Clinical trial results:
A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Investigate Safety, Tolerability, Pharmacokinetics, and Efficacy of NBI-921352 as Adjunctive Therapy in Adult Subjects with Focal Onset Seizures (FOS)

Summary

EudraCT number	2021-001433-39
Trial protocol	CZ HU FR IT BE ES
Global end of trial date	21 August 2023

Results information

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

Trial information

Trial identification

Sponsor protocol code	NBI-921352-FOS2021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05159908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Neurocrine Biosciences
Sponsor organisation address	12780 El Camino Real, San Diego, United States, 92130
Public contact	Neurocrine Medical Information, Neurocrine Biosciences Inc., +1 877-641-3461, medinfo@neurocrine.com
Scientific contact	Neurocrine Medical Information, Neurocrine Biosciences Inc., +1 877-641-3461, medinfo@neurocrine.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	04 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 August 2023
Global end of trial reached?	Yes
Global end of trial date	21 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the safety and tolerability and to characterize the pharmacokinetic (PK) and PK/pharmacodynamic (PD) relationship of NBI-921352 in adults with FOS taking concomitant background antiseizure medications (ASMs).

Protection of trial subjects:

This study was performed in full compliance with applicable Good Clinical Practice (GCP) and regulations, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Czechia: 36
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Australia: 10
Worldwide total number of subjects	101
EEA total number of subjects	91

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)	101
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized 1:1:1:1 to placebo, NBI-921352 low, medium, or high dose groups to achieve target doses during maintenance period.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received matching placebo.

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 matched to NBI-921352 was administered.

Arm title	NBI-921352 Low Dose

Arm description:

Participants received NBI-921352 low dose.

Arm type	Experimental
Investigational medicinal product name	NBI-921352
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

NBI-921352 was administered.

Arm title	NBI-921352 Medium Dose

Arm description:

Participants received NBI-921352 medium dose.

Arm type	Experimental
Investigational medicinal product name	NBI-921352
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
NBI-921352 was administered.

Arm title	NBI-921352 High Dose

Arm description:
Participants received NBI-921352 high dose.

Arm type	Experimental
Investigational medicinal product name	NBI-921352
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
NBI-921352 was administered.

Number of subjects in period 1	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose
Started	26	25	25
Received at Least 1 Dose of Study Drug	26	25	25
Completed	24	22	22
Not completed	2	3	3
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	1	2	3
Other than specified	1	-	-

Number of subjects in period 1	NBI-921352 High Dose
Started	25
Received at Least 1 Dose of Study Drug	25
Completed	22
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2
Other than specified	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo.	
Reporting group title	NBI-921352 Low Dose
Reporting group description:	
Participants received NBI-921352 low dose.	
Reporting group title	NBI-921352 Medium Dose
Reporting group description:	
Participants received NBI-921352 medium dose.	
Reporting group title	NBI-921352 High Dose
Reporting group description:	
Participants received NBI-921352 high dose.	

Reporting group values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose
Number of subjects	26	25	25
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.0	38.8	42.0
standard deviation	± 10.8	± 10.0	± 12.0
Gender categorical Units: Subjects			
Female	13	15	13
Male	13	10	12
Ethnicity Units: Subjects			
Hispanic or Latino	5	3	4
Not Hispanic or Latino	21	22	21
Race Units: Subjects			
Asian	0	1	0
White	25	22	23
Other	0	1	0
Not collected	1	1	2
28-Day Focal onset Seizure (FOS) Frequency			
Baseline 28-day FOS frequency was calculated as: 28 × Total number of FOS during the baseline period/Total number of days in the baseline period with non-missing diary data.			
Units: seizures per 28 days			
arithmetic mean	17.63	14.56	28.54
standard deviation	± 12.87	± 15.91	± 38.42

Reporting group values	NBI-921352 High Dose	Total	

Number of subjects	25	101	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	41.5		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	10	51	
Male	15	50	
Ethnicity Units: Subjects			
Hispanic or Latino	3	15	
Not Hispanic or Latino	22	86	
Race Units: Subjects			
Asian	0	1	
White	20	90	
Other	2	3	
Not collected	3	7	
28-Day Focal onset Seizure (FOS) Frequency			
Baseline 28-day FOS frequency was calculated as: 28 × Total number of FOS during the baseline period/Total number of days in the baseline period with non-missing diary data.			
Units: seizures per 28 days			
arithmetic mean	32.59		
standard deviation	± 53.42	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants received matching placebo.	
Reporting group title	NBI-921352 Low Dose
Reporting group description: Participants received NBI-921352 low dose.	
Reporting group title	NBI-921352 Medium Dose
Reporting group description: Participants received NBI-921352 medium dose.	
Reporting group title	NBI-921352 High Dose
Reporting group description: Participants received NBI-921352 high dose.	
Subject analysis set title	NBI-921352
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received NBI-921352.	

Primary: Number of Participants With Serious Treatment-emergent Adverse Events (TEAEs), TEAEs Leading to Discontinuation of Study Treatment, and Fatal TEAEs

End point title	Number of Participants With Serious Treatment-emergent Adverse Events (TEAEs), TEAEs Leading to Discontinuation of Study Treatment, and Fatal TEAEs[1]

End point description:

A TEAE was an adverse event (AE) with an onset date on or after first dose of study drug and within 14 days after the last dose of study drug. An AE was any untoward medical occurrence in a participant administered the study drug that did not necessarily have a causal relationship with the treatment. A serious adverse event (SAE) was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required in-patient hospitalization/prolongation of existing hospitalization, was a congenital anomaly, was infection that required treatment parenteral antibiotics, other important medical events which might jeopardize participants, or might require medical/surgical intervention to prevent any of the above. A summary of all Serious Adverse Events and Other Adverse Events (nonserious) regardless of causality is located in the 'Reported Adverse Events' Section. Safety analysis set: all randomized participants who received at least 1 dose of study treatment.

End point type	Primary

End point timeframe:

From first dose of study drug up to Week 15

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: The endpoint is descriptive in nature.

End point values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose	NBI-921352 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	25	25	25
Units: participants				
Serious TEAEs	1	1	1	0
TEAEs Leading to Study Treatment Discontinuation	2	3	3	3
Fatal TEAEs	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Slope Coefficient (β2) of Area Under the Plasma Concentration Versus Time Curve Over a Dosing Interval at Steady State (AUCtau) for Percent Change From Baseline in 28-Day FOS Frequency During the Treatment Period

End point title	Slope Coefficient (β2) of Area Under the Plasma Concentration Versus Time Curve Over a Dosing Interval at Steady State (AUCtau) for Percent Change From Baseline in 28-Day FOS Frequency During the Treatment Period[2]

End point description:

Percent change in 28-day FOS frequency during treatment period compared to baseline period as response variable and steady-state pharmacokinetic (PK) parameter of interest as exposure variable. Exposure was evaluated using AUCtau. Analysis model included 28-day FOS frequency at baseline as a covariate. Results were reported as least-squares (LS) mean estimate of percent change in 28-day FOS frequency for a 1-unit increase in PK parameter (β2 [slope]). The effect size and 95% confidence interval (CI) were obtained for each PK parameter of interest. PK analysis set: participants who received NBI-921352 and had at least 1 reportable plasma concentration value for NBI-921352. 'Overall number of participants analyzed' = participants evaluable for this endpoint. As pre-specified, data for this endpoint was collected and reported as a single Arm/Group for any participant who received at least 1 dose of study drug, regardless of their dose level, and who had evaluable data for this endpoint.

End point type	Primary

End point timeframe:

Day 1 (predose) up to Day 77

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: The statistical analysis was not planned for this endpoint.

End point values	NBI-921352			
Subject group type	Subject analysis set			
Number of subjects analysed	70			
Units: ratio				
least squares mean (confidence interval 95%)	0.00049 (-0.00123 to 0.00220)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Monthly FOS Frequency During the Treatment Period

End point title	Percent Change From Baseline in Monthly FOS Frequency During the Treatment Period

End point description:

Percent change from baseline in 28-day FOS frequency was calculated as: ([frequency during the specified period – frequency during baseline] ÷ frequency during baseline) x 100, where frequency during each period was calculated as: (number of seizures in the period ÷ number of non-missing days in the period) x 28. Non-missing days for seizure diary data were defined as days with >0 seizures documented or confirmation that no seizures occurred on that day. The baseline 28-day FOS frequency was based on seizure data reported in the 56 days immediately preceding randomization. LS mean and standard error (SE) were analyzed using analysis of covariance (ANCOVA). Full analysis set included all randomized participants who received at least 1 dose of study treatment and had at least 1 postbaseline seizure diary entry.

End point type	Secondary

End point timeframe:

From Baseline over the 11-Week treatment period (Day 1 through Day 77)

End point values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose	NBI-921352 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	25	25	25
Units: percent change				
least squares mean (standard error)	5.38 (± 9.86)	-11.83 (± 10.10)	-10.49 (± 10.05)	1.28 (± 10.11)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Monthly FOS Frequency During the Maintenance Period

End point title	Percent Change From Baseline in Monthly FOS Frequency During the Maintenance Period

End point description:

Percent change from baseline in 28-day FOS frequency was calculated as: ([frequency during the specified period – frequency during baseline] ÷ frequency during baseline) x 100, where frequency during each period was calculated as: (number of seizures in the period ÷ number of non-missing days in the period) x 28. Non-missing days for seizure diary data were defined as days with >0 seizures documented or confirmation that no seizures occurred on that day. The baseline 28-day FOS frequency was based on seizure data reported in the 56 days immediately preceding randomization. The maintenance period was an 8-week period from Day 21 through Day 77. LS mean and SE were analyzed using ANCOVA. Full analysis set included all randomized participants who received at least 1 dose of study treatment and had at least 1 postbaseline seizure diary entry. 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From Baseline over the 8-Week maintenance period (Day 21 through Day 77)

End point values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose	NBI-921352 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	23	25	25
Units: percent change				
least squares mean (standard error)	3.03 (± 10.13)	-25.39 (± 10.81)	-14.41 (± 10.32)	-2.32 (± 10.38)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Clinical Global Impression of Change (CGI-C) Responders at Day 77

End point title	Number of Clinical Global Impression of Change (CGI-C) Responders at Day 77

End point description:

The CGI-C is a 7-point scale that required the investigator (or qualified designee) to rate the overall change in the participant's clinical condition since the initiation of study drug dosing. Scores ranged from 1 (very much improved) to 7 (very much worse).
Participants whose CGI-C score was either a 1 (very much improved) or a 2 (much improved) were classified as responders.
The number of participants who were classified as responders has been reported.
Full analysis set included all randomized participants who received at least 1 dose of study treatment, and had at least 1 postbaseline seizure diary entry.

End point type	Secondary

End point timeframe:

Day 77

End point values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose	NBI-921352 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	25	25	25
Units: participants	4	3	5	7

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Response During the Treatment Period

End point title	Number of Participants With Treatment Response During the Treatment Period

End point description:

Treatment response was defined as a participant achieving ≥50% reduction from baseline in 28-day FOS frequency during the treatment period. Full analysis set included all randomized participants who received at least 1 dose of study treatment and had at least 1 postbaseline seizure diary entry.

End point type	Secondary

End point timeframe:

From Baseline over the 11-Week treatment period (Day 1 through Day 77)

End point values	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose	NBI-921352 High Dose
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	25	25	25
Units: participants	2	3	3	5

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Week 15

Adverse event reporting additional description:

Safety analysis set included all randomized participants who received at least 1 dose of study treatment. All-Cause Mortality, Serious Adverse Event, and Other Adverse Event data were pre-specified to be collected and reported for throughout the study period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo.

Reporting group title	NBI-921352 Low Dose

Reporting group description:

Participants received NBI-921352 low dose.

Reporting group title	NBI-921352 Medium Dose

Reporting group description:

Participants received NBI-921352 medium dose.

Reporting group title	NBI-921352 High Dose

Reporting group description:

Participants received NBI-921352 high dose.

Serious adverse events	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	1 / 25 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure cluster			

subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	0 / 25 (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

Serious adverse events	NBI-921352 High Dose		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure cluster			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	0 / 25 (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	Placebo	NBI-921352 Low Dose	NBI-921352 Medium Dose
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 26 (53.85%)	20 / 25 (80.00%)	15 / 25 (60.00%)
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	1	2	0
Fall			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	7 / 25 (28.00%)	3 / 25 (12.00%)
occurrences (all)	0	9	3
Headache			
subjects affected / exposed	0 / 26 (0.00%)	6 / 25 (24.00%)	2 / 25 (8.00%)
occurrences (all)	0	6	11
Seizure			
subjects affected / exposed	1 / 26 (3.85%)	2 / 25 (8.00%)	1 / 25 (4.00%)
occurrences (all)	1	2	1
Somnolence			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	2 / 25 (8.00%)
occurrences (all)	4	3	3
Tremor			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	3 / 25 (12.00%)
occurrences (all)	0	3	4
Fatigue			
subjects affected / exposed	4 / 26 (15.38%)	3 / 25 (12.00%)	3 / 25 (12.00%)
occurrences (all)	7	3	3
Gastrointestinal disorders			
Dyspepsia			

subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 26 (0.00%)	2 / 25 (8.00%)	0 / 25 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)	3 / 25 (12.00%)	0 / 25 (0.00%)
occurrences (all)	0	3	0
Insomnia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	0	1	1
Irritability			
subjects affected / exposed	0 / 26 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 25 (0.00%)	4 / 25 (16.00%)
occurrences (all)	1	0	4
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 26 (11.54%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	3	1	1
Influenza			
subjects affected / exposed	2 / 26 (7.69%)	0 / 25 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 25 (4.00%)	2 / 25 (8.00%)
occurrences (all)	1	1	2
Urinary tract infection			
subjects affected / exposed	2 / 26 (7.69%)	1 / 25 (4.00%)	1 / 25 (4.00%)
occurrences (all)	2	1	1

Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	 1 / 26 (3.85%) 1	 0 / 25 (0.00%) 0	 2 / 25 (8.00%) 2

Non-serious adverse events	NBI-921352 High Dose		
Total subjects affected by non-serious adverse events subjects affected / exposed	 18 / 25 (72.00%)		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) Fall subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 0 / 25 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Seizure subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 5 / 25 (20.00%) 6 7 / 25 (28.00%) 9 1 / 25 (4.00%) 1 3 / 25 (12.00%) 4 1 / 25 (4.00%) 2		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
General disorders and administration site conditions			

Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2 5 / 25 (20.00%) 6		
Gastrointestinal disorders Dyspepsia subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	0 / 25 (0.00%) 0 1 / 25 (4.00%) 1		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Irritability subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1 5 / 25 (20.00%) 5 2 / 25 (8.00%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Influenza	0 / 25 (0.00%) 0		

subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2021	It included following changes: • The study objectives were labeled as primary, secondary, or exploratory and revised to align with the primary, secondary, and exploratory endpoints. • The number of study sites was changed. • Inclusion criteria were revised.
04 March 2022	It included following changes: • Clarified that direct rollover into an extension study may occur only if a separate active extension study was open for enrollment. • Clarified the requirement for visual field testing before screening. • Reporting and follow-up for pregnancies in female partners of male participants was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported