Clinical trial results:
A Multicenter, Double Blind, Randomized, Placebo-Controlled Trial to Determine the Efficacy and Safety of Ganaxolone as Adjunctive Therapy for Adults With Drug-Resistant Partial-Onset Seizures Followed by Long-term Open-Label Treatment

Summary

EudraCT number	2014-004363-21
Trial protocol	BG DE PL
Global end of trial date	01 October 2016

Results information

Result version number	v1 (current)
This version publication date	23 November 2023
First version publication date	23 November 2023

Trial information

Trial identification

Sponsor protocol code	1042-0603

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01963208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Marinus Pharmaceuticals, Inc.
Sponsor organisation address	5 Radnor Corporate Center, 100 Matsonford Road, Suite 500, Radnor, United States, PA 19087
Public contact	Marinus Pharmaceuticals, Inc., Safety Department, 001 484-801-4670, clinicaltrials@marinuspharma.com
Scientific contact	Marinus Pharmaceuticals, Inc., Safety Department, 001 484-801-4670, clinicaltrials@marinuspharma.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	01 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy of ganaxolone compared to placebo as adjunctive therapy in adults with partial-onset seizures (POS), with or without secondary generalizations.

Protection of trial subjects:

At the first visit, prior to initiation of any study-related procedures, the parent(s) or legal guardian(s) of the subjects gave their written consent to participate in the study after having been informed about the nature and purpose of the study, participation / termination conditions, and risks and benefits. Before the informed consent document was signed, the investigator, or a person designated by the investigator, provided the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial were answered to the satisfaction of the subject or the subject's legally acceptable representative.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2013
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: 42
Country: Number of subjects enrolled	Bulgaria: 77
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Australia: 47
Country: Number of subjects enrolled	Russian Federation: 81
Country: Number of subjects enrolled	United States: 141
Worldwide total number of subjects	405
EEA total number of subjects	136

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)	391
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a 2-cohort study where each cohort comprised of 2 treatment phases. Phase 1 was a double-blind phase followed by Phase 2, an open-label phase. The study analyzed safety, tolerability and pharmacokinetics (PK) of Ganaxolone when compared with placebo in both the cohorts.

Pre-assignment

Screening details:

This was a 2-cohort study where each cohort comprised of 2 treatment phases. Phase 1 was a double-blind phase followed by Phase 2, an open-label phase. The study analyzed safety, tolerability and pharmacokinetics (PK) of Ganaxolone when compared with placebo in both the cohorts.

Period 1

Period 1 title	Treatment Phase 1 (Up to Week 14)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Double Blind: Cohort 1 - Ganaxolone

Arm description:

Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED). Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

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

Dosage and administration details:

Ganaxolone was administered

Arm title	Double Blind: Cohort 1 - Placebo

Arm description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

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 was administered.

Arm title	Double Blind: Cohort 2 - Ganaxolone

Arm description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while

participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

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

Dosage and administration details:

Ganaxolone will be administered

Arm title	Double Blind: Cohort 2 - Placebo

Arm description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

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 was administered.

Number of subjects in period 1	Double Blind: Cohort 1 - Ganaxolone	Double Blind: Cohort 1 - Placebo	Double Blind: Cohort 2 - Ganaxolone
Started	24	22	179
Completed	23	19	135
Not completed	1	3	44
Consent withdrawn by subject	-	2	8
Non-Compliance	-	-	4
Adverse event, non-fatal	1	-	30
Protocol violation	-	-	1
Insufficient Clinical Response	-	-	-
Unspecified	-	1	1
Lost to follow-up	-	-	-

Number of subjects in period 1	Double Blind: Cohort 2 - Placebo
Started	180
Completed	154
Not completed	26
Consent withdrawn by subject	9
Non-Compliance	-
Adverse event, non-fatal	11
Protocol violation	3
Insufficient Clinical Response	1

Unspecified	1
Lost to follow-up	1

Period 2

Period 2 title	Treatment Phase 2 (Up to Week 68)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Open Label: Ganaxolone in Double-blind Phase

Arm description:

Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase

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

Dosage and administration details:

Ganaxolone was administered.

Arm title	Open Label: Placebo in Double-blind Phase

Arm description:

Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase

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 was administered

Number of subjects in period 2	Open Label: Ganaxolone in Double-blind Phase	Open Label: Placebo in Double-blind Phase
Started	158	173
Completed	57	44
Not completed	101	129
Consent withdrawn by subject	7	19
Non-Compliance	-	1
Adverse event, non-fatal	16	15
Protocol violation	-	1
Death	-	1
Insufficient Clinical Response	20	17
Unspecified	58	75

Baseline characteristics

Reporting groups

Reporting group title	Treatment Phase 1 (Up to Week 14)

Reporting group description: -

Reporting group values	Treatment Phase 1 (Up to Week 14)	Total	
Number of subjects	405	405	
Age categorical 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	0	
Adults (18-64 years)	391	391	
From 65-84 years	14	14	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	40.99		
standard deviation	± 12.379	-	
Gender categorical Units: Subjects			
Female	243	243	
Male	162	162	

Subject analysis sets

Subject analysis set title	Double Blind: Cohort 1 – Ganaxolone
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered ganaxolone 1200 mg/day and 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

Subject analysis set title	Double Blind: Cohort 1 - Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.
Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at

Subject analysis set title	Double Blind: Cohort 2 - Ganaxolone
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Subject analysis set title	Double Blind: Cohort 2 - Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Reporting group values	Double Blind: Cohort 1 – Ganaxolone	Double Blind: Cohort 1 - Placebo	Double Blind: Cohort 2 - Ganaxolone
Number of subjects	24	21	178
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	35.1	41.1	40.6
standard deviation	± 10.25	± 11.83	± 12.48
Gender categorical Units: Subjects			
Female	13	12	113
Male	11	9	65

Reporting group values	Double Blind: Cohort 2 - Placebo		
Number of subjects	172		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	42.1		

standard deviation	± 12.37		

Gender categorical Units: Subjects			
Female	97		
Male	75		

End points reporting groups

Reporting group title	Double Blind: Cohort 1 - Ganaxolone

Reporting group description:

Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED). Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Reporting group title	Double Blind: Cohort 1 - Placebo

Reporting group description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Reporting group title	Double Blind: Cohort 2 - Ganaxolone

Reporting group description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Reporting group title	Double Blind: Cohort 2 - Placebo

Reporting group description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

Reporting group title	Open Label: Ganaxolone in Double-blind Phase

Reporting group description:

Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase

Reporting group title	Open Label: Placebo in Double-blind Phase

Reporting group description:

Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase

Subject analysis set title	Double Blind: Cohort 1 – Ganaxolone
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered ganaxolone 1200 mg/day and 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

Subject analysis set title	Double Blind: Cohort 1 - Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.
Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at

Subject analysis set title	Double Blind: Cohort 2 - Ganaxolone
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Ganaxolone 1800 mg/day + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Subject analysis set title	Double Blind: Cohort 2 - Placebo

Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants were administered Placebo + AED. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Primary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period[1]

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period (≤ 56 days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Primary analysis was performed using a rank analysis of covariance (ANCOVA). Modified intent to treat (mITT) population: all randomized participants who received at least 1 dose of study medication and provided any post Baseline seizure outcome data.

End point type	Primary

End point timeframe:

Baseline and Week 14

Notes:

[1] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percent change				
median (confidence interval 95%)	-21.28 (-29.60 to -14.29)	-10.25 (-20.14 to -1.28)		

Statistical analyses

Statistical analysis title	Week 14

Statistical analysis description:

Double Blind: Cohort 2 - Ganaxolone, Double Blind: Cohort 2 - Placebo

Comparison groups	Double Blind: Cohort 2 - Ganaxolone v Double Blind: Cohort 2 - Placebo
Number of subjects included in analysis	350
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1788 [2]
Method	Rank ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-7.06

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.44
upper limit	3.52

Notes:

[2] - The null hypothesis is that there is no difference between the distributions of the two treatment groups with respect to percent change in seizure frequency.

Secondary: Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 14

End point title	Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 14[3]

End point description:

The CGI-I scale is a clinician-rated 7-point Likert scale used to assess the degree to which the participant's epilepsy symptoms have changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher scores indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

At Week 14

Notes:

[3] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	140	159		
Units: Participants				
number (not applicable)				
Very much improved	7	5		
Much improved	28	30		
Minimally improved	41	47		
No change	56	67		
Minimally worse	6	8		
Much worse	2	2		
Very much worse	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Number of Participants With ≥50% Responder Rate During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Number of Participants With ≥50% Responder Rate During Titration + Maintenance Period[4]

End point description:

A 50% responder was a participant who experienced at least a 50% decrease in 28-day seizure

frequency compared to Baseline

End point type	Secondary

End point timeframe:

Up to Week 14

Notes:

[4] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Participants				
number (not applicable)	50	39		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Titration + Maintenance Period[5]

End point description:

Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire Baseline period (<=56 days) divided by the number of days with available seizure data in the baseline period and multiplied by 28. Post-Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire treatment period divided by the number of days with available seizure data in the treatment period and multiplied by 28. Change from Baseline in number of seizure free days per 28-day period from Baseline was calculated as: Post-Baseline number of seizure free days per 28-day period minus Baseline number of seizure free days per 28-day period. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Baseline and Week 14

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Seizure free days				
arithmetic mean (standard deviation)	1.47 (± 4.396)	1.01 (± 4.223)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Titration + Maintenance Period[6]

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period (≤ 56 days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value.

End point type	Secondary

End point timeframe:

Baseline and Week 14

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Seizures per 28 days				
arithmetic mean (standard deviation)	-1.46 (± 9.650)	-0.33 (± 11.040)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Maintenance Period

End point title	Double Blind: Cohort 2: Change From Baseline in 28-day Seizure Frequency During Maintenance Period[7]

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period (≤ 56 days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose. Change from Baseline was calculated by subtracting Baseline value from the post-dose visit value

End point type	Secondary

End point timeframe:

Baseline and Week 2 to Week 14

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	169		
Units: Seizures per 28 days				
arithmetic mean (standard deviation)	-1.67 (± 11.809)	-0.64 (± 12.153)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Maintenance Period

End point title	Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency During Maintenance Period[8]

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period (≤ 56 days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Baseline and Week 2 to Week 14

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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	169		
Units: Percent change				
median (confidence interval 95%)	-20.56 (-31.56 to -12.69)	-12.50 (-20.78 to -3.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Maintenance Period

End point title	Double Blind: Cohort 2: Change From Baseline in the Number of Seizure Free Days Per 28-day Period During Maintenance Period[9]

End point description:

Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire Baseline period (≤ 56 days) divided by the number of days with available seizure data

in the Baseline period and multiplied by 28. Post-Baseline number of seizure free days per 28-day period was calculated as: the number of seizure free days in the entire treatment period divided by the number of days with available seizure data in the treatment period and multiplied by 28. Change from Baseline in number of seizure free days per 28-day period from Baseline was calculated as: Post-Baseline number of seizure free days per 28-day period minus Baseline number of seizure free days per 28-day period. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Baseline and Week 2 to Week 14

Notes:

[9] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	169		
Units: Seizure free days				
arithmetic mean (standard deviation)	1.63 (± 4.824)	1.20 (± 4.462)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percentage of Responders Experiencing a ≥R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Percentage of Responders Experiencing a ≥R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Titration + Maintenance Period[10]

End point description:

Percentage of participants who had reductions of ≥ 80%, ≥ 60%, ≥ 40%, and ≥ 20% in 28-day seizure frequency from Baseline is presented. A responder is an individual whose reduction of percent change from Baseline in 28-day seizure frequency was ≥ 50%. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Up to Week 14

Notes:

[10] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percentage of participants				
number (not applicable)				
Reduction ≥ 80%	7.3	2.33		

Reduction ≥ 60%	20.79	16.86		
Reduction ≥ 40%	33.15	29.65		
Reduction ≥ 20%	51.69	43.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percentage of Responders Experiencing a ≥R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Maintenance Period

End point title	Double Blind: Cohort 2: Percentage of Responders Experiencing a ≥R% (80%, 60%, 40%, and 20%) Reduction From Baseline to the End of Treatment Period in 28-day Seizure Frequency During Maintenance Period[11]

End point description:

Percentage of participants who had reductions of ≥ 80%, ≥ 60%, ≥ 40%, and ≥ 20% in 28-day seizure frequency from Baseline is presented. A responder is an individual whose reduction of percent change from Baseline in 28-day seizure frequency was ≥ 50%. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Week 2 to Week 14

Notes:

[11] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percentage of participants				
number (not applicable)				
Reduction ≥ 80%	8.43	5.81		
Reduction ≥ 60%	24.16	18.02		
Reduction ≥ 40%	33.71	31.4		
Reduction ≥ 20%	47.19	42.44		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percentage of Seizure Free Participants During the Maintenance Period

End point title	Double Blind: Cohort 2: Percentage of Seizure Free Participants During the Maintenance Period[12]

End point description:

Percentage of participants who completed the study without any seizures is presented

End point type	Secondary

End point timeframe:

Week 2 to Week 14

Notes:

[12] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percentage of participants				
number (not applicable)	1.12	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percentage of Participants Who Experienced at Least One 28-day Seizure Free Period During Titration + Maintenance Phase

End point title	Double Blind: Cohort 2: Percentage of Participants Who Experienced at Least One 28-day Seizure Free Period During Titration + Maintenance Phase[13]

End point description:

Percentage of participants who experienced at least one 28-day seizure free period is presented

End point type	Secondary

End point timeframe:

Up to Week 14

Notes:

[13] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percentage of participants				
number (not applicable)	17.98	18.02		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency for Different Subtypes of Seizures During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Percent Change From Baseline in 28-day Seizure Frequency for Different Subtypes of Seizures During Titration + Maintenance Period[14]

End point description:

Seizure frequency was based on the number of seizures per 28 days, calculated as the number of seizures over the time interval multiplied by 28 and divided by the number of days in the interval. The analysis was conducted for Partial-Onset Seizure (POS) only which included seizure subtypes: Complex partial seizures (CPS), secondarily generalized tonic-clonic (SGTC) seizures, simple partial seizure with motor/observable component (SPS-Motor) and Simple partial seizure (SPS) without motor/observable component. Baseline 28-day seizure frequency was calculated as the number of seizures in the Baseline period (≤ 56 days) divided by the number of days with available seizure data in the Baseline period and multiplied by 28. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Baseline and Week 14

Notes:

[14] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	152		
Units: Percent change				
arithmetic mean (standard deviation)				
CPS (n= 150, 152)	-4.70 (± 92.373)	-6.52 (± 59.126)		
SGTC (n= 69, 82)	-27.42 (± 69.394)	1.02 (± 118.444)		
SPS-Motor (n= 44, 32)	-5.52 (± 93.228)	-21.97 (± 52.473)		
SPS (n= 33, 31)	12.57 (± 129.979)	-3.53 (± 87.071)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Longest Percent of Time Spent Seizure-free During Titration + Maintenance Period

End point title	Double Blind: Cohort 2: Longest Percent of Time Spent Seizure-free During Titration + Maintenance Period[15]

End point description:

The longest period of time seizure-free was defined as the percent of the longest seizure-free period (days) divided by the days with available seizure data, and then multiplied by 100%.

End point type	Secondary

End point timeframe:

Up to Week 14

Notes:

[15] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	172		
Units: Percentage of time spent				
arithmetic mean (standard deviation)	24.00 (± 22.457)	17.58 (± 12.743)		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Number of Participants With Patient Global Impression of Change – Improvement (PGI-I) at Week 8 and Week 14

End point title	Double Blind: Cohort 2: Number of Participants With Patient Global Impression of Change – Improvement (PGI-I) at Week 8 and Week 14[16]

End point description:

The PGI-I scale was a 7-point Likert scale completed by the Patient or Caregiver representing the degree to which the participant's epilepsy symptoms had changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher score indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

Week 8 and Week 14

Notes:

[16] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	161		
Units: Participants				
number (not applicable)				
Week 8: Very Much Improved	7	5		
Week 8: Much Improved	30	21		
Week 8: Minimally Improved	44	51		
Week 8: No Change	59	65		

Week 8: Minimally Worse	12	11		
Week 8: Much Worse	8	4		
Week 8: Very Much Worse	6	4		
Week 14: Very Much Improved	7	10		
Week 14: Much Improved	33	29		
Week 14: Minimally Improved	43	43		
Week 14: No Change	46	60		
Week 14: Minimally Worse	7	12		
Week 14: Much Worse	3	4		
Week 14: Very Much Worse	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 8

End point title	Double Blind: Cohort 2: Number of Participants With Clinical Global Impression of Change – Improvement (CGI-I) at Week 8[17]

End point description:

The CGI-I scale is a clinician-rated 7-point Likert scale used to assess the degree to which the participant's epilepsy symptoms have changed relative to Baseline. It was rated as 1. "very much improved"; 2. "much improved"; 3. "minimally improved"; 4. "no change"; 5. "minimally worse"; 6. "much worse"; 7. "very much worse". Higher scores indicated worse condition. Baseline was defined as non-missing value of last assessment before first dose.

End point type	Secondary

End point timeframe:

At Week 8

Notes:

[17] - 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: Per protocol, statistical analysis was not planned for this endpoint.

End point values	Double Blind: Cohort 2 - Ganaxolone	Double Blind: Cohort 2 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	162		
Units: Participants				
number (not applicable)				
Very much improved	3	4		
Much improved	27	20		
Minimally improved	50	49		
No change	68	71		
Minimally worse	8	12		
Much worse	9	5		
Very much worse	1	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week -8 through Week 14 in Double blind phase and from Week 16 to Week 68 in open label phase

Adverse event reporting additional description:

Safety Population: included all randomized participants who received at least 1 dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Open Label: Ganaxolone in Double-blind Phase

Reporting group description:

Following the completion of the double-blind phase, participants randomized to ganaxolone remained on the drug at 1800 mg/day + AED. Participants from Double Blind: Cohort 1 - Ganaxolone and Double Blind: Cohort 2 - Ganaxolone were combined to enter in Open Label: Ganaxolone in Double-blind Phase

Reporting group title	Open Label: Placebo in Double-blind Phase

Reporting group description:

Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone + AED. Participants from Double Blind: Cohort 1 - Placebo and Double Blind: Cohort 2 - Placebo were combined to enter in Open Label: Placebo in Double-blind Phase

Reporting group title	Double Blind: Cohort 1 and Cohort 2- Ganaxolone

Reporting group description:

Participants were administered ganaxolone 1200 milligrams per day (mg/day) and 1800 mg/day + Antiepileptic drug (AED) in Cohort 1 and Participants were administered Ganaxolone 1800 mg/day + AED in Cohort 2. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase.

Reporting group title	Double Blind: Cohort 1 and Cohort 2 - Placebo

Reporting group description:

Participants were administered Placebo + AED in Cohort 1 and Cohort 2. Following the completion of the double-blind phase, participants randomized to placebo were transitioned to ganaxolone while participants randomized to ganaxolone remained on the drug at 1800 mg/day in the open-label phase

Serious adverse events	Open Label: Ganaxolone in Double-blind Phase	Open Label: Placebo in Double-blind Phase	Double Blind: Cohort 1 and Cohort 2- Ganaxolone
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 158 (7.59%)	12 / 173 (6.94%)	9 / 203 (4.43%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events			0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Foot fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Clavicle fracture			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tongue injury			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ligament rupture			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Ankle fracture			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal column injury			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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

Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 158 (0.63%)	4 / 173 (2.31%)	2 / 203 (0.99%)
occurrences causally related to treatment / all	0 / 1	2 / 4	2 / 2
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 2
Epilepsy			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Toxic encephalopathy			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Seizure cluster			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Status epilepticus			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Speech disorder			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Somnolence			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Postictal psychosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Grand mal convulsion			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Oesophageal obstruction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Psychogenic seizure			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Depression			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Suicidal ideation			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Confusional state			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hallucination			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Delusion			

subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infections and infestations			
Pulmonary tuberculosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Appendicitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (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
Clostridium difficile colitis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung abscess			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Meningitis viral			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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
Pneumonia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (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

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Serious adverse events	Double Blind: Cohort 1 and Cohort 2 - Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 197 (4.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Foot fracture			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tongue injury			

subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ligament rupture				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ankle fracture				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal column injury				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Convulsion				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Epilepsy				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Toxic encephalopathy				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure cluster				

subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Speech disorder			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postictal psychosis			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Grand mal convulsion			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Small intestinal obstruction			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal obstruction			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Psychogenic seizure			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Depression			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Anxiety			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Confusional state			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Suicide attempt				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mental status changes				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delusion				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Rhabdomyolysis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pulmonary tuberculosis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Clostridium difficile colitis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Lung abscess			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Meningitis viral			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 197 (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: 0 %

Non-serious adverse events	Open Label: Ganaxolone in Double-blind Phase	Open Label: Placebo in Double-blind Phase	Double Blind: Cohort 1 and Cohort 2-Ganaxolone
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 158 (26.58%)	67 / 173 (38.73%)	134 / 203 (66.01%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign hepatic neoplasm			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Cervical polyp			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Intraductal papilloma of breast			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Fibroadenoma of breast			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	4 / 158 (2.53%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	4	2	1
Aortic disorder			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Ecchymosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Venous thrombosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Hypertensive crisis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	0	4	0
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Open reduction of fracture			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
General disorders and administration site conditions			

Night sweats			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	9 / 158 (5.70%)	15 / 173 (8.67%)	23 / 203 (11.33%)
occurrences (all)	10	19	30
Gait disturbance			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	5 / 203 (2.46%)
occurrences (all)	0	1	5
Asthenia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Chest pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Cyst			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	1	1	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0

Procedural pain			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Feeling abnormal			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Feeling cold			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Influenza like illness			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Pain			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Immune system disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Drug hypersensitivity			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Seasonal allergy			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Stress at work			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0

Vaginal haemorrhage			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	0	1	3
Breast cyst			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 158 (0.00%)	3 / 173 (1.73%)	0 / 203 (0.00%)
occurrences (all)	0	3	0
Erectile dysfunction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Metrorrhagia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Polymenorrhoea			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	1	1	0
Amenorrhoea			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Breast tenderness			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Vaginal inflammation			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Uterine polyp			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Menstruation irregular			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Uterine haemorrhage			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	3 / 203 (1.48%)
occurrences (all)	0	1	3
Asthma			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	1	1	0
Chest discomfort			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	2 / 158 (1.27%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	2	1	0
Nasal inflammation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 158 (0.63%)	3 / 173 (1.73%)	1 / 203 (0.49%)
occurrences (all)	1	3	1
Respiratory disorder			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Wheezing			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	2	1	0
Dysphonia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Rhonchi			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Sneezing			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Euphoric mood			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Mood swings			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Anger			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Panic attack			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Sleep disorder			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0

Stress			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Suicidal ideation			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Affective disorder			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Nervousness			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	3
Confusional state			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	1	1	2
Irritability			
subjects affected / exposed	0 / 158 (0.00%)	3 / 173 (1.73%)	2 / 203 (0.99%)
occurrences (all)	0	3	2
Anxiety			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	3 / 203 (1.48%)
occurrences (all)	2	0	3
Mood altered			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Mental status changes			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Libido decreased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	0	2	3
Suicide attempt			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Psychotic disorder			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Emotional distress			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Agitation			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Aggression			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Abnormal behaviour			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Depressed mood			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	2 / 203 (0.99%)
occurrences (all)	0	0	2
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Blood alkaline phosphatase abnormal			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Biopsy skin			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Weight increased			
subjects affected / exposed	0 / 158 (0.00%)	3 / 173 (1.73%)	0 / 203 (0.00%)
occurrences (all)	0	3	0
Blood potassium increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Blood glucose abnormal			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Diagnostic procedure			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Blood triglycerides increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Blood sodium decreased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase abnormal			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Arthroscopy			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Neutrophil count increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Neurological examination abnormal			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1

Lymphocyte count decreased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Liver function test abnormal			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Blood iron increased			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Platelet count increased			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 158 (0.00%)	4 / 173 (2.31%)	3 / 203 (1.48%)
occurrences (all)	0	8	3
Fall			
subjects affected / exposed	1 / 158 (0.63%)	3 / 173 (1.73%)	1 / 203 (0.49%)
occurrences (all)	1	6	2
Head injury			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	1	1	2
Ligament sprain			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	2 / 203 (0.99%)
occurrences (all)	1	2	2
Rib fracture			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Facial bones fracture			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Laceration			
subjects affected / exposed	3 / 158 (1.90%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	3	5	2
Excoriation			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	3	1
Joint injury			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Limb injury			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Muscle contusion			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Periorbital contusion			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Foot fracture			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Eye contusion			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Wound haemorrhage			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Tibia fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Tendon injury			

subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Road traffic accident			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Incision site erythema			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Soft tissue injury			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Upper limb fracture			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Burns third degree			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Clavicle fracture			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Concussion			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			

Coronary artery disease			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Paroxysmal arrhythmia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Silent myocardial infarction			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Bundle branch block left			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Cardiac failure congestive			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Somnolence			

subjects affected / exposed	12 / 158 (7.59%)	29 / 173 (16.76%)	46 / 203 (22.66%)
occurrences (all)	13	33	56
Dizziness			
subjects affected / exposed	8 / 158 (5.06%)	27 / 173 (15.61%)	38 / 203 (18.72%)
occurrences (all)	16	29	50
Headache			
subjects affected / exposed	9 / 158 (5.70%)	11 / 173 (6.36%)	18 / 203 (8.87%)
occurrences (all)	15	12	19
Ataxia			
subjects affected / exposed	2 / 158 (1.27%)	2 / 173 (1.16%)	6 / 203 (2.96%)
occurrences (all)	2	3	7
Balance disorder			
subjects affected / exposed	3 / 158 (1.90%)	1 / 173 (0.58%)	7 / 203 (3.45%)
occurrences (all)	3	1	7
Aphasia			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	5 / 203 (2.46%)
occurrences (all)	1	2	5
Convulsion			
subjects affected / exposed	5 / 158 (3.16%)	4 / 173 (2.31%)	5 / 203 (2.46%)
occurrences (all)	5	5	5
Tremor			
subjects affected / exposed	2 / 158 (1.27%)	2 / 173 (1.16%)	4 / 203 (1.97%)
occurrences (all)	24	2	4
Dysarthria			
subjects affected / exposed	2 / 158 (1.27%)	4 / 173 (2.31%)	3 / 203 (1.48%)
occurrences (all)	2	4	3
Memory impairment			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	1	2	1
Sedation			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	4 / 203 (1.97%)
occurrences (all)	1	2	4
Cerebellar syndrome			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Agitation			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Hypoaesthesia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Slow speech			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	0	1	2
Amnesia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	3 / 203 (1.48%)
occurrences (all)	0	0	3
Coordination abnormal			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Disorientation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	1	2	1
Dyskinesia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Essential tremor			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Migraine			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Grand mal convulsion			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Hypoaesthesia oral			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Loss of consciousness			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Mental impairment			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	1	2	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Psychomotor skills impaired			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Sleep terror			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Speech disorder			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	1 / 203 (0.49%)
occurrences (all)	0	2	1
Vertigo			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Seizure cluste			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	1	4	0
Restless legs syndrome			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Dementia Alzheimer''s type			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Initial insomnia			

subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Postictal state			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Radicular pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Delayed sleep phase			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Slow response to stimuli			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Splenomegaly			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Anaemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0

Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 158 (0.00%)	5 / 173 (2.89%)	4 / 203 (1.97%)
occurrences (all)	0	7	4
Ear pain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Tinnitus			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Nystagmus			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	1	1	2
Diplopia			
subjects affected / exposed	2 / 158 (1.27%)	4 / 173 (2.31%)	2 / 203 (0.99%)
occurrences (all)	2	4	2
Vision blurred			
subjects affected / exposed	3 / 158 (1.90%)	1 / 173 (0.58%)	7 / 203 (3.45%)
occurrences (all)	11	1	14
Eye swelling			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Eye pruritus			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Photophobia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Visual impairment			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	2 / 203 (0.99%)
occurrences (all)	0	0	2
Dry eye			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Eye allergy			

subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Blepharospasm			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Ocular dysmetria			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	2 / 203 (0.99%)
occurrences (all)	0	0	2
Nausea			
subjects affected / exposed	5 / 158 (3.16%)	4 / 173 (2.31%)	1 / 203 (0.49%)
occurrences (all)	13	5	1
Diarrhoea			
subjects affected / exposed	2 / 158 (1.27%)	3 / 173 (1.73%)	3 / 203 (1.48%)
occurrences (all)	2	5	3
Vomiting			
subjects affected / exposed	2 / 158 (1.27%)	7 / 173 (4.05%)	1 / 203 (0.49%)
occurrences (all)	2	7	1
Constipation			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	3 / 203 (1.48%)
occurrences (all)	1	2	3
Dry mouth			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Abdominal pain			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Oral pruritus			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1

Toothache			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	2	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 158 (0.63%)	3 / 173 (1.73%)	0 / 203 (0.00%)
occurrences (all)	1	3	0
Dyspepsia			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	1	2	0
Dental caries			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Disbacteriosis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Abdominal distension			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	1	1	1
Eructation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Abdominal discomfort			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Bowel movement irregularity			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0

Gingivitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Paraesthesia oral			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Epigastric discomfort			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Retching			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Cholecystitis chronic			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Rash pruritic			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Skin lesion			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Skin hypopigmentation			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Rash maculo-papular			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Acne			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	2 / 158 (1.27%)	1 / 173 (0.58%)	3 / 203 (1.48%)
occurrences (all)	2	1	3
Alopecia			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	4 / 203 (1.97%)
occurrences (all)	2	0	4
Rash			
subjects affected / exposed	3 / 158 (1.90%)	2 / 173 (1.16%)	5 / 203 (2.46%)
occurrences (all)	3	2	5
Dermatitis contact			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Swelling face			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1

Micturition urgency			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pollakiuria			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Urinary incontinence			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Menstruation irregular			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	2 / 203 (0.99%)
occurrences (all)	0	0	2
Adrenal cyst			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Gynaecomastia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	2	2	0
Musculoskeletal stiffness			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Muscle fatigue			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Hypertonia			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Exostosis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	3 / 158 (1.90%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	4	2	0
Neck pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	2
Myalgia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	2 / 203 (0.99%)
occurrences (all)	0	1	2
Muscle spasms			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	2 / 203 (0.99%)
occurrences (all)	1	2	2
Back pain			

subjects affected / exposed	1 / 158 (0.63%)	4 / 173 (2.31%)	1 / 203 (0.49%)
occurrences (all)	1	6	2
Sensation of heaviness			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Arthritis			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Osteochondrosis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Contusion			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1

Nasopharyngitis			
subjects affected / exposed	6 / 158 (3.80%)	9 / 173 (5.20%)	5 / 203 (2.46%)
occurrences (all)	6	9	5
Upper respiratory tract infection			
subjects affected / exposed	4 / 158 (2.53%)	5 / 173 (2.89%)	6 / 203 (2.96%)
occurrences (all)	6	5	6
Urinary tract infection			
subjects affected / exposed	3 / 158 (1.90%)	8 / 173 (4.62%)	3 / 203 (1.48%)
occurrences (all)	3	9	3
Sinusitis			
subjects affected / exposed	2 / 158 (1.27%)	3 / 173 (1.73%)	2 / 203 (0.99%)
occurrences (all)	2	4	2
Pharyngitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	6 / 158 (3.80%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	6	2	0
Corneal infection			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Cystitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Ear infection			
subjects affected / exposed	2 / 158 (1.27%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1

Gastroenteritis viral			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	1	2	0
Infected bites			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	1	1	1
Rhinitis			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Rotavirus infection			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Sinusitis bacterial			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Tooth infection			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	0	1	1
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	2 / 158 (1.27%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	2	3	0
Fungal infection			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	2	2	0

Gastrointestinal viral infection			
subjects affected / exposed	1 / 158 (0.63%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	1	2	0
Laryngitis			
subjects affected / exposed	0 / 158 (0.00%)	2 / 173 (1.16%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Impetigo			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Tonsillitis bacterial			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Viral diarrhoea			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 158 (1.27%)	1 / 173 (0.58%)	1 / 203 (0.49%)
occurrences (all)	2	1	1
Hypercholesterolaemia			

subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 158 (0.00%)	4 / 173 (2.31%)	1 / 203 (0.49%)
occurrences (all)	0	4	1
Thirst			
subjects affected / exposed	0 / 158 (0.00%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	0	0	0
Vitamin D deficiency			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	1 / 203 (0.49%)
occurrences (all)	1	0	1
Increased appetite			
subjects affected / exposed	1 / 158 (0.63%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	1	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Hypochloraemia			
subjects affected / exposed	0 / 158 (0.00%)	1 / 173 (0.58%)	0 / 203 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 158 (0.63%)	0 / 173 (0.00%)	0 / 203 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Double Blind: Cohort 1 and Cohort 2 - Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 197 (49.75%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign hepatic neoplasm			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Cervical polyp			

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Intraductal papilloma of breast			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Fibroadenoma of breast			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Vascular disorders			
Cardiovascular disorder			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Aortic disorder			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Ecchymosis			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Venous thrombosis			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypertensive crisis			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Haematoma			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			

subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Open reduction of fracture			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Night sweats			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	12 / 197 (6.09%)		
occurrences (all)	12		
Gait disturbance			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Asthenia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Cyst			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Hyperhidrosis			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Injection site pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Lethargy			

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Feeling abnormal			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Feeling cold			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Immune system disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Drug hypersensitivity			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Seasonal allergy			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		

Social circumstances			
Stress at work			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Menopausal symptoms			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Vaginal haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Breast cyst			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Dysmenorrhoea			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Erectile dysfunction			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Menorrhagia			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Metrorrhagia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Polymenorrhoea			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Amenorrhoea			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Breast tenderness			

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Vaginal inflammation			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Uterine polyp			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Menstruation irregular			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Uterine haemorrhage			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Nasal inflammation			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Respiratory disorder			

subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Respiratory tract congestion			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Rhonchi			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Sleep apnoea syndrome			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Euphoric mood			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Mood swings			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		

Anger				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Panic attack				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Sleep disorder				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Stress				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Suicidal ideation				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Affective disorder				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Nervousness				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Confusional state				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Irritability				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Anxiety				
subjects affected / exposed	3 / 197 (1.52%)			
occurrences (all)	3			
Mood altered				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Mental status changes				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			

Libido decreased			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Suicide attempt			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Psychotic disorder			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Emotional distress			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Agitation			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Aggression			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Abnormal behaviour			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Depressed mood			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase abnormal			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Biopsy skin			

subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Weight increased				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Blood potassium increased				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Blood glucose abnormal				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Diagnostic procedure				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Blood triglycerides increased				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Blood sodium decreased				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Blood pressure increased				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Blood creatinine increased				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Aspartate aminotransferase abnormal				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Arthroscopy				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			

Transaminases increased			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Neutrophil count increased			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Neurological examination abnormal			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Liver function test abnormal			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Blood iron increased			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Platelet count increased			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 197 (2.03%)		
occurrences (all)	4		
Fall			

subjects affected / exposed	3 / 197 (1.52%)			
occurrences (all)	3			
Head injury				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Ligament sprain				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Rib fracture				
subjects affected / exposed	3 / 197 (1.52%)			
occurrences (all)	3			
Facial bones fracture				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Laceration				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Excoriation				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Joint injury				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Limb injury				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Muscle contusion				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Periorbital contusion				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Foot fracture				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Eye contusion				

subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Wound haemorrhage				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Tibia fracture				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Tendon injury				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Road traffic accident				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Incision site erythema				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Hand fracture				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Procedural pain				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Soft tissue injury				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Thermal burn				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Upper limb fracture				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Wrist fracture				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Burns third degree				

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Clavicle fracture			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Concussion			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Paroxysmal arrhythmia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Silent myocardial infarction			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Atrioventricular block first degree			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Bradycardia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Bundle branch block left			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Left ventricular hypertrophy			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		

Tachycardia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Cardiac failure congestive				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Nervous system disorders				
Somnolence				
subjects affected / exposed	10 / 197 (5.08%)			
occurrences (all)	10			
Dizziness				
subjects affected / exposed	9 / 197 (4.57%)			
occurrences (all)	9			
Headache				
subjects affected / exposed	15 / 197 (7.61%)			
occurrences (all)	15			
Ataxia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Balance disorder				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Aphasia				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Convulsion				
subjects affected / exposed	5 / 197 (2.54%)			
occurrences (all)	5			
Tremor				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Dysarthria				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Memory impairment				

subjects affected / exposed	3 / 197 (1.52%)			
occurrences (all)	3			
Sedation				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Cerebellar syndrome				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Agitation				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Hypoaesthesia				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Slow speech				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Amnesia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Insomnia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Coordination abnormal				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Disorientation				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Disturbance in attention				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Dyskinesia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Essential tremor				

subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Migraine				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Grand mal convulsion				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Hypoaesthesia oral				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Loss of consciousness				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Mental impairment				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Gait disturbance				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Psychomotor hyperactivity				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Psychomotor skills impaired				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Sleep terror				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Speech disorder				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Vertigo				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Seizure cluste				

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Restless legs syndrome			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Dementia Alzheimer''s type			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Initial insomnia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Postictal state			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Radicular pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Delayed sleep phase			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Slow response to stimuli			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		

Splenomegaly subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Anaemia subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Ear pain subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Tinnitus subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Eye disorders Nystagmus subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Diplopia subjects affected / exposed occurrences (all)	2 / 197 (1.02%) 2		
Vision blurred subjects affected / exposed occurrences (all)	2 / 197 (1.02%) 2		
Eye swelling subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Eye pruritus subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Photophobia			

subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Eye allergy			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Blepharospasm			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Ocular dysmetria			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	8 / 197 (4.06%)		
occurrences (all)	8		
Diarrhoea			
subjects affected / exposed	5 / 197 (2.54%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	5 / 197 (2.54%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	3 / 197 (1.52%)		
occurrences (all)	3		

Abdominal pain				
subjects affected / exposed	3 / 197 (1.52%)			
occurrences (all)	3			
Oral pruritus				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Haematochezia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Toothache				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Dyspepsia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Gastroenteritis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Dental caries				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Disbacteriosis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Abdominal distension				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Abdominal pain upper				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			

Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Bowel movement irregularity subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Gastritis subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Gingivitis subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Paraesthesia oral subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Epigastric discomfort subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Oesophagitis subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Retching subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Hepatobiliary disorders Hepatic steatosis subjects affected / exposed occurrences (all)	1 / 197 (0.51%) 1		
Cholecystitis chronic subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash macular subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		
Rash pruritic			

subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Skin lesion				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Skin irritation				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Skin hypopigmentation				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Rash maculo-papular				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Pain of skin				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Acne				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Pruritus				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Alopecia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Rash				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Dermatitis contact				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Swelling face				

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Dysuria			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Micturition urgency			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Urinary incontinence			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Menstruation irregular			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Adrenal cyst			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Gynaecomastia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	3		
Musculoskeletal stiffness			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Muscle fatigue			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Joint swelling			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypertonia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Exostosis			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	2		
Neck pain			

subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Musculoskeletal pain				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Muscle spasms				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Back pain				
subjects affected / exposed	2 / 197 (1.02%)			
occurrences (all)	2			
Sensation of heaviness				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Arthritis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Spinal pain				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Sciatica				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Osteochondrosis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Muscular weakness				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Intervertebral disc protrusion				

subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Contusion			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Localised infection			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	9 / 197 (4.57%)		
occurrences (all)	9		
Upper respiratory tract infection			
subjects affected / exposed	3 / 197 (1.52%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	2 / 197 (1.02%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 197 (1.02%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	3 / 197 (1.52%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	2 / 197 (1.02%)		
occurrences (all)	2		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		

Corneal infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Cystitis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Ear infection				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Gastroenteritis viral				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Infected bites				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Rash pustular				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Respiratory tract infection viral				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	1 / 197 (0.51%)			
occurrences (all)	1			
Rotavirus infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Sinusitis bacterial				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			

Tooth infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Viral infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Fungal infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Gastrointestinal viral infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Laryngitis				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Impetigo				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Oral herpes				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Tonsillitis bacterial				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			
Tooth abscess				
subjects affected / exposed	0 / 197 (0.00%)			
occurrences (all)	0			

Viral diarrhoea			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 197 (1.02%)		
occurrences (all)	2		
Hypercholesterolaemia			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Thirst			
subjects affected / exposed	1 / 197 (0.51%)		
occurrences (all)	1		
Vitamin D deficiency			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Increased appetite			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypochloraemia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	0 / 197 (0.00%)		
occurrences (all)	0		
Hypokalaemia			

subjects affected / exposed occurrences (all)	0 / 197 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2013	Inclusion criterion 6.e was added: "Perampanel: The use of perampanel was allowed provided that the subject had been maintained on a stable dose of perampanel for ≥ 3 months and had not experienced any serious psychiatric and behavioral reactions such as hostility- or aggression related adverse reactions. Section 9.4.10 (Background antiepileptic drug [AED] Medications) was modified state that perampanel was permitted as a concomitant medication only if the subject had been on a stable dose for at least 3 months prior to screening and had not experienced any serious psychiatric and behavioral reactions, and was expected to remain on a constant dose through the double-blind phase of the study. An exclusion criterion was added (#12) and existing exclusion criteria #12 through #24 were re-numbered one number higher. The new exclusion criterion was: "Current use of ezogabine (retigabine; Potiga®; Trobalt®) was not permitted. Subjects who may have used this agent in the past were to have been off this medication for at least 3 months prior to screening and were to have had a documented normal fundoscopic examination by an ophthalmologist. Section 9.4.10 (Background AED Medications) was modified state that current use of ezogabine (retigabine) was not permitted, and that subjects who may have used this agent in the past were to have been off this medication for at least 3 months prior to screening and were to have had a documented normal fundoscopic exam by an ophthalmologist. Exclusion criterion #16 (history of drug abuse) was re-numbered to #17 and revised as follows: "The subject had a positive urine drug screen at screening or met criteria for current or historical Substance Use Disorder (Diagnostic and Statistical Manual of Mental Disorders [DSM]-V criteria) within the past 5 years. As with other AEDs, the use of alcohol was not advised.
10 March 2014	The original treatment scheme was 4 weeks of prospective baseline plus 63 weeks of treatment: 1 week of titration, 4 weeks at 1200 milligrams per day (mg/day), 4 weeks at 1800 mg/day for the double-blind phase, 1-week transition to open-label, and 51 weeks at 1800 mg/day for the open-label phase. Treatment was then de-escalated over 2 weeks. A second treatment scheme was added and called 'Cohort 2,' as follows: 4 weeks of prospective baseline plus 68 weeks of treatment: 2 weeks of titration, 12 weeks at 1800 mg/day for the double-blind phase, 2 weeks of transition to open-label, and 50 weeks at 1800 mg/day for the open-label phase. Treatment was then de-escalated over 2 weeks. The protocol was revised in other sections as appropriate to support the addition of the second treatment scheme (i.e., Cohort 2), as follows: A new secondary objective was added: "To evaluate serum levels of ganaxolone at 1200 mg/day and 1800 mg/day after chronic dosing."; The planned sample size was increased from 150 subjects to 200 subjects, with approximately 50 subjects being enrolled into Cohort 1 and 150 subjects being enrolled into Cohort 2. Randomization remained at 1:1 ganaxolone or placebo in both cohorts; A schedule of events was added for Cohort 2; The primary efficacy endpoint was the change from baseline in 28-day seizure frequency during the double-blind phase for subjects in Cohort 2; A graphic illustration of the study design for Cohort 2 was added; A table showing the dosing schedule for Cohort 2 was added. Inclusion criterion #5 and exclusion criterion #9 were clarified. Randomization was modified to be stratified by country. The Per Protocol (PP) population was re-defined to require that subjects receive at least 12 weeks of treatment, rather than 9 weeks, without major protocol violations. The analysis method for the primary efficacy variable was revised from an ANCOVA with treatment and pooled countries as factors to an ANCOVA with treatment and country as factors.

23 September 2014	The planned sample size for Cohort 2 was increased from 150 subjects to 292 subjects. The time period for determination of the baseline seizure frequency was modified from a 4-week retrospective period plus a 4-week prospective period to an 8-week prospective period. The number of study sites was increased from 30 to 55 (both approximately), and the estimate of the time required for enrollment of study subjects was increased from 20 months to 26 months. Inclusion criterion #5 and exclusion criterion #6 were clarified. Section 9.4.11 (Excluded Prior and Concomitant Medications) was modified to add that treatment with the 5-α-reductase inhibitor finasteride may not be initiated during the study because it affects endogenous levels of allopregnanolone, which could affect seizure frequency.
08 April 2016	The planned sample size for Cohort 1 was decreased from 50 subjects to 46 subjects. The planned sample size for Cohort 2 was increased from 292 subjects to 359 subjects. Instead of the single primary efficacy endpoint of percent change from baseline in 28-day seizure frequency, two co-primary efficacy endpoints were defined because of the difference in registration requirements in the US and the EU. The original primary endpoint was unchanged, and was to be used to support a US submission, and a second co-primary endpoint of 50% responder rate during the Maintenance Period was added to support an EU submission. This change was made throughout the study protocol. In addition to the second co-primary efficacy endpoint, three key secondary efficacy endpoints were identified, and a fixed sequence analysis procedure was established to protect the familywise error rate at 0.05. These endpoints were: 50% responder rate during the Titration + Maintenance Period (Cohort 2), change from baseline in the number of seizure-free days per 28-day period during the Titration + Maintenance Period (Cohort 2), and CGI-I at Week 14 of the double-blind phase (Cohort 2). It was stated that all remaining secondary efficacy endpoints would be tested at an alpha of 0.05 and that those p-values would be nominal. Exploratory efficacy endpoints of weekly seizure frequency for each week after randomization during the double-blind phase in Cohort 2 and 28-day seizure frequency for each 4-week period in the open-label phase of the study were added. For inclusion criterion #6, it was added that AEDs could be adjusted during the open-label phase of the study. A criterion for withdrawal from the study (liver function test abnormalities) was added to Section 9.3.4.1 of the study protocol. Specific values of liver function test elevations had to be met to fulfill this criterion, and these were defined in the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: