Clinical trial results:
Randomized, Double-Blind, Placebo-controlled, Parallel Group, Multi-center Trial of Pregabalin as Adjunctive Therapy in Pediatric and Adult Subjects With Primary Generalized Tonic-clonic Seizures (PGTC) - PROTOCOL A0081105

Summary

EudraCT number	2010-023263-18
Trial protocol	CZ GB HU LT NL SK AT BG ES PL EE GR BE HR DK PT DE
Global end of trial date	20 February 2019

Results information

Result version number	v1 (current)
This version publication date	24 August 2019
First version publication date	24 August 2019

Trial information

Trial identification

Sponsor protocol code	A0081105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01747915
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 February 2019

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate superior efficacy of pregabalin compared to placebo for treatment of PGTC seizures as measured by the 28 day seizure rate.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

Subjects were required to be taking 1-3 antiepileptic drugs (AEDs) to participate.

Evidence for comparator: -

Actual start date of recruitment	03 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Ukraine: 68
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belarus: 1
Country: Number of subjects enrolled	Bosnia and Herzegovina: 6
Country: Number of subjects enrolled	Bulgaria: 32
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	India: 9
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Montenegro: 1
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Serbia: 3
Worldwide total number of subjects	219
EEA total number of subjects	82

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)	36
Adolescents (12-17 years)	34
Adults (18-64 years)	149
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted at multiple sites in 21 countries in 219 subjects between 03 April 2013 and 20 February 2019.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day

Arm description:

Subjects aged less than (<) 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight greater than or equal to (>=)30 kg: Pregabalin 5 milligram per kilogram per day (mg/kg/day) as capsule or oral solution (using oral solution of strength 20 milligram per milliliter [mg/mL]), up to a maximum of 300 milligram per day (mg/day); 2) body weight <30 kg: pregabalin 7 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 300 mg/day. Subjects aged >=17 years received Pregabalin 300 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution, Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day, orally twice daily in equally divided doses for 12 weeks.

Arm title	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day

Arm description:

Subjects aged < 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight >=30 kg: Pregabalin 10 mg/kg/day as capsule or oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day; 2) body weight <30 kg: pregabalin 14 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day. Subjects aged >=17 years received Pregabalin 600 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day, orally twice daily in equally divided doses for 12 weeks.

Arm title	Placebo

Arm description:

Subjects aged <17 years received placebo matched to Pregabalin, orally, twice daily for the double-blind treatment phase of 12 weeks (in the form of solution for <30 kg subjects; in the form of capsule or liquid oral solution for >=30 kg subjects). Subjects aged >=17 years received placebo matched to Pregabalin, in the form of capsule or liquid oral solution, orally, twice daily for the double-blind treatment phase of 12 weeks.

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

Dosage and administration details:

Subjects received placebo matching pregabalin orally twice daily for 12 weeks.

Number of subjects in period 1	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo
Started	75	72	72
Completed	60	61	66
Not completed	15	11	6
Protocol deviation	1	-	-
Lack of efficacy	-	1	-
Pregnancy	-	-	1
Adverse event, serious fatal	-	-	1
Adverse event, non-fatal	8	5	2
Consent withdrawn by subject	4	4	1
Unspecified	1	1	1
Lost to follow-up	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day

Reporting group description:

Subjects aged less than (<) 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight greater than or equal to (>=)30 kg: Pregabalin 5 milligram per kilogram per day (mg/kg/day) as capsule or oral solution (using oral solution of strength 20 milligram per milliliter [mg/mL]), up to a maximum of 300 milligram per day (mg/day); 2) body weight <30 kg: pregabalin 7 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 300 mg/day. Subjects aged >=17 years received Pregabalin 300 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day

Reporting group description:

Subjects aged < 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight >=30 kg: Pregabalin 10 mg/kg/day as capsule or oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day; 2) body weight <30 kg: pregabalin 14 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day. Subjects aged >=17 years received Pregabalin 600 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects aged <17 years received placebo matched to Pregabalin, orally, twice daily for the double-blind treatment phase of 12 weeks (in the form of solution for <30 kg subjects; in the form of capsule or liquid oral solution for >=30 kg subjects). Subjects aged >=17 years received placebo matched to Pregabalin, in the form of capsule or liquid oral solution, orally, twice daily for the double-blind treatment phase of 12 weeks.

Reporting group values	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo
Number of subjects	75	72	72
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	13	12	11
Adolescents (12-17 years)	14	11	9
Adults (18-64 years)	48	49	52
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	24.0	25.4	26.2
standard deviation	± 13.3	± 12.7	± 13.2
Sex: Female, Male Units: Subjects			
Female	42	39	40

Male	33	33	32

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	8	8	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	67	64	65
More than one race	0	0	1

Reporting group values	Total		
Number of subjects	219		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	36		
Adolescents (12-17 years)	34		
Adults (18-64 years)	149		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	121		
Male	98		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	22		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	196		
More than one race	1		

End points

End points reporting groups

Reporting group title	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day

Reporting group description:

Subjects aged less than (<) 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight greater than or equal to (>=)30 kg: Pregabalin 5 milligram per kilogram per day (mg/kg/day) as capsule or oral solution (using oral solution of strength 20 milligram per milliliter [mg/mL]), up to a maximum of 300 milligram per day (mg/day); 2) body weight <30 kg: pregabalin 7 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 300 mg/day. Subjects aged >=17 years received Pregabalin 300 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day

Reporting group description:

Subjects aged < 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight >=30 kg: Pregabalin 10 mg/kg/day as capsule or oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day; 2) body weight <30 kg: pregabalin 14 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day. Subjects aged >=17 years received Pregabalin 600 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects aged <17 years received placebo matched to Pregabalin, orally, twice daily for the double-blind treatment phase of 12 weeks (in the form of solution for <30 kg subjects; in the form of capsule or liquid oral solution for >=30 kg subjects). Subjects aged >=17 years received placebo matched to Pregabalin, in the form of capsule or liquid oral solution, orally, twice daily for the double-blind treatment phase of 12 weeks.

Primary: Log-transformed 28-day Seizure Rate for all Primary Generalized Tonic-Clonic (PGTC) Seizures During 12-Week Double-Blind Treatment Phase

End point title	Log-transformed 28-day Seizure Rate for all Primary Generalized Tonic-Clonic (PGTC) Seizures During 12-Week Double-Blind Treatment Phase

End point description:

All PGTC seizures experienced during treatment phase were recorded by the subjects or their parents/legal guardian in a daily seizure diary. 28-day seizure rate for all PGTC seizures= ([number of seizures in the double blind treatment phase] divided by [number of days in double blind treatment phase minus {–} number of missing diary days in treatment phase])*28. For log-transformation, the quantity 1 was added to the 28-day seizure rate for all subjects to account for any possible "0" seizure incidence. This resulted in final calculation as: log transformed (28-day seizure rate +1). Intent to treat (ITT) population included all randomized subjects who took at least 1 dose of investigational product during the double-blind treatment phase, have a baseline value and at least 1 post-baseline efficacy assessment.

End point type	Primary

End point timeframe:

Day 1 up to Week 12

End point values	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	72	72	
Units: Seizure per 28 days				
least squares mean (standard error)	1.17 (± 0.097)	1.13 (± 0.095)	1.14 (± 0.098)	

Statistical analyses

Statistical analysis title	Pregabalin 5 mg/kg/day vs Placebo
Statistical analysis description:	
Estimates and p-values from an ANCOVA model including fixed effects for log transformed baseline value, region, age strata, and treatment group.	
Comparison groups	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8121
Method	ANCOVA
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.19
Variability estimate	Standard error of the mean
Dispersion value	0.088

Statistical analysis title	Pregabalin 10 mg/kg/day Vs Placebo
Statistical analysis description:	
Estimates and p-values from an ANCOVA model including fixed effects for log transformed baseline value, region, age strata, and treatment group.	
Comparison groups	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8889
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19

upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.088

Secondary: Percentage of Subjects With at Least 50 Percent (%) or Greater Reduction From Baseline in 28-day Primary Generalized Tonic-clonic (PGTC) Seizure Rate During the 12-Week Double-blind Treatment Phase

End point title	Percentage of Subjects With at Least 50 Percent (%) or Greater Reduction From Baseline in 28-day Primary Generalized Tonic-clonic (PGTC) Seizure Rate During the 12-Week Double-blind Treatment Phase

End point description:

Percentage of subjects with 50% or greater reduction from baseline in 28-day seizure rate during the 12 week double blind treatment phase were reported. 28-day seizure rate for all PGTC seizures= ([number of seizures in the double blind treatment phase] divided by [number of days in double blind treatment phase minus {–} number of missing diary days in treatment phase])*28. ITT population included all randomized subjects who took at least 1 dose of investigational product during the double-blind treatment phase, have a baseline value and at least 1 post-baseline efficacy assessment.

End point type	Secondary

End point timeframe:

Day 1 up to Week 12

End point values	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	72	72	
Units: percentage of subjects				
number (not applicable)	41.3	38.9	41.7	

Statistical analyses

Statistical analysis title	Pregabalin 5 mg/kg/day Vs Placebo
Comparison groups	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day v Placebo
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7973 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	2.186

Notes:

[1] - P-values were from a Logistic Regression Model including fixed effects for region, age strata and treatment.

Statistical analysis title	Pregabalin 10 mg/kg/day Vs Placebo
Comparison groups	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8474 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.934
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.465
upper limit	1.877

Notes:

[2] - P-values were from a Logistic Regression Model including fixed effects for region, age strata and treatment

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to end of study (Week 13)

Adverse event reporting additional description:

Same event may appear as adverse event (AE) and serious AE, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day

Reporting group description:

Subjects aged less than (<) 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight greater than or equal to (>=)30 kg: Pregabalin 5 milligram per kilogram per day (mg/kg/day) as capsule or oral solution (using oral solution of strength 20 milligram per milliliter [mg/mL]), up to a maximum of 300 milligram per day (mg/day); 2) body weight <30 kg: pregabalin 7 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 300 mg/day. Subjects aged >=17 years received Pregabalin 300 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day

Reporting group description:

Subjects aged < 17 years received Pregabalin, orally, twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks in following manner: 1) body weight >=30 kg: Pregabalin 10 mg/kg/day as capsule or oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day; 2) body weight <30 kg: pregabalin 14 mg/kg/day as oral solution (using oral solution of strength 20 mg/mL), up to a maximum of 600 mg/day. Subjects aged >=17 years received Pregabalin 600 mg/day, capsule or oral solution, orally twice daily in equally divided doses, for the double-blind treatment phase of 12 weeks.

Reporting group title	Placebo

Reporting group description:

Subjects aged <17 years received placebo matched to Pregabalin, orally, twice daily for the double-blind treatment phase of 12 weeks (in the form of solution for <30 kg subjects; in the form of capsule or liquid oral solution for >=30 kg subjects). Subjects aged >=17 years received placebo matched to Pregabalin, in the form of capsule or liquid oral solution, orally, twice daily for the double-blind treatment phase of 12 weeks.

Serious adverse events	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 75 (2.67%)	2 / 72 (2.78%)	3 / 72 (4.17%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	0 / 72 (0.00%)

occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden unexplained death in epilepsy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Pregabalin 5 mg/kg/day or 7 mg/kg/day or 300 mg/day	Pregabalin 10 mg/kg/day or 14 mg/kg/day or 600 mg/day	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 75 (52.00%)	41 / 72 (56.94%)	36 / 72 (50.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Thrombosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	5 / 75 (6.67%)	3 / 72 (4.17%)	3 / 72 (4.17%)
occurrences (all)	7	3	3
Influenza like illness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	2 / 72 (2.78%)
occurrences (all)	1	0	2
Sluggishness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Therapeutic response unexpected			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Anxiety			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	1	0
Anxiety disorder			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Apathy			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Bradyphrenia			
subjects affected / exposed	0 / 75 (0.00%)	2 / 72 (2.78%)	0 / 72 (0.00%)
occurrences (all)	0	2	0
Confusional state			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)

occurrences (all)	0	1	0
Enuresis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Epileptic psychosis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	2 / 75 (2.67%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	2	0	0
Mood swings			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Soliloquy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Suicidal ideation			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Thinking abnormal			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Cervical polyp			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Dysmenorrhoea			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Menstruation irregular			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1

Vaginal discharge			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	2	0
Face injury			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	3 / 72 (4.17%)
occurrences (all)	1	2	3
Foot fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Head injury			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Joint dislocation			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Periorbital haematoma			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Skin injury			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Skin laceration			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Soft tissue injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)

occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood glucose increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Blood pressure increased			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	2	0
Platelet count increased			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Weight increased			
subjects affected / exposed	1 / 75 (1.33%)	7 / 72 (9.72%)	0 / 72 (0.00%)
occurrences (all)	1	8	0
Lymphocyte morphology abnormal			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Eosinophilia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Disturbance in attention			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	13 / 75 (17.33%)	12 / 72 (16.67%)	5 / 72 (6.94%)
occurrences (all)	13	14	5
Dysgraphia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Epilepsy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Head titubation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	7 / 75 (9.33%)	11 / 72 (15.28%)	12 / 72 (16.67%)
occurrences (all)	23	16	22
Hypoaesthesia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Hypokinesia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)

occurrences (all)	0	1	0
Memory impairment			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Myoclonic epilepsy			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	2	0
Nystagmus			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Petit mal epilepsy			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Poor quality sleep			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Sedation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	1	0
Somnolence			
subjects affected / exposed	5 / 75 (6.67%)	11 / 72 (15.28%)	7 / 72 (9.72%)
occurrences (all)	6	12	8
Tremor			
subjects affected / exposed	0 / 75 (0.00%)	2 / 72 (2.78%)	1 / 72 (1.39%)
occurrences (all)	0	2	1
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	1 / 72 (1.39%)
occurrences (all)	1	1	1
Eye disorder			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Eye irritation			

subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	1	1	0
Visual impairment			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	3 / 75 (4.00%)	2 / 72 (2.78%)	1 / 72 (1.39%)
occurrences (all)	4	2	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Dental caries			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)	1 / 72 (1.39%)	1 / 72 (1.39%)
occurrences (all)	1	1	1
Dry mouth			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)

occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 75 (2.67%)	2 / 72 (2.78%)	1 / 72 (1.39%)
occurrences (all)	2	2	1
Salivary hypersecretion			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	1 / 72 (1.39%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Leukocyturia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Proteinuria			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 75 (2.67%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	3	0	0
Metatarsalgia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Muscular weakness			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Back Pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Increased appetite			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	3 / 72 (4.17%)
occurrences (all)	0	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Diarrhoea infectious			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1

Influenza			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 75 (1.33%)	2 / 72 (2.78%)	1 / 72 (1.39%)
occurrences (all)	1	2	1
Otitis media acute			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 75 (5.33%)	2 / 72 (2.78%)	4 / 72 (5.56%)
occurrences (all)	4	2	4
Urinary tract infection			
subjects affected / exposed	2 / 75 (2.67%)	0 / 72 (0.00%)	0 / 72 (0.00%)
occurrences (all)	2	0	0
Varicella zoster virus infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 72 (0.00%)	1 / 72 (1.39%)
occurrences (all)	0	0	1
Viral rhinitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 72 (1.39%)	0 / 72 (0.00%)
occurrences (all)	0	1	0

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 75 (1.33%) 1	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported