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

Summary

EudraCT number	2012-001091-11
Trial protocol	CZ PT IT HR RO
Global end of trial date	03 April 2020

Results information

Result version number	v1 (current)
This version publication date	28 January 2021
First version publication date	28 January 2021
Summary attachment (see zip file)	Synopsis (bia-2093-211.pdf)

Trial information

Trial identification

Sponsor protocol code	BIA-2093-211

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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000696-PIP02-10
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	11 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 April 2020
Global end of trial reached?	Yes
Global end of trial date	03 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary: To evaluate the steady state pharmacokinetic (PK) profile of ESL.
Secondary: To assess the safety and tolerability of ESL in the defined patient population at the doses used and to perform exploratory analyses of efficacy.

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	19 April 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:

The patient recruitment period lasted approximately 66 months. The actual overall study duration or patient recruitment period may vary.

Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 23 subjects were enrolled to the trial and 1 subject experienced an SAE of status epilepticus during the Screening Period that led to study discontinuation (recorded as a screen failure).

Pre-assignment period milestones

Number of subjects started	23
Number of subjects completed	23

Period 1

Period 1 title	Overall (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 1 - Age Cohort A

Arm description:

Age ≥1 to <6 months
Subjects in Group 1 Age cohort A had 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5).

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

Dosage and administration details:

After a Screening Period of up to 3 weeks, Group 1 began treatment. For Age cohort A, there was no titration and subjects were treated with 5 mg/kg once daily (QD) for 5 days in a 6-day Evaluation Period.

Arm title	Overall - Group 1 - Age Cohort B

Arm description:

Age ≥6 to <24 months
Subjects in Group 1 Age cohort B had up to 15 days of treatment: a 5-day Up-titration Period (from Visit 1a through Visit 1e [Day -5 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a 5-day Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.

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

Dosage and administration details:

After a Screening Period of up to 3 weeks, Group 1 began treatment. For Age cohort B, subjects had a 5-day Up-titration Period at 5 mg/kg QD before increasing to 10 mg/kg QD for the Evaluation Period and a 5-day Down-titration Period if subjects did not continue in the extension study or discontinued the study early.

Arm title	Overall - Group 2 - Age Cohort A

Arm description:

Age ≥1 to <6 months
Subjects in Group 2 Age cohort A had up to 20 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a one 5-day step Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.

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

Dosage and administration details:

After a Screening Period of up to 3 weeks, subjects in Group 2 began a 5-day Up-titration Period at 5 mg/kg QD, followed by a second 5-day Up-titration Period at 12.5 mg/kg QD, before proceeding to the evaluation dose at 20 mg/kg QD for 5 days in a 6-day Evaluation Period. If subjects did not continue in the subsequent extension study or discontinued the study early, down-titration was to occur as follows: one 5-day down-titration step at 12.5 mg/kg QD.

Arm title	Overall - Group 2 - Age Cohort B

Arm description:

Age ≥6 to <24 months
Subjects in Group 2 Age cohort B had up to 25 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a Down-titration Period in two 5-day steps (Day 6 through Day 15) if subjects did not continue in the extension study.

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

Dosage and administration details:

After a Screening Period of up to 3 weeks, subjects in Group 2 began a 5-day Up-titration Period at 5 mg/kg QD, followed by a second 5-day Up-titration Period at 12.5 mg/kg QD, before proceeding to the evaluation dose at 20 mg/kg QD for 5 days in a 6-day Evaluation Period. If subjects did not continue in the subsequent extension study or discontinued the study early, down-titration was to occur as follows: two 5-day down-titration steps, starting at 12.5 mg/kg QD followed by 5 mg/kg QD.

Number of subjects in period 1	Overall - Group 1 - Age Cohort A	Overall - Group 1 - Age Cohort B	Overall - Group 2 - Age Cohort A
Started	4	10	4
Completed	4	10	4

Number of subjects in period 1	Overall - Group 2 - Age Cohort B

Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall - Group 1 - Age Cohort A
Reporting group description:	
Age ≥1 to <6 months Subjects in Group 1 Age cohort A had 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5).	
Reporting group title	Overall - Group 1 - Age Cohort B
Reporting group description:	
Age ≥6 to <24 months Subjects in Group 1 Age cohort B had up to 15 days of treatment: a 5-day Up-titration Period (from Visit 1a through Visit 1e [Day -5 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a 5-day Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.	
Reporting group title	Overall - Group 2 - Age Cohort A
Reporting group description:	
Age ≥1 to <6 months Subjects in Group 2 Age cohort A had up to 20 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a one 5-day step Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.	
Reporting group title	Overall - Group 2 - Age Cohort B
Reporting group description:	
Age ≥6 to <24 months Subjects in Group 2 Age cohort B had up to 25 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a Down-titration Period in two 5-day steps (Day 6 through Day 15) if subjects did not continue in the extension study.	

Reporting group values	Overall - Group 1 - Age Cohort A	Overall - Group 1 - Age Cohort B	Overall - Group 2 - Age Cohort A
Number of subjects	4	10	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)	4	10	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	3.8	14.7	3.8
standard deviation	± 0.5	± 6.75	± 1.5

Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	2	5	3
Male	2	5	1

Reporting group values	Overall - Group 2 - Age Cohort B	Total	
Number of subjects	5	23	
Age Categorical			
Age Categorical Characteristic			
Units: Subjects			
In Utero	0	0	
Preterm newborn- gestational age < 37 wk	0	0	
Newborns (0-27days)	0	0	
Infants and toddlers (28days – 23months)	5	23	
Children (2-11 years)	0	0	
Adolescents (12-17 year)	0	0	
From 18 - 64 years	0	0	
From 65 – 84 years	0	0	
Over 85 years	0	0	
Age Continuous			
Age Continuous Characteristic			
Units: Months			
arithmetic mean	16.2		
standard deviation	± 5.81	-	
Gender Categorical			
Gender Categorical Characteristic			
Units: Subjects			
Female	2	12	
Male	3	11	

End points

End points reporting groups

Reporting group title	Overall - Group 1 - Age Cohort A
Reporting group description:	
Age ≥1 to <6 months Subjects in Group 1 Age cohort A had 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5).	
Reporting group title	Overall - Group 1 - Age Cohort B
Reporting group description:	
Age ≥6 to <24 months Subjects in Group 1 Age cohort B had up to 15 days of treatment: a 5-day Up-titration Period (from Visit 1a through Visit 1e [Day -5 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a 5-day Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.	
Reporting group title	Overall - Group 2 - Age Cohort A
Reporting group description:	
Age ≥1 to <6 months Subjects in Group 2 Age cohort A had up to 20 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a one 5-day step Down-titration Period (Day 6 through Day 10) if subjects did not continue in the extension study.	
Reporting group title	Overall - Group 2 - Age Cohort B
Reporting group description:	
Age ≥6 to <24 months Subjects in Group 2 Age cohort B had up to 25 days of treatment: an Up-titration Period in two 5-day steps (from Visit 1a through Visit 1j [Day -10 through Day -1]), 5 days of treatment during a 6-day Evaluation Period (Day 1 through Day 5), and a Down-titration Period in two 5-day steps (Day 6 through Day 15) if subjects did not continue in the extension study.	
Subject analysis set title	Group 1 - Age Cohort A x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of IMP	
Subject analysis set title	Group 1 - Age Cohort B x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of IMP	
Subject analysis set title	Group 2 - Age Cohort A x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of IMP	
Subject analysis set title	Group 2 - Age Cohort B x Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All subjects who received at least 1 dose of IMP	
Subject analysis set title	Group 1 - Age Cohort A x PK Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The pharmacokinetics set is defined as all safety set subjects that had adequate eslicarbazepine plasma concentration data	
Subject analysis set title	Group 1 - Age Cohort B x PK Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The pharmacokinetics set is defined as all safety set subjects that had adequate eslicarbazepine plasma	

concentration data

Subject analysis set title	Group 2 - Age Cohort A x PK Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The pharmacokinetics set is defined as all safety set subjects that had adequate eslicarbazepine plasma concentration data

Subject analysis set title	Group 2 - Age Cohort B x PK Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The pharmacokinetics set is defined as all safety set subjects that had adequate eslicarbazepine plasma concentration data

Primary: Steady state PK profile of ESL - Cmax

End point title	Steady state PK profile of ESL - Cmax[1]

End point description:

Cmax, derived by non-compartmental analysis from the plasma drug concentration versus time profiles

End point type	Primary

End point timeframe:

6 day Evaluation Period

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	10	3	5
Units: [ng/mL]				
geometric mean (geometric coefficient of variation)				
Cmax	3960 (± 63.1)	10400 (± 43)	10800 (± 92.1)	19800 (± 8.39)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - Cmax/dose

End point title	Steady state PK profile of ESL - Cmax/dose[2]

End point description:

Dose-normalised Cmax, derived by non-compartmental analysis from the plasma drug concentration versus time profiles

End point type	Primary

End point timeframe:

6 day Evaluation Period

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	10	3	5
Units: [ng/mL]/[mg/kg]				
geometric mean (geometric coefficient of variation)				
Cmax/dose	792 (± 63.1)	1040 (± 43)	542 (± 92.1)	992 (± 8.39)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - tmax

End point title	Steady state PK profile of ESL - tmax[3]
End point description:	
tmax, derived by non-compartmental analysis from the plasma drug concentration versus time profiles	
End point type	Primary
End point timeframe:	
6 day Evaluation Period	

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	10	3	5
Units: [h]				
median (full range (min-max))				
tmax	2.25 (0.5 to 3.0)	2.25 (0.5 to 4.5)	1.5 (0.5 to 3.0)	2 (0.5 to 6.0)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - AUC_T

End point title	Steady state PK profile of ESL - AUC_T[4]
End point description:	
AUC_T, derived by non-compartmental analysis from the plasma drug concentration versus time profiles	
End point type	Primary
End point timeframe:	
6 day Evaluation Period	

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	9	3	5
Units: [h*ng/mL]				
geometric mean (geometric coefficient of variation)				
AUCT	42100 (± 65.2)	122000 (± 62.8)	128000 (± 117)	229000 (± 23.1)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - AUCT/dose

End point title	Steady state PK profile of ESL - AUCT/dose[5]

End point description:

Dose-normalised AUCT, derived by non-compartmental analysis from the plasma drug concentration versus time profiles

End point type	Primary

End point timeframe:

6 day Evaluation Period

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	9	3	5
Units: [h*ng/mL]/[mg(kg]				
geometric mean (geometric coefficient of variation)				
AUCT/dose	8430 (± 65.2)	12200 (± 62.8)	6410 (± 117)	11500 (± 23.1)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - t1/2

End point title	Steady state PK profile of ESL - t1/2[6]

End point description:

t1/2, derived by non-compartmental analysis from the plasma drug concentration versus time profiles

End point type	Primary

End point timeframe:

6 day Evaluation Period

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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	7	3	4
Units: [h]				
geometric mean (geometric coefficient of variation)				
t1/2	6.36 (± 29.7)	7.25 (± 24.7)	7.37 (± 29.7)	6.98 (± 20.4)

Statistical analyses

No statistical analyses for this end point

Primary: Steady state PK profile of ESL - CL/F

End point title	Steady state PK profile of ESL - CL/F[7]

End point description:

CL/F, derived by non-compartmental analysis from the plasma drug concentration versus time profiles

End point type	Primary

End point timeframe:

6 day Evaluation Period

Notes:

[7] - 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: please refer to synopsis

End point values	Group 1 - Age Cohort A x PK Set	Group 1 - Age Cohort B x PK Set	Group 2 - Age Cohort A x PK Set	Group 2 - Age Cohort B x PK Set
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	4	9	3	5
Units: [mL/h/kg]				
geometric mean (geometric coefficient of variation)				
CL/F	119 (± 65.2)	82 (± 62.8)	156 (± 117)	87.2 (± 23.1)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent until the date of the EOT visit/EDV.

Adverse event reporting additional description:

From informed consent until EOT visit/EDV. This period was extended to follow-up on all ongoing AEs after the EOT visit/EDV until the AE was finally resolved or it was medically justifiable to stop further follow up (e.g. a chronic condition is reached). In case of death, AE(s) that were ongoing and did not cause death could be left ongoing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Group 1 - Age Cohort A x Safety Set

Reporting group description:

Subjects in the Safety Set treated with ESL

Reporting group title	Group 1 - Age Cohort B x Safety Set

Reporting group description:

Subjects in the Safety Set treated with ESL

Reporting group title	Group 2 - Age Cohort A x Safety Set

Reporting group description:

Subjects in the Safety Set treated with ESL

Reporting group title	Group 2 - Age Cohort B x Safety Set

Reporting group description:

Subjects in the Safety Set treated with ESL

Serious adverse events	Group 1 - Age Cohort A x Safety Set	Group 1 - Age Cohort B x Safety Set	Group 2 - Age Cohort A x Safety Set
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Group 2 - Age Cohort B x Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Group 1 - Age Cohort A x Safety Set	Group 1 - Age Cohort B x Safety Set	Group 2 - Age Cohort A x Safety Set
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	3 / 10 (30.00%)	2 / 4 (50.00%)
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 4 (0.00%)	2 / 10 (20.00%)	1 / 4 (25.00%)
occurrences (all)	0	3	1
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			

subjects affected / exposed	0 / 4 (0.00%)	1 / 10 (10.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Non-serious adverse events	Group 2 - Age Cohort B x Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)		
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Electrocardiogram PR prolongation			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Bronchitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0		
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2017	Local Amendment#1, Czech Republic 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. • 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 chemicallyrelated 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported