



Clinical trial results:

Open-label, 2-dose level trial to evaluate pharmacokinetics, safety and tolerability of eslicarbazepine acetate (ESL) as adjunctive therapy in infants with refractory epilepsy with partial-onset seizures aged from 1 month to <2 years – 1-YEAR EXTENSION

Summary

EudraCT number	2016-001072-29
Trial protocol	CZ PT IT HR RO
Global end of trial date	11 May 2021

Results information

Result version number	v1 (current)
This version publication date	20 March 2022
First version publication date	20 March 2022
Summary attachment (see zip file)	CSR (bia-2093-211 Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	BIA-2093-211/EXT
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	BIAL - Portela & CA, S.A.
Sponsor organisation address	À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457
Public contact	André Garrido, BIAL - Portela & Cª, S.A., 00351 229866100, andre.garrido@bial.com
Scientific contact	Joana Moreira, BIAL - Portela & Cª, S.A., 00351 229866100, joana.moreira@bial.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	12 October 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2021
Global end of trial reached?	Yes
Global end of trial date	11 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of 1 year of adjunctive treatment with eslicarbazepine acetate (ESL) in the defined patient population and to perform exploratory analyses of efficacy. No primary or secondary objectives were defined for this study. Instead, all objectives were used to collect long-term data and were evaluated descriptively

Protection of trial subjects:

This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice, including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Ukraine: 11
Worldwide total number of subjects	23
EEA total number of subjects	3

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)	23
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All 23 subjects who completed the BIA-2093-211 study continued in the BIA-2093-211/EXT study.

Pre-assignment

Screening details:

All 23 subjects were screened in BIA-2093-211 study before enrolled in BIA-2093-211/EXT study. There was no separate screening done in the BIA-2093-211/EXT study.

Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	23

Period 1

Period 1 title	Open-label ESL extension (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Overall - Group ≤ 20 mg/kg/day

Arm description:

Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was ≤ 20 mg/kg/day. In Down-titration Period (1 step of 5 days), Dose (QD) was reduced by half.

Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	BIA 2093
Other name	Zebinix
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was ≤ 20 mg/kg/day. In Down-titration Period (1 step of 5 days), Dose (QD) was reduced by half.

Arm title	Overall - Group > 20 - ≤ 25 mg/kg/day
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Arm description:

Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was > 20 - ≤ 25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.

Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	BIA 2093
Other name	Zebinix
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was > 20 - ≤ 25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.

Arm title	Overall - Group >25 mg/kg/day
Arm description: Age ≥1 to <24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was >25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.	
Arm type	Experimental
Investigational medicinal product name	Eslicarbazepine acetate
Investigational medicinal product code	BIA 2093
Other name	Zebinix
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Age ≥1 to <24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was >25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.

Number of subjects in period 1	Overall - Group ≤20 mg/kg/day	Overall - Group >20 - ≤25 mg/kg/day	Overall - Group >25 mg/kg/day
Started	12	7	4
Completed	9	5	4
Not completed	3	2	0
Consent withdrawn by subject	2	1	-
Adverse event, serious non-fatal	-	1	-
Violation of an inclusion/exclusion criterion	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Overall - Group ≤ 20 mg/kg/day
Reporting group description:	
Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was ≤ 20 mg/kg/day. In Down-titration Period (1 step of 5 days), Dose (QD) was reduced by half.	
Reporting group title	Overall - Group $> 20 - \leq 25$ mg/kg/day
Reporting group description:	
Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was $> 20 - \leq 25$ mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.	
Reporting group title	Overall - Group > 25 mg/kg/day
Reporting group description:	
Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was > 25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.	

Reporting group values	Overall - Group ≤ 20 mg/kg/day	Overall - Group $> 20 - \leq 25$ mg/kg/day	Overall - Group > 25 mg/kg/day
Number of subjects	12	7	4
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	0
Preterm newborn- gestational age < 37 wk	0	0	0
Newborns (0-27days)	0	0	0
Infants and toddlers (28days – 23months)	12	7	4
Children (2-11 years)	0	0	0
Adolescents (12-17 year)	0	0	0
From 18 - 64 years	0	0	0
From 65 – 84 years	0	0	0
Over 85 years	0	0	0
Age Continuous			
Age Continuous Characteristic			
Units: Months			
arithmetic mean	8	14	16
standard deviation	± 6.32	± 8.64	± 5.35
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	7	3	1
Male	5	4	3

Reporting group values	Total		
Number of subjects	23		
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			

In Utero	0		
Preterm newborn- gestational age < 37 wk	0		
Newborns (0-27days)	0		
Infants and toddlers (28days – 23months)	23		
Children (2-11 years)	0		
Adolescents (12-17 year)	0		
From 18 - 64 years	0		
From 65 – 84 years	0		
Over 85 years	0		
Age Continuous			
Age Continuous Characteristic			
Units: Months			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	11		
Male	12		

End points

End points reporting groups

Reporting group title	Overall - Group ≤ 20 mg/kg/day
Reporting group description: Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was ≤ 20 mg/kg/day. In Down-titration Period (1 step of 5 days), Dose (QD) was reduced by half.	
Reporting group title	Overall - Group > 20 - ≤ 25 mg/kg/day
Reporting group description: Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was > 20 - ≤ 25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.	
Reporting group title	Overall - Group > 25 mg/kg/day
Reporting group description: Age ≥ 1 to < 24 months. Subjects who received at least 1 dose of investigational medicinal product, Dose in Treatment Period was > 25 mg/kg/day. In Down-titration Period (2 steps of 5 days), Dose (QD) was reduced by half at each step.	
Subject analysis set title	Overall - Group ≤ 20 mg/kg/day x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least 1 dose of IMP. Treatment for each subject was to begin on Day 1, which was Day 6 of Study BIA-2093-211 and continue for 1 year.	
Subject analysis set title	Overall - Group > 20 - ≤ 25 mg/kg/day x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least 1 dose of IMP. Treatment for each subject was to begin on Day 1, which was Day 6 of Study BIA-2093-211 and continue for 1 year.	
Subject analysis set title	Overall - Group > 25 mg/kg/day x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description: All subjects who received at least 1 dose of IMP. Treatment for each subject was to begin on Day 1, which was Day 6 of Study BIA-2093-211 and continue for 1 year.	

Primary: Number of subjects with at least one TAE

End point title	Number of subjects with at least one TAE ^[1]
End point description: Absolute number of subjects with at least one Treatment-emergent Adverse Event (Safety Set)	
End point type	Primary
End point timeframe: overall	

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: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
TAE	11	7	2	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one serious TAE

End point title	Number of subjects with at least one serious TAE ^[2]
End point description:	
Absolute number of subjects with at least one serious	Treatment-emergent Adverse Event (Safety Set)
End point type	Primary
End point timeframe:	
overall	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
Serious TAE	3	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one related TAE

End point title	Number of subjects with at least one related TAE ^[3]
End point description:	
Absolute number of subjects with at least one related	Treatment-emergent Adverse Event (Safety Set)
End point type	Primary
End point timeframe:	
overall	

Notes:

[3] - 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: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
Related TAE	2	3	1	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one severe TAE

End point title	Number of subjects with at least one severe TAE ^[4]
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End point description:

Absolute number of subjects with at least one severe Treatment-emergent Adverse Event (Safety Set)

End point type	Primary
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End point timeframe:

overall

Notes:

[4] - 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: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
Severe TAE	2	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one TAE leading to discontinuation of IMP

End point title	Number of subjects with at least one TAE leading to
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End point description:

Absolute number of subjects with at least one Treatment-emergent Adverse Event leading to discontinuation of IMP (Safety Set)

End point type Primary

End point timeframe:

overall

Notes:

[5] - 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: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
TAE leading to discontinuation of IMP	0	1	0	

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with at least one TAE leading to death

End point title Number of subjects with at least one TAE leading to death^[6]

End point description:

Absolute number of subjects with at least one Treatment-emergent Adverse Event leading to death (Safety Set)

End point type Primary

End point timeframe:

overall

Notes:

[6] - 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: This is the a safety and tolerability study with no primary efficacy endpoint. Instead, all objectives were used to collect long-term data and were evaluated descriptively. Primary endpoints were added for upload due to EudraCT technical reasons

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
TAE leading to death	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Seizure-free subjects at Baseline (Safety Set)

End point title	Number of Seizure-free subjects at Baseline (Safety Set)
End point description: Absolute number of Seizure-free subjects at Baseline (Safety Set)	
End point type	Secondary
End point timeframe: at baseline	

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
seizure-free	2	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Seizure-free subjects in Treatment Period (Safety Set)

End point title	Number of Seizure-free subjects in Treatment Period (Safety Set)
End point description: Absolute number of Seizure-free subjects in Treatment Period (Safety Set)	
End point type	Secondary
End point timeframe: 1 year	

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	7	4	
Units: Participants				
number (not applicable)				
seizure-free	1	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Seizure-free subjects in Down-titration Period (Safety Set)

End point title	Number of Seizure-free subjects in Down-titration Period (Safety Set)
End point description: Absolute number of Seizure-free subjects in Down-titration Period (Safety Set)	
End point type	Secondary
End point timeframe: 5 days after treatment period if ≤20 mg/kg/day, 10 days after treatment period else	

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	11	7	4	
Units: Participants				
number (not applicable)				
seizure-free	6	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Seizure-free subjects in Follow-up Period (Safety Set)

End point title	Number of Seizure-free subjects in Follow-up Period (Safety Set)
End point description: Absolute number of Seizure-free subjects in Follow-up Period (Safety Set)	
End point type	Secondary
End point timeframe: 4 weeks after downtitration	

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	7	4	
Units: Participants				
number (not applicable)				
seizure-free	5	1	0	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Standardised Seizure Frequency Change (Safety Set)

End point title	Standardised Seizure Frequency Change (Safety Set)
End point description:	
Standardised Seizure Frequency - Relative change from baseline in Treatment Period (%)	
End point type	Other pre-specified
End point timeframe:	
1 year	

End point values	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	10	6	4	
Units: [%]				
median (geometric coefficient of variation)				
seizure frequency change	-86.01 (± -124.96)	-75.91 (± -57.18)	-12.68 (± 446.139000000)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE with onset or worsening after the first IMP intake during BIA-2093-211 until 4 weeks after the last IMP intake during BIA-2093-211/EXT

Adverse event reporting additional description:

AE with onset or worsening after the first IMP intake during BIA-2093-211 until 4 weeks after the last IMP intake during BIA-2093-211/EXT.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Overall - Group ≤20 mg/kg/day x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with ESL

Reporting group title	Overall - Group >25 mg/kg/day x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with ESL

Reporting group title	Overall - Group >20 - ≤25 mg/kg/day x Safety Set
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Reporting group description:

Subjects in the Safety Set treated with ESL

Serious adverse events	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma, low grade			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Exposure to toxic agent			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Akathisia	subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile convulsion	subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
	occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure	subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	1 / 7 (14.29%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations				
Laryngitis	subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection	subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Overall - Group ≤20 mg/kg/day x Safety Set	Overall - Group >25 mg/kg/day x Safety Set	Overall - Group >20 - ≤25 mg/kg/day x Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	2 / 4 (50.00%)	7 / 7 (100.00%)
Surgical and medical procedures			
Cleft palate repair			
	subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	1
Ear tube insertion			
	subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	1

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Adenoidal hypertrophy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vasomotor rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 4 (25.00%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood glucose increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Electrocardiogram PR prolongation			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Neutrophil count decreased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 4 (25.00%) 1	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications Overdose subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Tachycardia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Nervous system disorders Change in seizure presentation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Epilepsy subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Infantile spasms subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Intellectual disability subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Non-24-hour sleep-wake disorder subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Seizure			

subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	4
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypochromic anaemia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Strabismus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Flatulence			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Teething			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			

Dermatitis allergic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 2
Dermatitis atopic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Dermatitis diaper subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Infections and infestations			
Adenovirus infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Bronchitis subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 6	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Exanthema subitum subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Gastrointestinal infection subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Otitis media subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	0 / 4 (0.00%) 0	0 / 7 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 6	0 / 4 (0.00%) 0	1 / 7 (14.29%) 1
Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 5	0 / 4 (0.00%) 0	1 / 7 (14.29%) 2
Respiratory tract infection viral			

subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	3 / 7 (42.86%)
occurrences (all)	0	0	7
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Subglottic laryngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	3
Viral infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Viral rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 4 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 4 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2017	<p>Local Amendment#1, Czech Republic</p> <p>This protocol amendment amends Protocol Final Version No. 2.0 (21-DEC-2016). It was prepared in order to comply with the requirements issued by the Czech State Institute for Drug Control dated 20.03.2017.</p> <ul style="list-style-type: none">• The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry. Thus, although there are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine or chemically-related compounds treatment, and the use of carbamazepine or chemically-related compounds may be considered if the benefits are thought to exceed the risks, subjects who are known to be positive for HLA-A*3101 allele are not considered eligible due to safety reasons [1,2]. A new exclusion criterion was added.• Due to safety reasons, subjects with worsening of liver function must be withdrawn from the trial.• If an overnight stay/hospitalisation is required due to the subject's study participation, one parent will have the opportunity to stay together with his/her child as required. The resulting accommodation costs will be covered by the sponsor.
14 June 2017	<p>Global Amendment</p> <p>This protocol amendment amends Protocol Final Version No. 2.0 (21-DEC-2016). It was prepared since it was decided that during the Treatment Period, on-site visits will be performed every 4 weeks after Visit 2. The visits will be performed to adequately follow up the safety of the subjects and if necessary to adjust the volume of ESL suspension according to the subject's body weight. Safety laboratory tests will be performed at each visit during the Treatment Period.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported