Clinical trial results:
A Multicentre, Randomized, Double-blind, Placebo Controlled, Parallel-group Study in Children With Inadequately Controlled Partial Onset Seizures to Investigate Efficacy, Safety and Tolerability of TRI476 (Oxcarbazepine) as Adjunctive Therapy

Summary

EudraCT number	2015-004484-37
Trial protocol	Outside EU/EEA
Global end of trial date	17 October 2012

Results information

Result version number	v1 (current)
This version publication date	27 December 2016
First version publication date	27 December 2016

Trial information

Trial identification

Sponsor protocol code	CTRI476B1301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00975715
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals AG, +41 613241111,

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	17 October 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 October 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is is to demonstrate the superiority of TRI476 oral suspension over placebo based on the percent reduction in partial onset seizure frequency at Week 8 in pediatric epileptic patients with partial onset seizures refractory to other antiepileptics.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2009
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: 99
Worldwide total number of subjects	99
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)	69
Adolescents (12-17 years)	30
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of 3 phases: an 8-week screening phase, an 8-week double-blind phase (a 2-week titration phase, a 6-week maintenance phase), and a 3- to 5-week follow-up phase.

Period 1

Period 1 title	Titration Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	TRI476

Arm description:

Participants received TRI476 based on body weight with titration up to the maintenance dose, in addition to their traditional antiepileptics dosage.

Arm type	Experimental
Investigational medicinal product name	TRI476
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

TRI476 oral suspension doses, based on body weight twice daily.

Investigational medicinal product name	Benzodiazepines
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Benzodiazepines could be used as needed as rescue medication during the duration of the study.

Arm title	Placebo

Arm description:

Participants received placebo to TRI476 without any adjustment to the dosing regimen, in addition to their traditional antiepileptics dosage.

Arm type	Placebo
Investigational medicinal product name	Placebo to TRI476
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo oral suspension, taken twice daily.

Investigational medicinal product name	Benzodiazepines
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Benzodiazepines could be used as needed as rescue medication during the duration of the study.

Number of subjects in period 1	TRI476	Placebo
Started	48	51
Completed	41	51
Not completed	7	0
Protocol violation	1	-
Adverse event, non-fatal	6	-

Period 2

Period 2 title	Maintenance Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	TRI476

Arm description:

Participants received TRI476 based on body weight with titration up to the maintenance dose, in addition to their traditional antiepileptics dosage.

Arm type	Experimental
Investigational medicinal product name	TRI476
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

TRI476 oral suspension doses, based on body weight twice daily.

Investigational medicinal product name	Benzodiazepines
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Benzodiazepines could be used as needed as rescue medication during the duration of the study.

Arm title	Placebo

Arm description:

Participants received placebo to TRI476 without any adjustment to the dosing regimen, in addition to their traditional antiepileptics dosage.

Arm type	Placebo
Investigational medicinal product name	Placebo to TRI476
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Placebo oral suspension, taken twice daily.

Investigational medicinal product name	Benzodiazepines
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Benzodiazepines could be used as needed as rescue medication during the duration of the study.

Number of subjects in period 2	TRI476	Placebo
Started	41	51
Completed	39	50
Not completed	2	1
Adverse event, non-fatal	2	1

Baseline characteristics

Reporting groups	
Reporting group title	TRI476

Reporting group description:

Participants received TRI476 based on body weight with titration up to the maintenance dose, in addition to their traditional antiepileptics dosage.

Reporting group title	Placebo

Reporting group description:

Participants received placebo to TRI476 without any adjustment to the dosing regimen, in addition to their traditional antiepileptics dosage.

Reporting group values	TRI476	Placebo	Total
Number of subjects	48	51	99
Age categorical Units: Subjects			
Children (2-11 years)	31	38	69
Adolescents (12-17 years)	17	13	30
Age continuous Units: years			
arithmetic mean	9.8	9.2	
standard deviation	± 2.91	± 2.83	-
Gender categorical Units: Subjects			
Female	22	24	46
Male	26	27	53

End points

End points reporting groups

Reporting group title	TRI476

Reporting group description:

Participants received TRI476 based on body weight with titration up to the maintenance dose, in addition to their traditional antiepileptics dosage.

Reporting group title	Placebo

Reporting group description:

Participants received placebo to TRI476 without any adjustment to the dosing regimen, in addition to their traditional antiepileptics dosage.

Reporting group title	TRI476

Reporting group description:

Participants received TRI476 based on body weight with titration up to the maintenance dose, in addition to their traditional antiepileptics dosage.

Reporting group title	Placebo

Reporting group description:

Participants received placebo to TRI476 without any adjustment to the dosing regimen, in addition to their traditional antiepileptics dosage.

Primary: Percent Change in Partial Onset Seizure Frequency Per 28 Days From Baseline to the Double-blind Phase, by Treatment Group

End point title	Percent Change in Partial Onset Seizure Frequency Per 28 Days From Baseline to the Double-blind Phase, by Treatment Group[1]

End point description:

Percent change in partial onset seizure frequency per 28 days during the double-blind phase from the screening phase, was calculated according to the following formula: "Percent change in partial onset seizure frequency per 28 days from the screening phase" = (partial onset seizure frequency per 28 days during the double-blind phase - partial onset seizure frequency per 28 days during the screening phase) / partial onset seizure frequency per 28 days during the double-blind phase x 100 "Partial onset seizure frequency per 28 days" = Number of partial onset seizures during each phase (screening phase or double-blind phase) / number of days during the screening or double-blind phase × 28.

End point type	Primary

End point timeframe:

screening and 28 days

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: No statistical analysis provided for Percent Change in Partial Onset Seizure Frequency Per 28 Days From Baseline to the Double-blind Phase, by Treatment Group.

End point values	TRI476	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[2]	51		
Units: percentage change per 28 days				
arithmetic mean (standard deviation)	-2.85 (± 63.546)	14.82 (± 73.333)		

Notes:

[2] - The Full Analysis set included all participants who received study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Partial Seizure Frequency Per 28 Days, by Study Period (Every 28 Days) and Treatment Group

End point title	Partial Seizure Frequency Per 28 Days, by Study Period (Every 28 Days) and Treatment Group

End point description:

Partial onset seizure frequency per 28 days during a period between baseline and Week 4 was measured. Partial onset seizure frequency per 28 days (count/28 days)" = Number of partial onset seizures during each phase (screening phase or double-blind phase) / Number of days during the phase x 28.

End point type	Secondary

End point timeframe:

baseline, 28 days and 56 days

End point values	TRI476	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[3]	51		
Units: seizures per 28 days				
arithmetic mean (standard deviation)				
Baseline to Week 4 (day 0 to day 28)	65.58 (± 109.457)	90.61 (± 283.187)		
Week 4 to Week 8 (day 28 to day 56)	45.4 (± 70.209)	98.73 (± 291.781)		

Notes:

[3] - The Full Analysis set included all participants who received study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Participants With Response During Double-blind Phase, by Treatment Group

End point title	Percent of Participants With Response During Double-blind Phase, by Treatment Group

End point description:

Responder rate was defined as the percent of participants with an at least 50% reduction in partial onset seizure frequency per 28 days from the screening phase.

End point type	Secondary

End point timeframe:

screening to 28 days

End point values	TRI476	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[4]	51		
Units: percentage of participants				
number (not applicable)	23.4	3.9		

Notes:

[4] - The Full Analysis set included all participants who received study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change in Partial Onset Seizure Frequency During the Double-blind Phase by Seizure Type

End point title	Percent Change in Partial Onset Seizure Frequency During the Double-blind Phase by Seizure Type

End point description:

Percent change in seizure frequency from baseline = 100 (T-B)/B, B=Seizure frequency per 28 days during baseline phase, T=Seizure frequency per 28 days during the double-blind phase. Seizure frequency per 28 days is calculated as: (seizure frequency during the double-blind phase / the number of days the seizure information were provided) x 28. Only patients with both baseline and corresponding post-baseline values are included.

End point type	Secondary

End point timeframe:

28 days

End point values	TRI476	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[5]	51		
Units: percentage change in seizure frequency				
arithmetic mean (standard deviation)				
Simple partial seizures	-9.73 (± 51.329)	-16.89 (± 45.822)		
Complex partial seizures	-6.86 (± 78.583)	30.59 (± 91.551)		
Secondarily generalized seizures	-29.54 (± 64.66)	12.11 (± 82.879)		

Notes:

[5] - Includes all participants who received study drug and had baseline and post baseline data available

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinical Global Impression of Change (CGIC) at Final Assessment, by Treatment Group

End point title	Number of Participants With Clinical Global Impression of Change (CGIC) at Final Assessment, by Treatment Group

End point description:

Clinical Global Impression of Change (CGI) is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI-C scores range from 1 (very much improved) through to 7 (very much worse).

End point type	Secondary

End point timeframe:

56 days

End point values	TRI476	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47[6]	51		
Units: participants				
number (not applicable)				
Marked improvement	9	2		
Moderate improvement	8	2		
Slight improvement	8	6		
No change	21	38		
Slight aggravation	1	3		
Moderate aggravation	0	0		
Marked aggravation	0	0		

Notes:

[6] - Included all participants who received study drug and had data available for analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	TRI476
Reporting group description:	
TRI476	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	TRI476	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	1 / 51 (1.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 47 (2.13%)	0 / 51 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	TRI476	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 47 (80.85%)	27 / 51 (52.94%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	20 / 47 (42.55%)	5 / 51 (9.80%)	
occurrences (all)	20	5	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 47 (4.26%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	2 / 47 (4.26%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Diplopia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	3 / 47 (6.38%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	2 / 47 (4.26%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Vomiting			
subjects affected / exposed	5 / 47 (10.64%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 47 (4.26%)	2 / 51 (3.92%)	
occurrences (all)	4	3	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	2 / 47 (4.26%)	1 / 51 (1.96%)	
occurrences (all)	2	1	
Eczema			
subjects affected / exposed	2 / 47 (4.26%)	2 / 51 (3.92%)	
occurrences (all)	2	2	
Rash			
subjects affected / exposed	4 / 47 (8.51%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 47 (2.13%)	2 / 51 (3.92%)	
occurrences (all)	1	2	
Influenza			
subjects affected / exposed	2 / 47 (4.26%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Nasopharyngitis			
subjects affected / exposed	5 / 47 (10.64%)	9 / 51 (17.65%)	
occurrences (all)	5	10	
Otitis media			
subjects affected / exposed	2 / 47 (4.26%)	0 / 51 (0.00%)	
occurrences (all)	2	0	

Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 47 (8.51%) 6	5 / 51 (9.80%) 6	
Metabolism and nutrition disorders Hyponatraemia subjects affected / exposed occurrences (all)	2 / 47 (4.26%) 2	0 / 51 (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