Clinical trial results:
A Randomized, Placebo-Controlled Study of ABX-1431 in Adult Patients with Tourette Syndrome or Chronic Motor Tic Disorder

Summary

EudraCT number	2018-000100-41
Trial protocol	ES
Global end of trial date	14 January 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2020
First version publication date	13 December 2020

Trial information

Trial identification

Sponsor protocol code	18423A

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03625453
WHO universal trial number (UTN)	-
Other trial identifiers	Abide Therapeutics, Inc. : PN018

Notes:

Sponsors

Sponsor organisation name	H. Lundbeck A/S
Sponsor organisation address	Ottiliavej 9, Valby, Denmark, 2500
Public contact	LundbeckClinicalTrials@Lundbeck.com, Email contact via, +45 36301311, LundbeckClinicalTrials@Lundbeck.com
Scientific contact	LundbeckClinicalTrials@Lundbeck.com, Email contact via, +45 36301311, LundbeckClinicalTrials@Lundbeck.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	14 January 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of ABX-1431 in treating adult patients with Tourette Syndrome or Chronic Motor Tic Disorder as measured by the change from Baseline in Total Tic Score of the Yale Global Tic Severity Scale (YGTSS-TTS) compared with placebo.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice (1996).
The dose escalation could be adjusted for individual patients based on the occurrence of central nervous system (CNS) adverse events. Depending on the occurrence and severity of CNS adverse events, the protocol-specified dose-escalation guidelines allowed for dose increase, maintenance, and decrease, or the interruption of dosing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2018
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	Poland: 10
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Germany: 34
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	49
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

53 patients were screened: 37 patients at 5 centers in Germany, 5 patients at 2 centers in Spain, and 11 patients at 1 center in Poland. 4 patients were screening failures (3 patients in Germany, 1 patient in Poland) and 49 patients were randomized to study treatment.

Pre-assignment

Screening details:

Subjects who met each of the inclusion and none of the exclusion criteria were eligible to participate in the study.

Period 1

Period 1 title	Main treatment - Part 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

ABX-1431 and placebo capsules were identical in appearance.

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1: ABX-1431

Arm description:

The dose was escalated from 10 mg/day to a maximum of 40 mg/day ABX-1431 between Day 1 and Day 56.

Arm type	Experimental
Investigational medicinal product name	ABX-1431
Investigational medicinal product code	ABX-1431
Other name	Lu AG06466
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules were swallowed once daily in the morning with food (within 30 minutes of eating). The dose was escalated from 10 mg/day (1 capsule) to 40 mg/day (4 capsules) ABX-1431 between Day 1 and Day 56.
Daily dosing schedule: Days 1 to 3 - 10 mg (1 capsule); Days 4 to 28 - 20 mg (2 capsules); Days 29 to 35 - 30 mg (3 capsules); Days 36 to 56 - 40 mg (4 capsules).

Arm title	Part 1: Placebo

Arm description:

The number of placebo capsules was increased from 1 (matching 10 mg/day) to a maximum of 4 (matching 40 mg/day) between Day 1 and Day 56.

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

Dosage and administration details:

Capsules were swallowed once daily in the morning with food (within 30 minutes of eating). Placebo was escalated following the same scheme as ABX-1431 from 1 capsule (matching 10 mg/day) to 4 capsules (matching 40 mg/day) between Day 1 and Day 56.

Daily dosing schedule: Days 1 to 3 - 1 capsule; Days 4 to 28 - 2 capsules; Days 29 to 35 - 3 capsules; Days 36 to 56 - 4 capsules.

Number of subjects in period 1	Part 1: ABX-1431	Part 1: Placebo
Started	23	26
Completed	19	25
Not completed	4	1
Physician decision	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	3	-

Period 2

Period 2 title	Open-label - Part 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All subjects received ABX-1431.

Arms

Arm title	Part 2: ABX-1431

Arm description:

Upon completion of Day 56 of Part 1, patients could proceed to Part 2. During Part 2, patients took 10 mg/day ABX-1431 and escalated to a maximum dose of 20 mg/day.

Arm type	Experimental
Investigational medicinal product name	ABX-1431
Investigational medicinal product code	ABX-1431
Other name	Lu AG06466
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Capsules were swallowed once daily in the morning with food (within 30 minutes of eating). The dose was escalated from 10 mg/day (1 capsule) to 20 mg/day (2 capsules) ABX-1431 between Day 1 and Day 28.
Daily dosing schedule: Days 1 to 3 - 10 mg (1 capsule); Days 4 to 28 - 20 mg (2 capsules).

Number of subjects in period 2[1]	Part 2: ABX-1431
Started	35
Completed	33
Not completed	2
Consent withdrawn by subject	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: As Part 2 of the trial was optional, not all patients completing Part 1 continued in Part 2.

Baseline characteristics

Reporting groups	
Reporting group title	Part 1: ABX-1431
Reporting group description:	
The dose was escalated from 10 mg/day to a maximum of 40 mg/day ABX-1431 between Day 1 and Day 56.	
Reporting group title	Part 1: Placebo
Reporting group description:	
The number of placebo capsules was increased from 1 (matching 10 mg/day) to a maximum of 4 (matching 40 mg/day) between Day 1 and Day 56.	

Reporting group values	Part 1: ABX-1431	Part 1: Placebo	Total
Number of subjects	23	26	49
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	23	26	49
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
median	32.0	31.0	
full range (min-max)	19 to 55	20 to 58	-
Gender categorical			
Units: Subjects			
Female	3	5	8
Male	20	21	41
Yale global tic severity scale total tic score (YGTSS-TTS)			
Units: Score			
median	28.0	29.0	
full range (min-max)	14 to 48	22 to 44	-
Adult tic questionnaire (ATQ)			
Units: score			
median	7.0	7.0	
full range (min-max)	4 to 12	0 to 14	-
Premonitory urge for tics (PUTS) scale			
Units: score			
median	24.0	20.5	
full range (min-max)	12 to 33	9 to 33	-

End points

End points reporting groups

Reporting group title	Part 1: ABX-1431
Reporting group description:	
The dose was escalated from 10 mg/day to a maximum of 40 mg/day ABX-1431 between Day 1 and Day 56.	
Reporting group title	Part 1: Placebo
Reporting group description:	
The number of placebo capsules was increased from 1 (matching 10 mg/day) to a maximum of 4 (matching 40 mg/day) between Day 1 and Day 56.	
Reporting group title	Part 2: ABX-1431
Reporting group description:	
Upon completion of Day 56 of Part 1, patients could proceed to Part 2. During Part 2, patients took 10 mg/day ABX-1431 and escalated to a maximum dose of 20 mg/day.	

Primary: Change from Baseline in YGTSS-TTS - Part 1

End point title	Change from Baseline in YGTSS-TTS - Part 1
End point description:	
The YGTSS is a clinician-administered interview considering tics in the prior week based on a semi-structured interview. The YGTSS-TTS (0 to 50) consists of ratings for motor tics (0 to 25) and vocal tics (0 to 25) concerning dimensions of number, frequency, intensity, complexity, and interference, with each dimension graded 0 to 5. Higher scores represents greater severity.	
End point type	Primary
End point timeframe:	
Change from Baseline to Day 28 and Day 56.	

End point values	Part 1: ABX-1431	Part 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	26		
Units: Score				
least squares mean (standard error)				
Day 28	-2.5 (± 0.9)	-2.9 (± 0.8)		
Day 56	-2.7 (± 1.1)	-5.7 (± 1.0)		

Statistical analyses

Statistical analysis title	Mean difference in YGTSS-TTS changes at Day 56
Statistical analysis description:	
The mean difference in change from Baseline (ABX-1431 vs placebo) at Day 56 was estimated based on the least squares means for the treatment-by-visit interaction. The changes from Baseline were analysed using a restricted maximum likelihood (REML)-based linear mixed model with repeated measures (MMRM). The model included treatment, visit (as a categorical variable), pooled site, YGTSS-TTS at Baseline, YGTSS-TTS at baseline-by-visit interaction, and a treatment-by-visit interaction term.	
Comparison groups	Part 1: ABX-1431 v Part 1: Placebo

Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0428 [2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	5.9
Variability estimate	Standard error of the mean
Dispersion value	1.4

Notes:

[1] - A positive point estimate indicates larger improvement in the placebo arm. An unstructured covariance matrix was used for within-patient correlation. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The model converged and no adaptations were used.
[2] - A 1-sided alpha level of 0.025 was used to determine significance.

Statistical analysis title	Mean difference in YGTSS-TTS changes at Day 28

Statistical analysis description:

The mean difference in change from Baseline (ABX-1431 vs placebo) at Day 28 was estimated based on the least squares means for the treatment-by-visit interaction. The changes from baselinewere analysed using a REML-based linear MMRM. The model included treatment, visit (as a categorical variable), pooled site, YGTSS-TTS at Baseline, YGTSS-TTS at baseline-by-visit interaction, and a treatment-by-visit interaction term.

Comparison groups	Part 1: ABX-1431 v Part 1: Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.7463 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	2.7
Variability estimate	Standard error of the mean
Dispersion value	1.2

Notes:

[3] - A positive point estimate indicates larger improvement in the placebo arm. An unstructured covariance matrix was used for within-patient correlation. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The model converged and no adaptations were used.
[4] - A 1-sided alpha level of 0.025 was used to determine significance.

Secondary: Change from Baseline in ATQ scores - Part 1

End point title	Change from Baseline in ATQ scores - Part 1

End point description:

The ATQ is a patient self-assessment of frequency and intensity for several common motor and vocal tics. The ATQ was analysed by summing the intensity (1 to 4) and frequency (1 to 4) to determine the severity (2 to 8) across all endorsed tics. The clinical relevance of changes in the ATQ was presented by the change in the average intensity score (that is total intensity score divided by total number of tics)

and average frequency score (that is total frequency score divided by total number of tics). Higher scores indicate greater tic burden.

End point type	Secondary

End point timeframe:

Change from Baseline to Day 28 and Day 56

End point values	Part 1: ABX-1431	Part 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[5]	26[6]		
Units: Score				
median (full range (min-max))				
Day 28 - total number of motor+vocal tics	-1.0 (-6 to 5)	-0.5 (-7 to 6)		
Day 56 - total number of motor+vocal tics	-1.0 (-6 to 4)	-1.0 (-8 to 2)		
Day 28 - total frequency score of motor+vocal tics	-6.0 (-21 to 8)	0.0 (-35 to 10)		
Day 56 - total frequency score of motor+vocal tics	-6.5 (-19 to 7)	-2.0 (-41 to 11)		
Day 28 - total intensity score of motor+vocal tics	-1.0 (-16 to 11)	-2.5 (-25 to 8)		
Day 56 - total intensity score of motor+vocal tics	-3.5 (-20 to 8)	-3.0 (-31 to 8)		
Day 28 - average frequency score motor+vocal tics	0.0 (-1 to 1)	0.0 (-1 to 1)		
Day 56 - average frequency score motor+vocal tics	0.0 (-1 to 1)	0.0 (-2 to 1)		
Day 28 - average intensity score motor+vocal tics	0.0 (-1 to 1)	0.0 (-1 to 1)		
Day 56 - average intensity score motor+vocal tics	0.0 (-2 to 1)	0.0 (-1 to 1)		

Notes:

[5] - Day 28: N=21 with N=1 missing
Day 56: N=20
[6] - Day 56: N=25

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ATQ scores - Part 2

End point title	Change from Baseline in ATQ scores - Part 2

End point description:

The ATQ is a patient self-assessment of frequency and intensity for several common motor and vocal tics. The ATQ was analysed by summing the intensity (1 to 4) and frequency (1 to 4) to determine the severity (2 to 8) across all endorsed tics. The clinical relevance of changes in the ATQ was presented by the change in the average intensity score (that is total intensity score divided by total number of tics) and average frequency score (that is total frequency score divided by total number of tics). Higher scores indicate greater tic burden.

End point type	Secondary

End point timeframe:

Change from Baseline to Day 28

End point values	Part 2: ABX-1431			
Subject group type	Reporting group			
Number of subjects analysed	35[7]			
Units: Scores				
median (full range (min-max))				
Total number of motor+vocal tics	-1.0 (-6 to 3)			
Total frequency score of motor+vocal tics	0.0 (-46 to 18)			
Total intensity score of motor+vocal tics	-1.0 (-31 to 13)			
Average frequency score motor+vocal tics	0.0 (-2 to 2)			
Average intensity score motor+vocal tics	0.0 (-1 to 1)			

Notes:

[7] - Day 28: N=33

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PUTS scores - Part 1

End point title	Change from Baseline in PUTS scores - Part 1

End point description:

The PUTS is a patient self-assessment of the intensity of agreement of several statements about premonitory feelings preceding tics, each scored on a Likert scale (1 to 4). The scale asks about current feelings. The PUTS (item 1-9) total score ranges from 9 to 36, that is the sum of single items.

End point type	Secondary

End point timeframe:

Change from Baseline to Day 28 and Day 56

End point values	Part 1: ABX-1431	Part 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[8]	26[9]		
Units: Score				
median (full range (min-max))				
Day 28 - PUTS total score	2.0 (-14 to 7)	0.0 (-10 to 5)		
Day 56 - PUTS total score	-1.0 (-12 to 8)	0.0 (-10 to 7)		

Notes:

[8] - Day 28: N=22
Day 56: N=20
[9] - Day 56: N=25

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PUTS scores - Part 2

End point title	Change from Baseline in PUTS scores - Part 2

End point description:

The PUTS is a patient self-assessment of the intensity of agreement of several statements about premonitory feelings preceding tics, each scored on a Likert scale (1 to 4). The scale asks about current feelings. The PUTS (item 1-9) total score ranges from 9 to 36, that is the sum of single items.

End point type	Secondary

End point timeframe:

Change from Baseline to Day 28

End point values	Part 2: ABX-1431			
Subject group type	Reporting group			
Number of subjects analysed	35[10]			
Units: Score				
median (full range (min-max))				
PUTS total score	0.0 (-7 to 12)			

Notes:

[10] - Day 28: N=33

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical global impressions scale for improvement (CGI-I) - Part 1

End point title	Clinical global impressions scale for improvement (CGI-I) - Part 1

End point description:

The CGI-I is a 7-point ordinal, clinician-rated scale used to assess the patient’s overall improvement or worsening in disease status relative to their condition at baseline. Rating is: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

End point type	Secondary

End point timeframe:

Improvement at Day 28 and Day 56

End point values	Part 1: ABX-1431	Part 1: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[11]	26[12]		
Units: Score				
median (full range (min-max))				
Day 28 - CGI-I score	4.0 (2 to 5)	4.0 (1 to 6)		
Day 56 - CGI-I score	3.5 (1 to 5)	4.0 (1 to 6)		

Notes:

[11] - Day 28: N=22
Day 56: N=20
[12] - Day 56: N=25

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-I - Part 2

End point title	CGI-I - Part 2

End point description:

The CGI-I is a 7-point ordinal, clinician-rated scale used to assess the patient's overall improvement or worsening in disease status relative to their condition at baseline. Rating is: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

End point type	Secondary

End point timeframe:

Score at Day 28

End point values	Part 2: ABX-1431			
Subject group type	Reporting group			
Number of subjects analysed	35[13]			
Units: Score				
median (full range (min-max))				
CGI-I	3.0 (1 to 4)			

Notes:

[13] - Day 28: N=33

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in YGTSS-TTS - Part 2

End point title	Change from Baseline in YGTSS-TTS - Part 2

End point description:

The YGTSS is a clinician-administered interview considering tics in the prior week based on a semi-structured interview. The YGTSS-TTS (0 to 50) consists of ratings for motor tics (0 to 25) and vocal tics (0 to 25) concerning dimensions of number, frequency, intensity, complexity, and interference, with each dimension graded 0 to 5. Higher scores represents greater severity.

End point type	Secondary

End point timeframe:

Change from Baseline to Day 28

End point values	Part 2: ABX-1431			
Subject group type	Reporting group			
Number of subjects analysed	35[14]			
Units: Score				
median (full range (min-max))				
YGTSS-TTS	-1.0 (-20 to 7)			

Notes:

[14] - Day 28: N=33

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of ABX-1431 or placebo until the end of the study.

Adverse event reporting additional description:

Adverse events with start date after the first dose of ABX-1431 or placebo in the first period but before the first dose of ABX-1431 in the second period were allocated to Part 1. Adverse events with start date, stop date, or ongoing during the second period were allocated to Part 2.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	ABX-1431 Part 1

Reporting group description:

During Part 1, the dose was escalated from 10 mg/day (1 capsule) to 40 mg/day (4 capsules) ABX-1431 between Day 1 and Day 56.
Daily dosing schedule: Days 1 to 3 - 10 mg (1 capsule); Days 4 to 28 - 20 mg (2 capsules); Days 29 to 35 - 30 mg (3 capsules); Days 36 to 56 - 40 mg (4 capsules).

Reporting group title	Placebo Part 1

Reporting group description:

During Part 1, placebo was escalated following the same scheme as ABX-1431 from 1 capsule (matching 10 mg/day) to 4 capsules (matching 40 mg/day) between Day 1 and Day 56.
Daily dosing schedule: Days 1 to 3 - 1 capsule; Days 4 to 28 - 2 capsules; Days 29 to 35 - 3 capsules; Days 36 to 56 - 4 capsules.

Reporting group title	ABX-1431 Part 2

Reporting group description:

During Part 2, the dose was escalated from 10 mg/day (1 capsule) to 20 mg/day (2 capsules) ABX-1431 between Day 1 and Day 28.
Daily dosing schedule: Days 1 to 3 - 10 mg (1 capsule); Days 4 to 28 - 20 mg (2 capsules).

Serious adverse events	ABX-1431 Part 1	Placebo Part 1	ABX-1431 Part 2
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 35 (2.86%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	ABX-1431 Part 1	Placebo Part 1	ABX-1431 Part 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	24 / 26 (92.31%)	29 / 35 (82.86%)
Congenital, familial and genetic disorders			
Tourette's disorder			
subjects affected / exposed	2 / 23 (8.70%)	3 / 26 (11.54%)	3 / 35 (8.57%)
occurrences (all)	3	3	4
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	6 / 23 (26.09%)	3 / 26 (11.54%)	5 / 35 (14.29%)
occurrences (all)	7	3	5
Dizziness			
subjects affected / exposed	4 / 23 (17.39%)	2 / 26 (7.69%)	6 / 35 (17.14%)
occurrences (all)	6	2	7
Headache			
subjects affected / exposed	3 / 23 (13.04%)	8 / 26 (30.77%)	4 / 35 (11.43%)
occurrences (all)	4	10	6
Memory impairment			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	2	0	2
Migraine			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Paraesthesia			
subjects affected / exposed	5 / 23 (21.74%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	6	0	2
Somnolence			
subjects affected / exposed	2 / 23 (8.70%)	4 / 26 (15.38%)	6 / 35 (17.14%)
occurrences (all)	2	6	10
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 23 (34.78%)	4 / 26 (15.38%)	5 / 35 (14.29%)
occurrences (all)	9	4	5
Feeling abnormal			

subjects affected / exposed	4 / 23 (17.39%)	5 / 26 (19.23%)	3 / 35 (8.57%)
occurrences (all)	7	5	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 23 (17.39%)	4 / 26 (15.38%)	3 / 35 (8.57%)
occurrences (all)	4	5	3
Eye disorders			
Ocular discomfort			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 23 (8.70%)	3 / 26 (11.54%)	0 / 35 (0.00%)
occurrences (all)	3	4	0
Dry mouth			
subjects affected / exposed	3 / 23 (13.04%)	0 / 26 (0.00%)	0 / 35 (0.00%)
occurrences (all)	4	0	0
Vomiting			
subjects affected / exposed	1 / 23 (4.35%)	2 / 26 (7.69%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Nausea			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Toothache			
subjects affected / exposed	0 / 23 (0.00%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 23 (8.70%)	0 / 26 (0.00%)	0 / 35 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 23 (13.04%)	0 / 26 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Psychiatric disorders			

Sleep disorder			
subjects affected / exposed	1 / 23 (4.35%)	4 / 26 (15.38%)	2 / 35 (5.71%)
occurrences (all)	1	5	2
Depressive symptom			
subjects affected / exposed	0 / 23 (0.00%)	1 / 26 (3.85%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Disorientation			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Micturition urgency			
subjects affected / exposed	1 / 23 (4.35%)	0 / 26 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	1 / 35 (2.86%)
occurrences (all)	0	2	1
Myalgia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 26 (7.69%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	0 / 23 (0.00%)	3 / 26 (11.54%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 23 (26.09%)	4 / 26 (15.38%)	5 / 35 (14.29%)
occurrences (all)	6	4	5
Oral herpes			
subjects affected / exposed	1 / 23 (4.35%)	2 / 26 (7.69%)	0 / 35 (0.00%)
occurrences (all)	1	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 July 2018	Study title, protocol flexibility criteria, primary and secondary objectives, study design, dose escalation, and inclusion and exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported