Clinical trial results:
A multi-center, uncontrolled, open-label, evaluation of Lamotrigine monotherapy on newly diagnosed typical absence seizures in children and adolescents

Summary

EudraCT number	2017-001514-29
Trial protocol	Outside EU/EEA
Global end of trial date	20 November 2015

Results information

Result version number	v1 (current)
This version publication date	20 October 2017
First version publication date	20 October 2017

Trial information

Trial identification

Sponsor protocol code	115377

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	10 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of lamotrigine monotherapy orally administered once daily in children and adolescent patients with newly diagnosed typical absence seizures in Japan and South Korea.

Protection of trial subjects:
Not applicable
Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	29 September 2011
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	Japan: 16
Country: Number of subjects enrolled	Korea, Republic of: 4
Worldwide total number of subjects	20
EEA total number of subjects	0

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)	19
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with newly diagnosed and untreated typical absence seizure; aged 2-15 years in Japan, 2-12 years in South Korea at the time of obtaining consent; weighing at least 7 kilograms (kg); without partial seizure or generalized seizures other than typical absence; and without a history of rash associated with other treatment were enrolled.

Pre-assignment

Screening details:

The study consisted of an Escalation Phase (EP), a 12-week (W) Maintenance Phase (MP), a >=2-week Taper Phase, and post-study examination within 1-4 weeks after the last dose of lamotrigine. Participants could have entered the Extension Phase (ExP) until approval for this indication or until 24 months after the Last Subject Last Visit in the MP.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Lamotrigine

Arm description:

In the EP, lamotrigine 0.3 milligrams per kilogram per day (mg/kg/day) was administered orally once daily from Week W1 to W2, and 0.6 mg/kg/day from W3 to W4. From W5, the dose was escalated by 0.6 mg/kg/day once every 1 or 2 weeks, up to a maximum of 10.2 mg/kg/day or 400 mg/day, whichever was less (WWL), until a seizure-free (SF) status was confirmed by hyperventilation (HV)-clinical signs. After a SF confirmation, the dose was increased by one level and HV-electroencephalography was assessed twice at the same dose level to confirm the SF status. In the MP, the same dose was continued for 12 weeks. An increase/decrease in dose (0.6 mg/kg/day at >=1-week intervals) was allowed within the range of 1.2 to 10.2 mg/kg/day or 400 mg/day, WWL. In the ExP, doses of 1.2 to 10.2 mg/kg/day or 400 mg/day (WWL) were administered based on seizure status/safety. If a dose <1.2 mg/kg/day or >10.2 mg/kg/day or 400 mg/day (WWL) was necessary, the participant was withdrawn from the study.

Arm type	Experimental
Investigational medicinal product name	Lamotrigine 2 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

White chewable dispersible tablet containing Lamotrigine 2 mg was administered once daily in the evening.

Investigational medicinal product name	Lamotrigine 5 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

White chewable dispersible tablet containing Lamotrigine 5 mg was administered once daily in the evening.

Investigational medicinal product name	Lamotrigine 25 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

White chewable dispersible tablet containing Lamotrigine 25 mg was administered once daily in the evening.

Investigational medicinal product name	Lamotrigine 100 mg tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

White chewable dispersible tablet containing Lamotrigine 100 mg was administered once daily in the evening.

Number of subjects in period 1	Lamotrigine
Started	20
Completed	6
Not completed	14
Physician decision	1
Consent withdrawn by subject	1
Met Protocol-defined Stopping Criteria	4
Adverse event, non-fatal	6
Lack of efficacy	2

Baseline characteristics

Reporting groups	
Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 0.3 milligrams per kilogram per day (mg/kg/day) was administered orally once daily from Week W1 to W2, and 0.6 mg/kg/day from W3 to W4. From W5, the dose was escalated by 0.6 mg/kg/day once every 1 or 2 weeks, up to a maximum of 10.2 mg/kg/day or 400 mg/day, whichever was less (WWL), until a seizure-free (SF) status was confirmed by hyperventilation (HV)-clinical signs. After a SF confirmation, the dose was increased by one level and HV-electroencephalography was assessed twice at the same dose level to confirm the SF status. In the MP, the same dose was continued for 12 weeks. An increase/decrease in dose (0.6 mg/kg/day at >=1-week intervals) was allowed within the range of 1.2 to 10.2 mg/kg/day or 400 mg/day, WWL. In the ExP, doses of 1.2 to 10.2 mg/kg/day or 400 mg/day (WWL) were administered based on seizure status/safety. If a dose <1.2 mg/kg/day or >10.2 mg/kg/day or 400 mg/day (WWL) was necessary, the participant was withdrawn from the study.

Reporting group values	Lamotrigine	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Age continuous			
Age continuous description			
Units: years			
arithmetic mean	7.7		
standard deviation	± 1.95	-	
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	13	13	
Male	7	7	
Race/Ethnicity, Customized Units: Subjects			
East Asian Heritage	3	3	
Japanese Heritage	16	16	
South East Asian Heritage	1	1	

End points

End points reporting groups

Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 0.3 milligrams per kilogram per day (mg/kg/day) was administered orally once daily from Week W1 to W2, and 0.6 mg/kg/day from W3 to W4. From W5, the dose was escalated by 0.6 mg/kg/day once every 1 or 2 weeks, up to a maximum of 10.2 mg/kg/day or 400 mg/day, whichever was less (WWL), until a seizure-free (SF) status was confirmed by hyperventilation (HV)-clinical signs. After a SF confirmation, the dose was increased by one level and HV-electroencephalography was assessed twice at the same dose level to confirm the SF status. In the MP, the same dose was continued for 12 weeks. An increase/decrease in dose (0.6 mg/kg/day at >=1-week intervals) was allowed within the range of 1.2 to 10.2 mg/kg/day or 400 mg/day, WWL. In the ExP, doses of 1.2 to 10.2 mg/kg/day or 400 mg/day (WWL) were administered based on seizure status/safety. If a dose <1.2 mg/kg/day or >10.2 mg/kg/day or 400 mg/day (WWL) was necessary, the participant was withdrawn from the study.

Primary: Number of participants who were seizure free as confirmed by hyperventilation (HV)-electroencephalography (EEG) at the end of the Maintenance Phase (MP)

End point title	Number of participants who were seizure free as confirmed by hyperventilation (HV)-electroencephalography (EEG) at the end of the Maintenance Phase (MP)[1]

End point description:

EEG is a diagnostic test for epilepsy. The EEG machine records the brain's electrical activity as a series of waveforms. HV is an activation technique used to provoke seizures during an EEG recording. An approximately 30-minute EEG with HV was performed on participants in a supine position. In the HV test, participants breathed through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes using a pin-wheel provided to them. The estimated value reflects the percentage of participants who were seizure free.
Full Analysis Set (FAS): all participants who took at least one dose of investigational product and contributed data to at
least one efficacy measure after the first dosing of investigational product

End point type	Primary

End point timeframe:

Week 12 of the Maintenance Phase (up to Study Week 50)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical Analyses for one arm studies can not be entered into the system.

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[2]			
Units: Participants	7			

Notes:

[2] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were seizure free as confirmed by HV-EEG at two consecutive visits in the Escalation Phase (EP)

End point title	Number of participants who were seizure free as confirmed by HV-EEG at two consecutive visits in the Escalation Phase (EP)

End point description:

EEG is a diagnostic test for epilepsy. The EEG machine records the brain's electrical activity as a series of waveforms. HV is an activation technique used to provoke seizures during an EEG recording. An approximately 30-minute EEG with HV was performed on participants in a supine position. In the HV test, participants breathed through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes using a pin-wheel provided to them.

End point type	Secondary

End point timeframe:

Up to Study Week 49

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[3]			
Units: Participants	8			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were seizure free as confirmed by HV-clinical signs at each dose during the Escalation Phase

End point title	Number of participants who were seizure free as confirmed by HV-clinical signs at each dose during the Escalation Phase

End point description:

HV is an activation technique used to provoke seizures. Participants were instructed to breathe through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes while sitting using a pin-wheel and were observed for clinical signs of seizures like impairment of consciousness; staring; eye enrollment; eye blinking; chewing movements; hand movement; other automatisms; atonic, tonic, clonic components; autonomic components; or any other signs. During the Escalation Phase, HV-clinical signs were assessed to confirm a status of seizure free. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

Up to Study Week 49

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[4]			
Units: Participants				
0.6 mg/kg, n=17	1			
1.2 mg/kg, n=17	1			
1.8 mg/kg, n=16	2			
2.4 mg/kg, n=16	2			
3.0 mg/kg, n=16	2			

3.6 mg/kg, n=15	1			
4.2 mg/kg, n=15	0			
4.8 mg/kg, n=14	4			
5.4 mg/kg, n=14	1			
6.0 mg/kg, n=11	1			
6.6 mg/kg, n=11	0			
7.2 mg/kg, n=9	3			
7.8 mg/kg, n=9	0			
8.4 mg/kg, n=6	2			
9.0 mg/kg, n=6	1			
9.6 mg/kg, n=1	1			

Notes:

[4] - FAS. Only those participants given the indicated dose of investigational product were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were seizure free as confirmed by HV-clinical signs during Week 4 and Week 8 of the Maintenance Phase

End point title	Number of participants who were seizure free as confirmed by HV-clinical signs during Week 4 and Week 8 of the Maintenance Phase

End point description:

HV is an activation technique used to provoke seizures. Participants were instructed to breathe through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes while sitting using a pin-wheel and were observed for clinical signs of seizures like impairment of consciousness; staring; eye enrollment; eye blinking; chewing movements; hand movement; other automatisms; atonic, tonic, clonic components; autonomic components; or any other signs. During the Maintenace Phase, HV-clinical signs were assessed at Visit 1 (Week 4) and Visit 2 (Week 4).
FAS. Only those participants who were dosed with investigational product at the indicated time points were analyzed.

End point type	Secondary

End point timeframe:

Week 4 and Week 8 of the Maintenance Phase (up to Study Weeks 42 and 46, respectively)

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	7[5]			
Units: Participants				
Week 4	7			
Week 8	7			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were seizure free as confirmed by HV-EEG

at each assessment point in the Extension Phase (ExP)

End point title	Number of participants who were seizure free as confirmed by HV-EEG at each assessment point in the Extension Phase (ExP)

End point description:

EEG is a diagnostic test for epilepsy. The EEG machine records the brain's electrical activity as a series of waveforms. HV is an activation technique used to provoke seizures during an EEG recording. An approximately 30-minute EEG with HV was performed on participants in a supine position. In the HV test, participants breathed through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes using a pin-wheel provided to them. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

Extension Week 12 (Extension Visit 1 [Ext-V1]), every 24 weeks after Ext-V1 and until withdrawal

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[6]			
Units: Participants				
Extension Week 12, n=7	6			
Extension Week 36, n=7	5			
Extension Week 60, n=7	6			
Extension Week 84, n=6	6			
Extension Week 108, n=6	6			
Extension Week 132, n=6	6			
Extension Week 156, n=2	2			

Notes:

[6] - FAS. Only those participants given the indicated dose of investigational product were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who were seizure free as confirmed by HV-clinical signs at each assessment point in the Extension Phase (ExP)

End point title	Number of participants who were seizure free as confirmed by HV-clinical signs at each assessment point in the Extension Phase (ExP)

End point description:

HV is an activation technique used to provoke seizures. Participants were instructed to breathe through their mouths deeply and rapidly (at a rate of approximately 20-25 breaths/minute) for 4 continuous minutes while sitting using a pin-wheel and were observed for clinical signs of seizures like impairment of consciousness; staring; eye enrollment; eye blinking; chewing movements; hand movement; other automatisms; atonic, tonic, clonic components; autonomic components; or any other signs. During the ExP, HV-clinical signs were assessed to confirm a status of seizure free. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title).

End point type	Secondary

End point timeframe:

Extension Week 24 (Extension Visit 2 [Ext-V2], every 24 weeks after the Ext-V2 and until withdrawal

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[7]			
Units: Participants				
Extension Week 24, n=7	5			
Extension Week 48, n=7	6			
Extension Week 72, n=7	5			
Extension Week 96, n=6	6			
Extension Week 120, n=6	5			
Extension Week 144, n=4	2			
Extension Week 168, n=1	1			

Notes:

[7] - FAS. Only those participants given the indicated dose of investigational product were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with seizure episodes per week in the main study phase (Fixed Escalation Phase [FEP], Escalation Phase [EP], Maintenance Phase [MP]), and FEP+EP+MP)

End point title	Number of days with seizure episodes per week in the main study phase (Fixed Escalation Phase [FEP], Escalation Phase [EP], Maintenance Phase [MP]), and FEP+EP+MP)

End point description:

Participants were asked to record the seizure codes, seizure duration, and their physical condition in a diary provided. Only participants data available at the analysis time point were analyzed (represented as n=X, X, X in category title)

End point type	Secondary

End point timeframe:

Up to Study Week 50

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	20[8]			
Units: Days				
arithmetic mean (standard deviation)				
Fixed Escalation Phase, n=20	4.93 (± 1.488)			
Escalation Phase, n=17	2.60 (± 2.060)			
Maintenance Phase, n=8	0.06 (± 0.161)			
FEP+EP+MP, n=20	2.98 (± 1.976)			

Notes:

[8] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with seizure episodes per week in the Extension Phase

(ExP) Overall

End point title	Number of days with seizure episodes per week in the Extension Phase (ExP) Overall

End point description:

Participants were asked to record the seizure codes, seizure duration, and their physical condition in a diary provided.

End point type	Secondary

End point timeframe:

Extension Week 12 (Extension Visit 1 [Ext-V1], every 12 week after Ext-V1 and until withdrawal

End point values	Lamotrigine			
Subject group type	Reporting group			
Number of subjects analysed	7[9]			
Units: Days				
arithmetic mean (standard deviation)	0.03 (± 0.048)			

Notes:

[9] - FAS. Only those participants given the indicated dose of investigational product were analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs were collected from study medication start until the end of treatment (up to Study Week 50) (EP, MP, and ExP).

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in members of the Safety Population, comprised of all participants who had taken at least one dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Lamotrigine

Reporting group description:

In the EP, lamotrigine 0.3 mg/kg/day was administered orally once daily from W1 to W2, and 0.6 mg/kg/day from W3 to W4. From W5, the dose was escalated by 0.6 mg/kg/day once every 1 or 2 weeks, up to a maximum of 10.2 mg/kg/day or 400 mg/day, WWL, until a SF status was confirmed by HV-clinical signs. After a SF confirmation, the dose was increased by one level and HV-electroencephalography was assessed twice at the same dose level to confirm the SF status. In the MP, the same dose was continued for 12 weeks. An increase/decrease in dose (0.6 mg/kg/day at >=1-week intervals) was allowed within the range of 1.2 to 10.2 mg/kg/day or 400 mg/day, WWL. In the ExP, doses of 1.2 to 10.2 mg/kg/day or 400 mg/day (WWL) were administered based on seizure status/safety. If a dose <1.2 mg/kg/day or >10.2 mg/kg/day or 400 mg/day (WWL) was necessary, the participant was withdrawn from the study.

Serious adverse events	Lamotrigine		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Lamotrigine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 20 (85.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	3		
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Skin papilloma subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 2		
Injury, poisoning and procedural complications Fracture subjects affected / exposed occurrences (all) Arthropod bite subjects affected / exposed occurrences (all) Arthropod sting subjects affected / exposed occurrences (all) Chillblains subjects affected / exposed occurrences (all) Skin abrasion subjects affected / exposed occurrences (all) Hand fracture subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 3 / 20 (15.00%) 3 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Psychomotor hyperactivity subjects affected / exposed occurrences (all) Febrile convulsion subjects affected / exposed occurrences (all)	 4 / 20 (20.00%) 4 1 / 20 (5.00%) 1 1 / 20 (5.00%) 2		
General disorders and administration			

site conditions Pain subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Gastrointestinal disorders Stomatitis subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Enteritis subjects affected / exposed occurrences (all) Enterocolitis subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 5 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Epistaxis	 1 / 20 (5.00%) 3		

subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Drug eruption subjects affected / exposed occurrences (all) Dermatitis atopic subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 6 / 20 (30.00%) 7 2 / 20 (10.00%) 2 1 / 20 (5.00%) 1 2 / 20 (10.00%) 4 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 1 / 20 (5.00%) 2		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all) Hematuria subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 2 1 / 20 (5.00%) 1		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis	 5 / 20 (25.00%) 10		

subjects affected / exposed	7 / 20 (35.00%)			
occurrences (all)	48			
Upper respiratory tract infection				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	4			
Cellulitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Gastroenteritis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	7			
Paronychia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Scarlet fever				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Varicella				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Adenovirus infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Otitis media acute				

subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 2 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 2 / 20 (10.00%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 November 2011	To change Sponsor's representative; To change PGx contact information; To correct typos and error
09 April 2012	To change Study Director; To change the corporate name and the responsible person of emergency contact information (Japan only); To change the necessity of Hyperventilation electroencephalography (HV-EEG) test on withdrawal visit during the escalation Phase.
18 February 2013	To change Study Director; By reorganization of sponsor; By modification to sponsor information (Japan only); To correct typos and errors (Japan)
03 July 2014	To change Study Administrative Structure (Japan only)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported