Clinical trial results:
A 19-week, randomized, double-blind, multicenter, placebo-controlled safety study to evaluate the cognitive and neuropsychological effects of levetiracetam 20-60 mg/kg/day, divided in twice daily dosing, as adjunctive treatment in children 4-16 years old, inclusive, with refractory partial onset seizures

Summary

EudraCT number	2014-004396-23
Trial protocol	Outside EU/EEA
Global end of trial date	21 March 2007
Results information	
Result version number	v1 (current)
This version publication date	28 June 2016
First version publication date	24 July 2015

Trial information

Trial identification	
Sponsor protocol code	N01103
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00105040
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	UCB Pharma, Inc.
Sponsor organisation address	1950 Lake Park Drive, Smyrna, United States, 30080
Public contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, clinicaltrials@ucb.com
Scientific contact	Clinical Trial Registries and Results Disclosure, UCB BIOSCIENCES GmbH, +49 2173 48 15 15, 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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 April 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 March 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to characterize potential cognitive and neuropsychological effects of LEV (20-60 mg/kg/d), as adjunctive treatment in children 4-16 years old, inclusive, with partial onset seizures, as non-inferior when compared to adjunctive treatment with PBO.

Protection of trial subjects:

None specific

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	28 September 2004
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	30 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	United States: 80
Worldwide total number of subjects	98
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)	60

Adolescents (12-17 years)	38
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This double-blind, randomized, multicenter, placebo-controlled safety study started recruiting in September 2004.

Pre-assignment

Screening details:

The ITT population included all subjects randomized to treatment who received at least 1 dose of study medication.

Period 1

Period 1 title	Study Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Levetiracetam (LEV)

Arm description:

Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.

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

Dosage and administration details:

Levetericatem: Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.

Arm title	Matching Placebo (PBO)

Arm description:

Oral tablets and oral solution.

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

Dosage and administration details:

Matching Placebo: Oral tablets and oral solution.

Number of subjects in period 1	Levetiracetam (LEV)	Matching Placebo (PBO)
Started	64	34
Completed	50	29
Not completed	14	5
Consent withdrawn by subject	4	-
AE, non-serious non-fatal	7	2
' Increase in concomitant medication'	1	-
Lost to follow-up	1	1
Lack of efficacy	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Levetiracetam (LEV)
Reporting group description:	
Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.	
Reporting group title	Matching Placebo (PBO)
Reporting group description:	
Oral tablets and oral solution.	

Reporting group values	Levetiracetam (LEV)	Matching Placebo (PBO)	Total
Number of subjects	64	34	98
Age Categorical Units: Subjects			
4 - 7	18	10	28
8 - 12	28	15	43
13 - 16	18	9	27
Age Continuous Units: years			
arithmetic mean	10.58	10.27	
standard deviation	± 3.49	± 3.67	-
Gender Categorical Units: Subjects			
Male	39	17	56
Female	25	17	42
Race/Ethnicity, Customized Units: Subjects			
Caucasian	40	18	58
Other/ mixed race	6	5	11
Black	15	8	23
Asian	3	3	6
Race (NIH/OMB) Units: Subjects			
Hispanic or latino	6	4	10
Not hispanic or not latino	58	30	88

End points

End points reporting groups

Reporting group title	Levetiracetam (LEV)
Reporting group description: Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.	
Reporting group title	Matching Placebo (PBO)
Reporting group description: Oral tablets and oral solution.	
Subject analysis set title	Per Protocol Set (Placebo Treated Subjects)
Subject analysis set type	Per protocol
Subject analysis set description: Oral tablets and oral solution.	
Subject analysis set title	Per Protocol Set (Levetiracetam Treated Subjects)
Subject analysis set type	Per protocol
Subject analysis set description: Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.	

Primary: Change from Baseline in the Leiter International Performance Scale-Revised (Leiter-R) Attention and Memory (AM) Battery's Memory Screen Composite Score from Baseline (Visit 2) to the end of the Evaluation Period (Week 12 or Early Discontinuation Visit)

End point title	Change from Baseline in the Leiter International Performance Scale-Revised (Leiter-R) Attention and Memory (AM) Battery's Memory Screen Composite Score from Baseline (Visit 2) to the end of the Evaluation Period (Week 12 or Early Discontinuation Visit)

End point description:

The Leiter-R includes two groupings of sub-tests: (1) the Visualization and Reasoning (VR) Battery with 10 sub-tests of nonverbal intellectual ability related to visualization, reasoning, and spatial ability; and (2) the Attention and Memory (AM) Battery with 10 sub-tests of nonverbal attention and memory function. The Examiner Rating Scale has 49 items that describe the child's activity level, attention, impulse control, and other emotional characteristics that may interact with test performance. The focus of the items is on actions, verbalizations, moods and other behaviors of the child. The examiner rates the child using the following scale: 0 = rarely or never; 1 = sometimes; 2 = often; 3 = usually or always.

End point type	Primary

End point timeframe:

Baseline (Visit 2) to the end of the Evaluation Period (Week 12 or Early Discontinuation Visit)

End point values	Per Protocol Set (Levetiracetam Treated Subjects)	Per Protocol Set (Placebo Treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	27		
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	5.37 (± 11.15)	5.24 (± 12.79)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Per Protocol Set (Levetiracetam Treated Subjects) v Per Protocol Set (Placebo Treated Subjects)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9473
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.69
upper limit	5.08
Variability estimate	Standard error of the mean
Dispersion value	2.93

Secondary: Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) General Memory from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point title	Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) General Memory from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point description:

The WRAML-2 is comprised of 2 Verbal, 2 Visual, and 2 Attention-Concentration sub-tests, yielding a Verbal Memory Index, a Visual Memory Index and an Attention-Concentration Index. Together these sub-tests yield a General Memory Index. Scaled and standard scores allow performance comparisons based on age and 4 delayed recall sub-tests include guidelines for determining the level of recall. A composite General Memory Index score will be computed.

End point type	Secondary

End point timeframe:

Baseline to Week 12 or EDV

End point values	Per Protocol Set (Levetiracetam Treated Subjects)	Per Protocol Set (Placebo Treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	23		
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	3.14 (± 9.93)	7.39 (± 10.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Comparison groups	Per Protocol Set (Levetiracetam Treated Subjects) v Per Protocol Set (Placebo Treated Subjects)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2022
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.75
upper limit	1.89
Variability estimate	Standard error of the mean
Dispersion value	2.66

Secondary: Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Visual Memory Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point title	Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Visual Memory Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point description:

The WRAML-2 is comprised of 2 Verbal, 2 Visual, and 2 Attention-Concentration sub-tests, yielding a Verbal Memory Index, a Visual Memory Index and an Attention-Concentration Index. Together these sub-tests yield a General Memory Index. Scaled and standard scores allow performance comparisons based on age and 4 delayed recall sub-tests include guidelines for determining the level of recall. A composite General Memory Index score will be computed.

End point type	Secondary

End point timeframe:

Baseline to Week 12 or EDV

End point values	Per Protocol Set (Levetiracetam Treated Subjects)	Per Protocol Set (Placebo Treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	43	23		
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	6.16 (± 12.45)	12.91 (± 17.02)		

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Per Protocol Set (Levetiracetam Treated Subjects) v Per Protocol Set (Placebo Treated Subjects)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3107
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.19
upper limit	3.29
Variability estimate	Standard error of the mean
Dispersion value	3.37

Secondary: Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Verbal Memory Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point title	Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Verbal Memory Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point description:

The WRAML-2 is comprised of 2 Verbal, 2 Visual, and 2 Attention-Concentration sub-tests, yielding a Verbal Memory Index, a Visual Memory Index and an Attention-Concentration Index. Together these sub-tests yield a General Memory Index. Scaled and standard scores allow performance comparisons based on age and 4 delayed recall sub-tests include guidelines for determining the level of recall. A composite General Memory Index score will be computed.

End point type	Secondary

End point timeframe:

Baseline to Week 12 or EDV

End point values	Per Protocol Set (Levetiracetam Treated Subjects)	Per Protocol Set (Placebo Treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	27		
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	2.23 (± 11.95)	2.04 (± 12.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 4
Comparison groups	Per Protocol Set (Levetiracetam Treated Subjects) v Per Protocol Set (Placebo Treated Subjects)
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6574
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.65
upper limit	7.32
Variability estimate	Standard error of the mean
Dispersion value	3

Secondary: Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Attention/Concentration Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point title	Change from Baseline in Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2) Attention/Concentration Index from Baseline to Week 12 or Early Discontinuation Visit (EDV)

End point description:

The WRAML-2 is comprised of 2 Verbal, 2 Visual, and 2 Attention-Concentration sub-tests, yielding a Verbal Memory Index, a Visual Memory Index and an Attention-Concentration Index. Together these sub-tests yield a General Memory Index. Scaled and standard scores allow performance comparisons based on age and 4 delayed recall sub-tests include guidelines for determining the level of recall. A composite General Memory Index score will be computed.

End point type	Secondary

End point timeframe:

Baseline to Week 12 or EDV

End point values	Per Protocol Set (Levetiracetam Treated Subjects)	Per Protocol Set (Placebo Treated Subjects)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	23		
Units: units on a scale				
arithmetic mean (standard deviation)				
mean (standard deviation)	-0.27 (± 8.62)	2.13 (± 9.72)		

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Comparison groups	Per Protocol Set (Levetiracetam Treated Subjects) v Per Protocol Set (Placebo Treated Subjects)
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3544
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.73
upper limit	2.44
Variability estimate	Standard error of the mean
Dispersion value	2.3

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Treatment-emergent Adverse Events were collected during the study, which began on 28 September 2004 and concluded on 21 March 2007.	
Adverse event reporting additional description:	
Adverse Events refer to the ITT Population, which included all subjects randomized to treatment who received at least 1 dose of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	9.0

Reporting groups	
Reporting group title	Matching Placebo (PBO)
Reporting group description:	
Oral tablets and oral solution.	
Reporting group title	Levetiracetam (LEV)
Reporting group description:	
Oral tablets or oral solution at 20-60 mg/kg/d, divided into twice daily dosing.	

Serious adverse events	Matching Placebo (PBO)	Levetiracetam (LEV)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 34 (2.94%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 34 (2.94%)	0 / 64 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Matching Placebo (PBO)	Levetiracetam (LEV)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 34 (82.35%)	51 / 64 (79.69%)	
Nervous system disorders			

Headache			
subjects affected / exposed	5 / 34 (14.71%)	17 / 64 (26.56%)	
occurrences (all)	7	26	
Somnolence			
subjects affected / exposed	3 / 34 (8.82%)	9 / 64 (14.06%)	
occurrences (all)	4	11	
Dizziness			
subjects affected / exposed	4 / 34 (11.76%)	6 / 64 (9.38%)	
occurrences (all)	4	9	
Psychomotor hyperactivity			
subjects affected / exposed	5 / 34 (14.71%)	4 / 64 (6.25%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 34 (11.76%)	9 / 64 (14.06%)	
occurrences (all)	4	10	
Pyrexia			
subjects affected / exposed	3 / 34 (8.82%)	5 / 64 (7.81%)	
occurrences (all)	3	7	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 34 (8.82%)	11 / 64 (17.19%)	
occurrences (all)	5	17	
Vomiting			
subjects affected / exposed	3 / 34 (8.82%)	9 / 64 (14.06%)	
occurrences (all)	3	10	
Stomach discomfort			
subjects affected / exposed	2 / 34 (5.88%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 34 (0.00%)	6 / 64 (9.38%)	
occurrences (all)	0	8	
Cough			
subjects affected / exposed	2 / 34 (5.88%)	4 / 64 (6.25%)	
occurrences (all)	2	4	

Epistaxis			
subjects affected / exposed	2 / 34 (5.88%)	3 / 64 (4.69%)	
occurrences (all)	2	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 34 (5.88%)	3 / 64 (4.69%)	
occurrences (all)	2	3	
Acne			
subjects affected / exposed	2 / 34 (5.88%)	0 / 64 (0.00%)	
occurrences (all)	2	0	
Psychiatric disorders			
Aggression			
subjects affected / exposed	3 / 34 (8.82%)	8 / 64 (12.50%)	
occurrences (all)	4	9	
Abnormal behaviour			
subjects affected / exposed	0 / 34 (0.00%)	5 / 64 (7.81%)	
occurrences (all)	0	5	
Anxiety			
subjects affected / exposed	0 / 34 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Insomnia			
subjects affected / exposed	1 / 34 (2.94%)	4 / 64 (6.25%)	
occurrences (all)	1	4	
Mood altered			
subjects affected / exposed	0 / 34 (0.00%)	4 / 64 (6.25%)	
occurrences (all)	0	4	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 34 (26.47%)	12 / 64 (18.75%)	
occurrences (all)	11	16	
Nasopharyngitis			
subjects affected / exposed	4 / 34 (11.76%)	10 / 64 (15.63%)	
occurrences (all)	4	11	
Pharyngitis			
subjects affected / exposed	2 / 34 (5.88%)	1 / 64 (1.56%)	
occurrences (all)	2	1	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	1 / 34 (2.94%)	5 / 64 (7.81%)	
occurrences (all)	1	5	
Increased appetite			
subjects affected / exposed	3 / 34 (8.82%)	0 / 64 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2004	No subjects had been enrolled when Amendment 1 was issued. This amendment included changes to the study entry criteria based on discussions at the Investigator's Meeting. These changes were as follows: • Subjects who had received treatment with benzodiazepines on a chronic or routine Basis were allowed to enter the study if they discontinued These medications 4 weeks prior to Visit 1 • Excluded psychiatric diagnoses were specified more narrowly as serious, unstable psychiatric diagnoses that would confound the Investigator's ability to conduct the trial or prevent the subject from completing the requirements of the protocol • Any ADHD medication intake was to remain stable during the study and had to be stable 1 month prior to Visit 1 • Subjects taking phenobarbital or primidone prior to Visit 1 were excluded • Subjects with seizures too close together to be accurately counted were excluded Other minor changes included addition or clarification of procedural details that were unlikely to significantly affect enrollment or study outcome.
22 August 2005	Amendment 2 allowed for establishment of a greater number of study sites and allowed for sites to be established in Canada and South Africa. Minor changes were made in the study safety assessments in order to satisfy requirements of the EMEA. These changes included addition of height and TSH measurements. Amendment 2 incorporated information about the FDA approval of LEV for use in children (4 years of age and above) with partial onset seizures (approval occurred in June 2005), and included information about the efficacy and safety results of other ongoing studies of LEV. Amendment 2 allowed for subjects with previous exposure to LEV to enroll in the study under limited circumstances. One impact of these changes was to allow more subjects to enroll, particularly subjects outside the US.

06 January 2006	Amendment 3 modified the Inclusion and Exclusion criteria in the following ways, to make the sample more representative of the target population: • The IQ criterion for study inclusion was reduced from 70 to 65 • The weight criterion was changed from ≤ 80 kg to ≤ 100 kg • Exclusions for subjects with current psychiatric diagnoses were relaxed from the Initial trict criteria after data from pivotal study N159 showed that LEV did not exacerbate ifficulties in children with history of psychiatric illnesses. Serious, unstable sychiatric illnesses were still excluded (such as suicide risk within the past 6 months, sychotic disorder, or acute mania) • The requirement for 2 partial onset seizures within the 4 weeks prior to Visit 1 was reduced to a requirement of only 1 partial onset seizure within the same time period. This criterion change, which is consistent with the intended population on the current LEC label, would terefore enable the collection of additional relevant safety data. There is no evidence that reducing the seizure number criterion would impair the sensitivity of the study to demonstrate potential psychiatric or neuropsychological effects of LEV Assumptions for the sample size estimation were adjusted in Amendment 3, so the sample size was recalculated and the total evaluable n was reduced by 13 subjects. Due to difficulties with enrollment, the sample size calculation was reviewed. During the review, it was determined that the Leiter-R Memory Screen un-inflated standard deviation of 6.94 that was used in the initial sample size was miscalculated. The actual un-inflated standard deviation should have been 10.19. To adjust for the younger age group in N01103, their epileptic disease state, and the unknown time between test and re-test, the estimate was inflated to 13.00 (a little more than 25%). Additionally, the type II error rate was relaxed from 15% to 20%, reducing statistical power to 80%.
06 January 2006	The increase to the type II error rate results in a smaller subject requirement, an acknowledgement of the difficulty enrolling subjects from this population while staying within generally accepted constraints for sample size determinations. Finally, the drop-out rate/major protocol deviation rate assumption was increased from 20% to 30% to more accurately reflect the actual rate occurring in the study. These changes were discussed with the FDA and accepted prior to implementing the changes. Amendment 3 also increased the number of study centers.

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/20547106

http://www.ncbi.nlm.nih.gov/pubmed/19702752