Clinical trial results:
A Multi-Center, Open-Label, Long-Term, Follow-Up Study Of The Safety And Efficacy Of Levetiracetam In Children With Partial Onset Seizures

Summary

EudraCT number	2004-000200-40
Trial protocol	CZ GB BE IT HU
Global end of trial date	24 June 2008

Results information

Result version number	v1 (current)
This version publication date	30 June 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	N01148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00152516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UCB Biosciences Inc.
Sponsor organisation address	8010 Arco Corporate Drive, Raleigh, United States, NC 27617
Public contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, clinicaltrials@ucb.com
Scientific contact	CTRRD, UCB Biosciences GmbH, +49 2173481515, clinicaltrials@ucb.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 August 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to obtain long-term descriptive safety and efficacy data in pediatric epileptic patients with partial onset seizures receiving long-term treatment with levetiracetam at individualized doses. This study in conjunction with Study N157 (NCT00150709) (UCBs other long-term, follow-up pediatric study) will be used to fulfill the requirement from the FDA written request to determine the long-term safety of levetiracetam as adjunctive therapy in the treatment of partial onset seizures in pediatric patients.

Protection of trial subjects:

Before any study procedures were initiated for any subject in this study, an IRB/IEC approved written informed consent form and assent form, where appropriate, were to be properly executed and documented.

Selection criteria for the study were specified globally in the protocol and were further clarified in country specific amendments to the protocol.

Background therapy:

Concomitant anti epileptic drugs and other medication were allowed as specified in the study protocol.

Evidence for comparator: -

Actual start date of recruitment	23 October 2004
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	South Africa: 7
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Brazil: 29
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	India: 20
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 123

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	255
EEA total number of subjects	52

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)	81
Children (2-11 years)	147
Adolescents (12-17 years)	27
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

102 sites in 17 countries participated in the study, of which 85 sites in 16 countries enrolled subjects in the study.

Pre-assignment

Screening details:

The country specific protocol amendment C2 (August 7, 2006) allowed direct enrollment from India, Australia, and New Zealand bypassing the blinded feeder studies N01009 (2004-000199-14/NCT00175890) and N01103 (2014-004396-23/NCT00105040).

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	Levetiracetam

Arm description:

Oral tablets or oral solution at 10 to 30 mg/kg/day bid for 48 weeks, or approximately 52 weeks should a subject choose to discontinue levetiracetam (LEV) at the end of the maintenance period.

Arm type	Experimental
Investigational medicinal product name	Levetiracetam
Investigational medicinal product code	IMP1
Other name	
Pharmaceutical forms	Oral solution, Tablet
Routes of administration	Oral use

Dosage and administration details:

Per protocol oral tablets or oral solution at 10 to 30 mg/kg/day bid for 48 weeks, or approximately 52 weeks should a subject choose to discontinue levetiracetam (LEV) at the end of the maintenance period.

Number of subjects in period 1	Levetiracetam
Started	255
Completed	180
Not completed	75
Other: Seizure Worsening, Seeking 2nd Opinion	1
AE, serious fatal	2
Other: Non-Compliance	2
Other: Mother Refused To Cooperate	1
Other: Underwent Surgery for Epilepsy	1
Other: Primary Care Physician's Decision	1
AE, non-serious non-fatal	10
Other: Parents Withdrew Consent	2

Consent withdrawn by subject	8
Unknown AE	1
Other: Moved Out Of State	1
Lack and Loss of Efficacy	30
Lost to follow-up	5
SAE, non-fatal	5
Protocol deviation	3
Other: Given Commercial Drug in Error	2

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam
Reporting group description:	
Oral tablets or oral solution at 10 to 30 mg/kg/day bid for 48 weeks, or approximately 52 weeks should a subject choose to discontinue levetiracetam (LEV) at the end of the maintenance period.	

Reporting group values	Levetiracetam	Total	
Number of subjects	255	255	
Age Categorical Units: Subjects			
<=18 years	255	255	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	5.28		
standard deviation	± 4.69	-	
Gender Categorical Units: Subjects			
Female	116	116	
Male	139	139	

End points

End points reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Oral tablets or oral solution at 10 to 30 mg/kg/day bid for 48 weeks, or approximately 52 weeks should a subject choose to discontinue levetiracetam (LEV) at the end of the maintenance period.

Primary: Percentage change (reduction) of partial (type I) seizure frequency per week from baseline over time during treatment period

End point title	Percentage change (reduction) of partial (type I) seizure frequency per week from baseline over time during treatment period[1]

End point description:

Positive changes from Baseline indicate an improvement (i.e., a reduction) in seizure frequency per week.

End point type	Primary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

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 formal statistical hypothesis testing was planned for this study. Results were summarized in tables as descriptive statistics only.

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	247			
Units: Percent reduction in seizures Per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion	51.06 (-10.7 to 91.59)			
Maintenance	68.87 (-3.6 to 96.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change (reduction) of total (type I, II, III) seizure frequency per week from baseline over time during treatment period

End point title	Percentage change (reduction) of total (type I, II, III) seizure frequency per week from baseline over time during treatment period

End point description:

Positive changes from Baseline indicate an improvement (i.e., a reduction) in seizure frequency per week.

End point type	Secondary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	248			
Units: Percent Reduction in Seizures per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion Period Maintenance Period	47.44 (-21.18 to 88.7) 66.02 (-3.98 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial (type I) seizure frequency per week over time during treatment period

End point title	Partial (type I) seizure frequency per week over time during treatment period

End point description:

End point type	Secondary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Seizures Per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion Period Maintenance Period	2.85 (0.23 to 26.3) 1.49 (0.07 to 17.89)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total (type I, II, III) seizure frequency per week over time during treatment period

End point title	Total (type I, II, III) seizure frequency per week over time during treatment period

End point description:

End point type	Secondary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Seizures Per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion Period	3.15 (0.25 to 31.17)			
Maintenance Period	1.91 (0.09 to 24.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change (reduction) from baseline in partial (type I) seizure frequency per week over time during treatment period

End point title	Change (reduction) from baseline in partial (type I) seizure frequency per week over time during treatment period

End point description:

Positive changes from Baseline indicate an improvement (i.e., a reduction) in seizure frequency per week.

End point type	Secondary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	250			
Units: Seizures Per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion Period	0.72 (-0.81 to 7.14)			
Maintenance Period	0.93 (-0.33 to 8.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change (reduction) from baseline in total (type I, II, III) seizure frequency per week over time during treatment period

End point title	Change (reduction) from baseline in total (type I, II, III) seizure frequency per week over time during treatment period

End point description:

Positive changes from Baseline indicate an improvement (i.e., a reduction) in seizure frequency per week.

End point type	Secondary

End point timeframe:

Up-titration/Conversion Period (2-8 weeks); Maintenance Period (2-8 weeks to 40-46 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	250			
Units: Seizures Per Week				
median (inter-quartile range (Q1-Q3))				
Up-titration/Conversion Period	0.69 (-0.89 to 7.84)			
Maintenance Period	0.93 (-0.33 to 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure (type I) Responder rate (percent) during the up-titration/conversion phase and by visit during the maintenance phase

End point title	Partial seizure (type I) Responder rate (percent) during the up-titration/conversion phase and by visit during the maintenance phase

End point description:

The responder rate is defined as the number of responders. A responder is a patient with a 50% or greater change (reduction) in partial seizure frequency per week.

Note: Rates were reported as percentages.

End point type	Secondary

End point timeframe:

Up-titration (4 weeks); Maintenance Visits 3-4 (weeks 4-14, 6-15, or 8-16); Visits 4-5 (weeks 14-24, 15-24, or 16-24); Visits 5-6 (weeks 24-36); Visits 6-7 (weeks 36-48)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	247			
Units: Percentage of Participants				
number (not applicable)				
Up-titration/Conversion (4 weeks)	50.6			
Maintenance Visits 3-4 (weeks 4-14, 6-15, or 8-16)	59.8			
Maint. Visits 4-5 (weeks 14-24, 15-24, or 16-24);	65.5			
Maintenance Visits 5-6 (weeks 24-36)	68.2			
Maintenance Visits 6-7 (weeks 36-48)	71.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure (type I) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point title	Partial seizure (type I) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point description:

For subjects with up to 24 weeks in the evaluation phase the denominator for each subject is their number of days in the evaluation phase.

End point type	Secondary

End point timeframe:

Subjects with up to 24 weeks of exposure

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Percentage of Days				
median (inter-quartile range (Q1-Q3))				
Overall	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Partial seizure (type I) Maximum Seizure Free Interval (percentage of

days belonging to a seizure free interval of 28 days or more)	
End point title	Partial seizure (type I) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point description:

For subjects with greater than 24 weeks in the evaluation phase the denominator for each subject is their number of days in the evaluation phase.

End point type	Secondary

End point timeframe:

Subjects with greater than 24 weeks of exposure

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: Percentage of days				
median (inter-quartile range (Q1-Q3))				
Overall	61.49 (0 to 94.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total seizure (type I, II, III) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)	
End point title	Total seizure (type I, II, III) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point description:

For subjects with up to 24 weeks in the evaluation phase the denominator for each subject is their number of days in the evaluation phase.

End point type	Secondary

End point timeframe:

Subjects with up to 24 weeks of exposure

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: Percentage of Days				
median (inter-quartile range (Q1-Q3))				
Overall	0 (0 to 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total seizure (type I, II, III) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point title	Total seizure (type I, II, III) Maximum Seizure Free Interval (percentage of days belonging to a seizure free interval of 28 days or more)

End point description:

For subjects with greater than 24 weeks in the evaluation phase the denominator for each subject is their number of days in the evaluation phase.

End point type	Secondary

End point timeframe:

Subjects with greater than 24 weeks of exposure

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	203			
Units: Percentage of Days				
median (inter-quartile range (Q1-Q3))				
Overall	58.41 (0 to 93.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total seizure (type I, II, III) Continuously Seizure Free during the maintenance period

End point title	Total seizure (type I, II, III) Continuously Seizure Free during the maintenance period

End point description:

The measure description is the product limit adjusted percent of subjects seizure free starting from the beginning of the maintenance period.

The up-titration period is the up to 6 week period of increasing dose prior to the maintenance period. The maintenance period is the period of stable dosing, subsquent to the up-titration period, which could last from 42 to 48 weeks.

End point type	Secondary

End point timeframe:

Greater than or equal to 24 weeks, greater than or equal to 40 weeks

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	233			
Units: Percentage of Participants				
number (not applicable)				
>= 24 Weeks	16.5			
>= 40 Weeks	14.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of subjects with each seizure type during the evaluation period

End point title	Percent of subjects with each seizure type during the evaluation period

End point description:

Type I Seizure is a partial onset Seizure (see International League Against Epilepsy definitions).

Type II Seizure is a Generalized Seizure (see International League Against Epilepsy definitions).

Type III Seizure is a Unknown Seizure Type (see International League Against Epilepsy definitions).

A subject could experience more than one seizure type.

End point type	Secondary

End point timeframe:

Evaluation period (48 weeks)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	254			
Units: Percentage of Participants				
number (not applicable)				
Type I	88.6			
Type II	12.9			
Type III	7.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Investigator Global Evaluation Scale

End point title	Investigator Global Evaluation Scale

End point description:

There are 7 categories, 3 for improvement (Marked improvement, Moderate improvement, Slight improvement), 3 for worsening (Slight worsening, Moderate worsening, Marked worsening), and 1 for no change (No change).

End point type	Secondary

End point timeframe:

End of Evaluation period (week 48 or at point of early discontinuation)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	222			
Units: Percentage of Participants				
number (not applicable)				
Improved	76.1			
No Change	15.3			
Worsened	8.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Parent/Guardian Global Evaluation Scale

End point title	Parent/Guardian Global Evaluation Scale

End point description:

There are 7 categories, 3 for improvement (Marked improvement, Moderate improvement, Slight improvement), 3 for worsening (Slight worsening, Moderate worsening, Marked worsening), and 1 for no change (No change).

End point type	Secondary

End point timeframe:

End of Evaluation period (week 48 or at point of early discontinuation)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	214			
Units: Percentage of Participants				
number (not applicable)				
Improved	75.7			
No Change	12.6			
Worsened	11.7			

Statistical analyses

No statistical analyses for this end point

Secondary: Subject (>=8 years old) Global Evaluation Scale

End point title	Subject (>=8 years old) Global Evaluation Scale

End point description:

There are 7 categories, 3 for improvement (Marked improvement, Moderate improvement, Slight improvement), 3 for worsening (Slight worsening, Moderate worsening, Marked worsening), and 1 for no change (No change).

End point type	Secondary

End point timeframe:

End of Evaluation period (week 48 or at point of early discontinuation)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Percentage of Participants				
number (not applicable)				
Improved	78.9			
No Change	15.5			
Worsened	5.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Leiter-R Associated Memory (AM) Memory Screen Composite Score Change from Baseline to Visit 5 (week 24) and Visit 7 (week 48) (4 to 16 year olds)

End point title	Leiter-R Associated Memory (AM) Memory Screen Composite Score Change from Baseline to Visit 5 (week 24) and Visit 7 (week 48) (4 to 16 year olds)

End point description:

The Leiter-R AM battery has 10 subtests. The raw scores of the subtests are converted into scaled scores. Six composite scores are constructed from the 10 subtest scaled scores. The Memory Screen is one of them. It is composed of 2 subtests the Associated Pairs and Forward Memory. The sum of the Associated Pairs and Forward Memory subtest scaled scores are converted into a Memory composite score normally distributed with a mean and standard deviation of 100 (±15). Higher scores and positive changes from baseline are better. The range of the Memory Screen composite score is 44 to 155.

End point type	Secondary

End point timeframe:

Baseline to Visit 5 (Week 24) and Visit 7 (Week 48)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	87			
Units: Score on a scale				
arithmetic mean (standard deviation)				
Visit 5 (week 24)	4.8 (± 12.6)			
Visit 7 (week 48)	4.5 (± 15.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley Scale of Infant Development (BSID) II Mental Development Index Scores Classification Shift from Baseline at Visit 5 (week 24) (1 month to < 4 year olds)

End point title	Bayley Scale of Infant Development (BSID) II Mental Development Index Scores Classification Shift from Baseline at Visit 5 (week 24) (1 month to < 4 year olds)

End point description:

This score is obtained from a total raw score which is the sum of a battery of individual questions. It is adjusted for a child's age, has an expected mean of 100 and standard deviation of 15, and can be categorized as: (1) Accelerated Performance (>= 115), (2) Within Normal Limits (85-114), (3) Mildly Delayed Performance (70-84), and (4) Significantly Delayed Performance (<=69). Changes from baseline are then further categorized where 'Improved' is any positive category change, 'Stable' is no category change, and 'Worsened' is any negative category change, from baseline.

End point type	Secondary

End point timeframe:

Visit 5 (Week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Number of subjects				
Worsened	5			
Stable	21			
Improved	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley Scale of Infant Development (BSID) II Mental Development Index Scores Classification Shift from Baseline at Visit 7 (week 48) (1 month to < 4 year olds)

End point title	Bayley Scale of Infant Development (BSID) II Mental Development Index Scores Classification Shift from Baseline at Visit 7 (week 48) (1 month to < 4 year olds)

End point description:

This score is obtained from a total raw score which is the sum of a battery of individual questions. It is adjusted for a child's age, has an expected mean of 100 and standard deviation of 15, and can be categorized as: (1) Accelerated Performance (>= 115), (2) Within Normal Limits (85-114), (3) Mildly Delayed Performance (70-84), and (4) Significantly Delayed Performance (<=69). Changes from

baseline are then further categorized where 'Improved' is any positive category change, 'Stable' is no category change, and 'Worsened' is any negative category change, from baseline.

End point type	Secondary

End point timeframe:

Visit 7 (week 48)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Number of subjects				
Worsened	7			
Stable	17			
Improved	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley Scale of Infant Development (BSID) II Psychomotor Development Index Scores Classification Shift from Baseline at Visit 5 (week 24) (1 month to < 4 year old)

End point title	Bayley Scale of Infant Development (BSID) II Psychomotor Development Index Scores Classification Shift from Baseline at Visit 5 (week 24) (1 month to < 4 year old)

End point description:

This score is obtained from a total raw score which is the sum of a battery of individual questions. It is adjusted for a child's age, has an expected mean of 100 and standard deviation of 15, and can be categorized as: (1) Accelerated Performance (>= 115), (2) Within Normal Limits (85-114), (3) Mildly Delayed Performance (70-84), and (4) Significantly Delayed Performance (<=69). Changes from baseline are then further categorized where 'Improved' is any positive category change, 'Stable' is no category change, and 'Worsened' is any negative category change, from baseline.

End point type	Secondary

End point timeframe:

Visit 5 (week 24)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	29			
Units: Number of subjects				
Worsened	1			
Stable	20			
Improved	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Bayley Scale of Infant Development (BSID) II Psychomotor Development Index Scores Classification Shift from Baseline at Visit 7 (week 48) (1 month to < 4 year old)

End point title	Bayley Scale of Infant Development (BSID) II Psychomotor Development Index Scores Classification Shift from Baseline at Visit 7 (week 48) (1 month to < 4 year old)

End point description:

This score is obtained from a total raw score which is the sum of a battery of individual questions. It is adjusted for a child's age, has an expected mean of 100 and standard deviation of 15, and can be categorized as: (1) Accelerated Performance (>= 115), (2) Within Normal Limits (85-114), (3) Mildly Delayed Performance (70-84), and (4) Significantly Delayed Performance (<=69). Changes from baseline are then further categorized where 'Improved' is any positive category change, 'Stable' is no category change, and 'Worsened' is any negative category change, from baseline.

End point type	Secondary

End point timeframe:

Visit 7 (week 48)

End point values	Levetiracetam			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Number of subjects				
Worsened	1			
Stable	15			
Improved	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 1 year

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups

Reporting group title	Levetiracetam

Reporting group description:

Oral tablets or oral solution at 10 to 30 mg/kg/day bid for 48 weeks, or approximately 52 weeks should a subject choose to discontinue levetiracetam (LEV) at the end of the maintenance period.

Serious adverse events	Levetiracetam		
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 255 (18.04%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Oesophagogastric fundoplasty			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	4 / 255 (1.57%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			

subjects affected / exposed	2 / 255 (0.78%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Choking				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive airways disorder				
subjects affected / exposed	2 / 255 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia aspiration				
subjects affected / exposed	2 / 255 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory disorder				
subjects affected / exposed	2 / 255 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 255 (0.78%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tonsillar hypertrophy				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Crying				

subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Drug toxicity			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Feeding tube complication			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	2 / 255 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumothorax traumatic			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hip dysplasia			

subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 255 (0.78%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Convulsion			
subjects affected / exposed	18 / 255 (7.06%)		
occurrences causally related to treatment / all	9 / 22		
deaths causally related to treatment / all	0 / 0		
Infantile spasms			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Status epilepticus			
subjects affected / exposed	6 / 255 (2.35%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Exanthema subitum			

subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis adenovirus				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasopharyngitis				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	6 / 255 (2.35%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection viral				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 255 (0.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				

subjects affected / exposed	2 / 255 (0.78%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	5 / 255 (1.96%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Feeding disorder of infancy or early childhood			
subjects affected / exposed	1 / 255 (0.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Levetiracetam		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 255 (80.78%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	20 / 255 (7.84%)		
occurrences (all)	24		
Convulsion			
subjects affected / exposed	17 / 255 (6.67%)		
occurrences (all)	20		
Headache			
subjects affected / exposed	31 / 255 (12.16%)		
occurrences (all)	46		
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	27 / 255 (10.59%)		
occurrences (all)	33		
Pyrexia			

subjects affected / exposed	81 / 255 (31.76%)		
occurrences (all)	131		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	18 / 255 (7.06%)		
occurrences (all)	24		
Diarrhoea			
subjects affected / exposed	34 / 255 (13.33%)		
occurrences (all)	45		
Vomiting			
subjects affected / exposed	41 / 255 (16.08%)		
occurrences (all)	62		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 255 (11.37%)		
occurrences (all)	39		
Pharyngolaryngeal pain			
subjects affected / exposed	14 / 255 (5.49%)		
occurrences (all)	20		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	24 / 255 (9.41%)		
occurrences (all)	28		
Psychiatric disorders			
Aggression			
subjects affected / exposed	15 / 255 (5.88%)		
occurrences (all)	17		
Infections and infestations			
Bronchitis			
subjects affected / exposed	16 / 255 (6.27%)		
occurrences (all)	22		
Ear infection			
subjects affected / exposed	18 / 255 (7.06%)		
occurrences (all)	29		
Influenza			

subjects affected / exposed	16 / 255 (6.27%)		
occurrences (all)	22		
Nasopharyngitis			
subjects affected / exposed	38 / 255 (14.90%)		
occurrences (all)	53		
Otitis media			
subjects affected / exposed	21 / 255 (8.24%)		
occurrences (all)	34		
Pharyngitis			
subjects affected / exposed	15 / 255 (5.88%)		
occurrences (all)	30		
Rhinitis			
subjects affected / exposed	14 / 255 (5.49%)		
occurrences (all)	20		
Upper respiratory tract infection			
subjects affected / exposed	62 / 255 (24.31%)		
occurrences (all)	105		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 255 (5.49%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2004	The primary reason for this amendment is to allow enrollment of a homogeneous patient population for testing with the Leiter-R and CBCL and to align the inclusion/exclusion criteria for N01148 with N01103 (2014-004396-23 / NCT00105040) and N01009 (2004-000199-14 / NCT00175890). Secondarily, correction of errors, updates to the study team and central lab, addition of a visit window to allow flexibility in visit scheduling, more accurate descriptions of the titration period length, drug packaging and pregnancy testing are also provided.
02 September 2005	This amendment serves to make revisions to the protocol summary, background information, study procedures, and treatment of patients sections of the protocol. Changes in the study procedures include the incorporation of an additional height assessment at Visit 7 and the addition of thyroid testing [thyroid-stimulating hormone (TSH)] at Visit 1 and Visit 7 to satisfy requirements imparted by the European Medicines Agency (EMEA). Changes in the protocol summary reflect the addition of possibly Argentina, India, Russia, Hungary, Poland, South Africa, and Croatia. Changes to the background information reflect the recent FDA approval of Keppra® for partial onset seizures in children, ages four and above. Changes in the treatment of patient section includes the removal of an appendix related to dosing and the addition of a statement related to IVRS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/21095488