years			
arithmetic mean	55.9	51.6	53.8
standard deviation	± 7.65	± 10.84	± 8.47
Gender categorical Units: Subjects			
Female	7	10	10
Male	9	6	6
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	0
Black or African American	0	1	0
White	16	15	16

Reporting group values	Placebo	Total	
Number of subjects	17	65	
Age categorical Units: Subjects			
≥18 years and <64 years	12	54	
≥64 years	5	11	
Age continuous Units: years			
arithmetic mean	53.5		
standard deviation	± 13.92	-	

Gender categorical Units: Subjects			
Female	14	41	
Male	3	24	
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	
Black or African American	0	1	
White	16	63	

End points

End points reporting groups

Reporting group title	DS-1211b low dose
Reporting group description:	
Participants who were randomized to receive DS-1211 tablets once daily for 12 weeks.	
Reporting group title	DS-1211b middle dose
Reporting group description:	
Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.	
Reporting group title	DS-1211b high dose
Reporting group description:	
Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants who were randomized to receive placebo tablets once daily for 12 weeks.	

Primary: Number of Participants with Treatment-emergent Adverse Events (TEAEs) in Participants Receiving DS-1211b

End point title	Number of Participants with Treatment-emergent Adverse Events (TEAEs) in Participants Receiving DS-1211b[1]
End point description:	
TEAEs are defined as events that start on or after the first dose of study drug or start prior to but then worsen after the first dose of study drug. Adverse events are coded using MedDRA version 26.1.	
End point type	Primary
End point timeframe:	
From the date of signing informed consent form up to Day 98 (14 days after last dose of study drug) post-dose of 12-week treatment period	

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: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	17
Units: participants				
Any TEAE	8	7	6	6
Any TEAE leading to death	0	0	0	0
Any TEAE by maximum severity, mild	4	6	4	3
Any TEAE by maximum severity, moderate	3	1	2	3
Any TEAE by maximum severity, severe	1	0	0	0
Any serious TEAE	1	0	0	0
Any serious TEAE leading to drug interruption	0	0	0	0
Any serious TEAE leading to drug discontinuation	0	0	0	0
Any serious TEAE related to study drug	0	0	0	0
Any TEAE leading to drug interruption	1	0	0	0

Any TEAE leading to drug discontinuation	1	0	0	0
Any TEAE related to study drug	2	2	1	1
Any related TEAE leading to drug interruption	1	0	0	0
Any related TEAE leading to drug discontinuation	1	0	0	0
Any TEAE related to COVID-19	0	0	1	1

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Pharmacodynamic Parameter Alkaline Phosphatase (ALP) Levels

End point title	Percent Change from Baseline in Pharmacodynamic Parameter Alkaline Phosphatase (ALP) Levels[2]

End point description:

ALP levels were assessed using the IFCC serum assay.

End point type	Primary

End point timeframe:

Pre-dose on Days 15, 43, 84; Day 86-88 and Day 98 of 12-week treatment period

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: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	17
Units: percentage				
arithmetic mean (standard deviation)				
Day 15	17.93 (± 10.60)	24.39 (± 14.45)	39.40 (± 11.52)	-0.48 (± 6.14)
Day 43	25.02 (± 17.54)	42.89 (± 30.26)	63.48 (± 35.68)	-2.54 (± 10.38)
Day 84	25.54 (± 16.89)	39.81 (± 20.19)	61.90 (± 37.86)	-4.31 (± 9.58)
Day 86-88	16.60 (± 18.39)	29.93 (± 14.61)	49.67 (± 26.00)	-3.20 (± 9.46)
Day 98	7.65 (± 15.34)	9.48 (± 14.99)	22.95 (± 22.42)	-0.05 (± 13.72)

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Pharmacodynamic Parameter Inorganic Pyrophosphate (PPi) Levels

End point title	Percent Change from Baseline in Pharmacodynamic Parameter

	Inorganic Pyrophosphate (PPi) Levels[3]

End point description:

PPi levels were assessed from collected plasma.

End point type	Primary

End point timeframe:

Pre-dose on Days 15, 43, and 84 of 12-week treatment period

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: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	17
Units: percentage				
arithmetic mean (standard deviation)				
Day 15	118.97 (± 362.42)	11.32 (± 50.13)	23.95 (± 69.94)	13.33 (± 61.00)
Day 43	17.75 (± 50.05)	-5.55 (± 36.74)	4.59 (± 19.47)	12.97 (± 38.33)
Day 84	23.48 (± 78.04)	81.77 (± 313.08)	24.27 (± 97.87)	4.28 (± 41.45)

Statistical analyses

No statistical analyses for this end point

Primary: Percent Change from Baseline in Pharmacodynamic Parameter Pyridoxal 5’-phosphate (PLP) Levels

End point title	Percent Change from Baseline in Pharmacodynamic Parameter Pyridoxal 5’-phosphate (PLP) Levels[4]

End point description:

PLP levels were assessed from collected plasma.

End point type	Primary

End point timeframe:

Pre-dose on Days 15, 43, 84; Day 86-88 and Day 98 of 12-week treatment period

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: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	16	16	17
Units: percentage				
arithmetic mean (standard deviation)				
Day 15	11.01 (± 53.93)	45.42 (± 92.18)	50.97 (± 56.78)	3.42 (± 36.86)
Day 43	8.56 (± 42.26)	36.73 (± 79.89)	25.00 (± 48.51)	16.25 (± 35.09)

Day 84	12.03 (± 46.95)	53.07 (± 110.74)	6.04 (± 38.72)	-8.44 (± 41.44)
Day 86-88	-5.96 (± 27.93)	-6.52 (± 41.25)	-28.76 (± 31.72)	-10.77 (± 45.53)
Day 98	6.10 (± 47.54)	-10.96 (± 45.58)	-8.41 (± 35.10)	17.07 (± 98.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Maximum Concentration (Cmax)

End point title	Pharmacokinetic Parameter Maximum Concentration (Cmax)[5]

End point description:

Pharmacokinetic parameter Cmax was estimated using population PK modeling.

End point type	Secondary

End point timeframe:

Day1 and Day 84 post-dose of 12-week treatment period

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	16	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Day 1	252 (± 20.5)	540 (± 34.8)	713 (± 26.9)	
Day 84	255 (± 20.6)	547 (± 34.9)	726 (± 27.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Trough Plasma Concentration (Ctrough)

End point title	Pharmacokinetic Parameter Trough Plasma Concentration (Ctrough)[6]

End point description:

Pharmacokinetic parameter Ctrough was assessed using observed concentrations at 10 hours post-dose.

End point type	Secondary

End point timeframe:

Day 1 and Day 84 post-dose of 12-week treatment period

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	16	
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (10 hour)	17.15 (± 11.58)	26.30 (± 13.71)	48.43 (± 46.50)	
Day 84 (10 hour)	15.19 (± 9.00)	38.53 (± 30.45)	54.48 (± 40.79)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Time to Maximum Concentration (Tmax)

End point title	Pharmacokinetic Parameter Time to Maximum Concentration (Tmax)[7]

End point description:

Pharmacokinetic parameter Tmax was assessed using population PK modeling.

End point type	Secondary

End point timeframe:

Day 1 and Day 84 post-dose of 12-week treatment period

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	16	
Units: hours				
median (full range (min-max))				
Day 1	1.25 (0.75 to 2.00)	1.13 (0.75 to 3.75)	1.25 (0.75 to 1.75)	
Day 84	1.25 (0.75 to 2.00)	1.13 (0.75 to 3.75)	1.25 (0.75 to 1.75)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic Parameter Area Under the Plasma Concentration-time Curve (AUC)

End point title	Pharmacokinetic Parameter Area Under the Plasma Concentration-time Curve (AUC)[8]

End point description:

Pharmacokinetic parameter AUCtau was assessed using population PK modeling.

End point type	Secondary

End point timeframe:

Day 1 and Day 84 post-dose of 12-week treatment period

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Descriptive statistics were used to assess this outcome.

End point values	DS-1211b low dose	DS-1211b middle dose	DS-1211b high dose	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	16	16	16	
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Day 1, AUCtau	978 (± 28.3)	2090 (± 28.0)	2780 (± 32.1)	
Day 84, AUCtau	1020 (± 29.3)	2210 (± 29.0)	3000 (± 33.7)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the time of signing the informed consent form up to 14 (±5) days after the last dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	DS-1211b middle dose

Reporting group description:

Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.

Reporting group title	DS-1211b high dose

Reporting group description:

Participants who were randomized to receive DS-1211b tablets once daily for 12 weeks.

Reporting group title	DS-1211b low dose

Reporting group description:

Participants who were randomized to receive DS-1211 tablets once daily for 12 weeks.

Reporting group title	Placebo

Reporting group description:

Participants who were randomized to receive placebo tablets once daily for 12 weeks.

Serious adverse events	DS-1211b middle dose	DS-1211b high dose	DS-1211b low dose
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
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	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from	0		

adverse events			
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	DS-1211b middle dose	DS-1211b high dose	DS-1211b low dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	6 / 16 (37.50%)	8 / 16 (50.00%)
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Hot flush			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Investigations			
Heart rate increased			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Heart rate irregular			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

SARS CoV-2 test positive			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Stress fracture			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Sciatica			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Ophthalmic migraine			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Head discomfort			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Dizziness			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Eye disorders			
Blepharospasm			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Central vision loss			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	2	0	1
Paraesthesia oral			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Fascitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Arthralgia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	1 / 16 (6.25%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Otitis media chronic			

subjects affected / exposed	1 / 16 (6.25%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Menstrual disorder			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Investigations			
Heart rate increased			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Heart rate irregular			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
SARS CoV-2 test positive			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Stress fracture			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Tremor			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Ophthalmic migraine			

subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Head discomfort			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ear discomfort			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Eye disorders			
Blepharospasm			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Central vision loss			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Paraesthesia oral			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 17 (0.00%)		
occurrences (all)	0		
Constipation			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Renal and urinary disorders Nephrolithiasis subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0		
Musculoskeletal and connective tissue disorders Flank pain subjects affected / exposed occurrences (all) Fascitis subjects affected / exposed occurrences (all) Arthritis subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Musculoskeletal stiffness subjects affected / exposed occurrences (all) Musculoskeletal discomfort subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all)	 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 1 / 17 (5.88%) 1 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0 0 / 17 (0.00%) 0		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Otitis media chronic subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
Influenza subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		
COVID-19 subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 17 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 October 2022	Updated the Schedule of Events for study assessments, clarified the process for safety monitoring, and other minor updates regarding data collection.
16 January 2023	Updated exploratory analyses, clarified Schedule of Events during treatment period, and revised patient rescreening and AE monitoring procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported