Clinical trial results:
A Randomized, Open-Label, Multicenter Study With Open-Label Extension of the Pharmacokinetics and Safety of Topiramate Administered as the Oral Liquid and Sprinkle Formulations as an Adjunct to Concurrent Anticonvulsant Therapy in Infants (Aged 1 to 24 Months, Inclusive) With Refractory Partial-Onset Seizures.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

EudraCT number	2005-001339-31
Trial protocol	ES
Global end of trial date	31 October 2007

Results information

Result version number	v2 (current)
This version publication date	15 July 2016
First version publication date	02 August 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	TOPMAT-PEP-1002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00233012
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	Archimedsweg 29-2333CM, Leiden, Netherlands, B235-0
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	31 October 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 October 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to determine the concentration-time profile for topiramate using a sparse sampling scheme following topiramate administration at fixed doses between 3 to 25 milligram per kilogram per day (mg/kg/day), of either oral liquid or sprinkle capsule formulations in infants aged 1 to 24 months, inclusive, with refractory partial-onset seizures (POS) taking at least 1 concomitant antiepileptic drug (AED).

Protection of trial subjects:

The Safety assessments include type and number of seizures, clinical laboratory results, physical examination, 12-lead electrocardiogram (ECG), vital signs, neurologic examination, vineland scales of adaptive behavior, and renal ultrasound. Adverse events and vital signs were monitored throughout the study.
Assessments for adequate food and liquid intake, hyperthermia, oligohydrosis, and rash were also to be performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 June 2005
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 1
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	55
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)	55
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: -

Pre-assignment

Screening details:

A total of 61 subjects were screened, among those 55 subjects were received at least 1 dose of study drug and finally 50 Subjects completed the study.

Period 1

Period 1 title	Open Label Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Topiramate (TPM) 3 mg/kg/day

Arm description:

Participants were administered with Topiramate 3 Milligram per Kilogram (mg/kg) liquid formulation orally twice in a day.

Arm type	Experimental
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	TOPAMAX
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were administered Topiramate 3 mg (milligram)/kilogram (kg) oral liquid/ oral capsule twice daily for 42 days.

Arm title	Topiramate (TPM) 5 mg/kg/day

Arm description:

Participants were administered with Topiramate 5 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.

Arm type	Experimental
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	TOPAMAX
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were administered Topiramate 5 mg (milligram)/kilogram (kg) oral liquid/ oral capsule twice daily for 42 days.

Arm title	Topiramate (TPM) 15 mg/kg/day

Arm description:

Participants were administered with Topiramate 15 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.

Arm type	Experimental

Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	TOPAMAX
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were administered Topiramate 15 mg (milligram)/kilogram (kg) oral liquid/ oral capsule twice daily for 42 days.

Arm title	Topiramate (TPM) 25 mg/kg/day

Arm description:

Participants were administered with Topiramate 25 Milligram per Kilogram (mg/kg) oral liquid/oral capsule formulation orally twice in a day.

Arm type	Experimental
Investigational medicinal product name	Topiramate Sprinkle Capsules
Investigational medicinal product code	
Other name	TOPAMAX
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants were administered Topiramate 25 milligram per kilogram (mg/kg) oral liquid/ oral capsule twice daily for 42 days.

Number of subjects in period 1	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day
Started	14	13	13
Completed	14	12	11
Not completed	0	1	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	1	-
Adverse event	-	-	2
Lost to follow-up	-	-	-

Number of subjects in period 1	Topiramate (TPM) 25 mg/kg/day
Started	15
Completed	13
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Adverse event	-
Lost to follow-up	1

Period 2

Period 2 title	Open Label Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Topiramate (TPM) upto 60 mg/kg/day

Arm description:

Subjects entering the open-label extension phase at dosages less than 25 mg/kg per day were titrated to this dosage or maximum dosages tolerated over 4 weeks. Subsequently, subjects were titrated up or down depending on tolerability and seizure frequency up to 60 mg/kg per day maximum final dosage

Arm type	Experimental
Investigational medicinal product name	Topiramate
Investigational medicinal product code	
Other name	TOPAMAX
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects who entered the open-label extension phase at dosages less than 25 mg/kg per day were titrated to this dosage or maximum dosages tolerated over 4 weeks. Subsequently, subjects were titrated up or down depending on tolerability and seizure frequency up to 60 mg/kg per day maximum final dosage

Number of subjects in period 2	Topiramate (TPM) upto 60 mg/kg/day
Started	50
Completed	16
Not completed	34
Withdrawn due to early termination by sponsor	20
Adverse event, non-fatal	6
Other	3
Subject choice (parent withdrew consent)	5

Baseline characteristics

Reporting groups	
Reporting group title	Topiramate (TPM) 3 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 3 Milligram per Kilogram (mg/kg) liquid formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 5 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 5 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 15 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 15 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 25 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 25 Milligram per Kilogram (mg/kg) oral liquid/oral capsule formulation orally twice in a day.	

Reporting group values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day
Number of subjects	14	13	13
Title for AgeCategorical			
Units: subjects			
infants and toddlers(28 days-23 months)	14	13	13
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65 to 84 years	0	0	0
85 years and over	0	0	0
Title for AgeContinuous			
Units: Months			
arithmetic mean	10.9	12	11.6
standard deviation	± 5.38	± 5.46	± 6.74
Title for Gender			
Units: subjects			
Female	8	3	7
Male	6	10	6

Reporting group values	Topiramate (TPM) 25 mg/kg/day	Total	
Number of subjects	15	55	
Title for AgeCategorical			
Units: subjects			
infants and toddlers(28 days-23 months)	15	55	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65 to 84 years	0	0	

85 years and over	0	0	

Title for AgeContinuous Units: Months			
arithmetic mean	11.3		
standard deviation	± 6.11	-	
Title for Gender Units: subjects			
Female	5	23	
Male	10	32	

End points

End points reporting groups

Reporting group title	Topiramate (TPM) 3 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 3 Milligram per Kilogram (mg/kg) liquid formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 5 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 5 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 15 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 15 Milligram per Kilogram (mg/kg) oral liquid / oral capsule formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 25 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 25 Milligram per Kilogram (mg/kg) oral liquid/oral capsule formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) upto 60 mg/kg/day
Reporting group description:	
Subjects entering the open-label extension phase at dosages less than 25 mg/kg per day were titrated to this dosage or maximum dosages tolerated over 4 weeks. Subsequently, subjects were titrated up or down depending on tolerability and seizure frequency up to 60 mg/kg per day maximum final dosage	

Primary: Serum Trough Concentration (C-trough) of Topiramate

End point title	Serum Trough Concentration (C-trough) of Topiramate[1]
End point description:	
The C-trough is the observed serum concentration immediately prior to the next administration of topiramate.	
End point type	Primary
End point timeframe:	
Predose, within the intervals of 1 to 3, 4 to 6, and 8 to 10 hours postdose on Day 7	
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 were performed for this endpoint.	

End point values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day	Topiramate (TPM) 25 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: microgram per millilitre (µg/mL)				
arithmetic mean (standard deviation)	1.91 (± 1.04)	3.25 (± 1.89)	9.74 (± 4.82)	13.6 (± 5.19)

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration-Time Curve From Time 0 to 12 Hours

End point title	Area Under the Plasma Concentration-Time Curve From Time 0 to 12 Hours[2]

End point description:

The AUC(0-12) is defined as Area under the plasma concentration-time curve from time 0 through 12 hours post dosing.

End point type	Primary

End point timeframe:

Predose, within the intervals of 1 to 3, 4 to 6, and 8 to 10 hours postdose on Day 7

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: No statistical analysis were performed for this endpoint.

End point values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day	Topiramate (TPM) 25 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: microgram*hour per millilitre (µg.h/mL)				
arithmetic mean (standard deviation)	29.1 (± 12.4)	50 (± 19.6)	143 (± 53.8)	211 (± 58)

Statistical analyses

No statistical analyses for this end point

Primary: Creatinine Clearance (CLCR) of Topiramate

End point title	Creatinine Clearance (CLCR) of Topiramate[3]

End point description:

The CLCR is defined as the volume of serum or plasma that would be cleared of creatinine by one minute's excretion of urine.

End point type	Primary

End point timeframe:

Up to Day 42

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: No statistical analysis were performed for this endpoint.

End point values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day	Topiramate (TPM) 25 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: millilitre per minute per 1.73 meter^3				
arithmetic mean (standard deviation)	111 (± 37.2)	102 (± 12.7)	87.8 (± 20.8)	90.9 (± 17.3)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Oral Clearance (CLss/F) of Topiramate

End point title	Apparent Oral Clearance (CLss/F) of Topiramate[4]

End point description:

The CLss/F is defined as total clearance of the drug from plasma after oral administration.

End point type	Primary

End point timeframe:

Up to Day 42

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: No statistical analysis were performed for this endpoint.

End point values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day	Topiramate (TPM) 25 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: millilitre per minute (mL/min)				
arithmetic mean (standard deviation)	7.73 (± 3.38)	9.04 (± 4.57)	9.1 (± 5.08)	8.49 (± 2.44)

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Oral Clearance (CLss/F) of Topiramate

End point title	Apparent Oral Clearance (CLss/F) of Topiramate[5]

End point description:

The CLss/F is defined as total clearance of the drug from plasma after oral administration.

End point type	Primary

End point timeframe:

Up to Day 42

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: No statistical analysis were performed for this endpoint.

End point values	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 5 mg/kg/day	Topiramate (TPM) 15 mg/kg/day	Topiramate (TPM) 25 mg/kg/day
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: Litre per hour (L/h)				
arithmetic mean (standard deviation)	0.464 (± 0.203)	0.542 (± 0.274)	0.546 (± 0.305)	0.509 (± 0.147)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to Follow-up (up to 30 days after prior visit)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	WHOART
Dictionary version	SOC3

Reporting groups	
Reporting group title	Topiramate (TPM) 3 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 3-Milligram per Kilogram (mg/kg) liquid formulation orally twice in a day.	
Reporting group title	Topiramate (TPM) 25 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 25-Milligram per Kilogram (mg/kg) oral liquid /oral capsule formulation twice in a day.	
Reporting group title	Topiramate (TPM) 15 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 15-Milligram per Kilogram (mg/kg) oral liquid/oral capsule formulation twice in a day.	
Reporting group title	Topiramate (TPM) 5 mg/kg/day
Reporting group description:	
Participants were administered with Topiramate 5-Milligram per Kilogram (mg/kg) oral liquid/oral capsule formulation twice in a day.	

Serious adverse events	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 25 mg/kg/day	Topiramate (TPM) 15 mg/kg/day
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	2 / 10 (20.00%)	7 / 20 (35.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm Benign			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsions Aggravated			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Convulsions Grand Mal			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Psychomotor Development Impaired			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse Event Nos			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug Level Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection Viral			

subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	3 / 20 (15.00%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis Media			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatomegaly			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	3 / 20 (15.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Resp Tract Infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Somnolence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperammonaemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Topiramate (TPM) 5 mg/kg/day		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain Neoplasm Benign			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Convulsions Aggravated			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Convulsions Grand Mal			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Psychomotor Development Impaired			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Splenomegaly			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Adverse Event Nos			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Drug Level Increased				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infection Viral				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Otitis Media				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastroenteritis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatomegaly				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Bronchitis				

subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngitis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stridor				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper Resp Tract Infection				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Somnolence				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Pyelonephritis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				

subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperammonaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Topiramate (TPM) 3 mg/kg/day	Topiramate (TPM) 25 mg/kg/day	Topiramate (TPM) 15 mg/kg/day
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)	10 / 10 (100.00%)	20 / 20 (100.00%)
Vascular disorders			
Extrasystoles Supraventricular			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vasospasm			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pregnancy, puerperium and perinatal conditions			
Autism Infantile			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Atrial Septal Defect			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Congenital Anomaly Nos			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

Microcephaly			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Psychomotor Development Impaired			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Adverse Event Nos			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Allergy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Drug Level Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Fever			
subjects affected / exposed	5 / 13 (38.46%)	4 / 10 (40.00%)	6 / 20 (30.00%)
occurrences (all)	19	10	16
Infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Injury			
subjects affected / exposed	2 / 13 (15.38%)	2 / 10 (20.00%)	0 / 20 (0.00%)
occurrences (all)	4	2	0
Infection Viral			
subjects affected / exposed	5 / 13 (38.46%)	2 / 10 (20.00%)	5 / 20 (25.00%)
occurrences (all)	11	3	6
Otitis Media			
subjects affected / exposed	3 / 13 (23.08%)	3 / 10 (30.00%)	4 / 20 (20.00%)
occurrences (all)	6	5	13
Pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	6 / 20 (30.00%)
occurrences (all)	3	0	10
Bronchospasm			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences (all)	2	0	4
Coughing			
subjects affected / exposed	4 / 13 (30.77%)	0 / 10 (0.00%)	4 / 20 (20.00%)
occurrences (all)	6	0	4
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	4 / 13 (30.77%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences (all)	4	0	2
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	3
Pneumothorax			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Respiratory Disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	2 / 13 (15.38%)	2 / 10 (20.00%)	5 / 20 (25.00%)
occurrences (all)	4	2	6
Sinusitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	4
Stridor			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0

Upper Resp Tract Infection			
subjects affected / exposed	5 / 13 (38.46%)	3 / 10 (30.00%)	9 / 20 (45.00%)
occurrences (all)	12	11	12
Psychiatric disorders			
Anorexia			
subjects affected / exposed	4 / 13 (30.77%)	2 / 10 (20.00%)	4 / 20 (20.00%)
occurrences (all)	9	4	6
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Nervousness			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	2	0	3
Somnolence			
subjects affected / exposed	1 / 13 (7.69%)	3 / 10 (30.00%)	4 / 20 (20.00%)
occurrences (all)	2	5	13
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Convulsions Aggravated			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Coordination Abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	3
Hypertonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Hypotonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Granulocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Leucopenia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Vision Abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Diarrhoea			
subjects affected / exposed	5 / 13 (38.46%)	2 / 10 (20.00%)	2 / 20 (10.00%)
occurrences (all)	5	3	4
Eructation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Gastro-Intestinal Disorder Nos			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Melaena			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Tooth Discolouration			

subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Stomatitis Ulcerative			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Tooth Disorder			
subjects affected / exposed	3 / 13 (23.08%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	6	0	3
Vomiting			
subjects affected / exposed	7 / 13 (53.85%)	2 / 10 (20.00%)	3 / 20 (15.00%)
occurrences (all)	17	2	6
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gamma-Gt Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	4
SGOT Increased			
subjects affected / exposed	0 / 13 (0.00%)	2 / 10 (20.00%)	1 / 20 (5.00%)
occurrences (all)	0	3	1
Hepatic Function Abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
SGPT Increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dermatitis Contact			

subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Rash			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Rash Maculo-Papular			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Seborrhoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin Discolouration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin Dry			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Sweating Decreased			
subjects affected / exposed	3 / 13 (23.08%)	1 / 10 (10.00%)	1 / 20 (5.00%)
occurrences (all)	5	2	1
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Bladder Calculus			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	4	0	0
Haematuria			
subjects affected / exposed	2 / 13 (15.38%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Hydronephrosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Nephropathy Toxic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Oliguria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Renal Calculus			
subjects affected / exposed	1 / 13 (7.69%)	1 / 10 (10.00%)	1 / 20 (5.00%)
occurrences (all)	2	2	1
Urine Abnormal			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Urinary Tract Infection			
subjects affected / exposed	2 / 13 (15.38%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	4	2	0
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Acidosis			
subjects affected / exposed	6 / 13 (46.15%)	4 / 10 (40.00%)	6 / 20 (30.00%)
occurrences (all)	13	9	8
Calcinosis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	7	0	0
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	2
Hyperchloraemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Hyperammonaemia			
subjects affected / exposed	2 / 13 (15.38%)	3 / 10 (30.00%)	4 / 20 (20.00%)
occurrences (all)	3	5	7
Hyperkalaemia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
LDH Increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Hypocalcaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 10 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Phosphatase Alkaline Increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 10 (10.00%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Weight Decrease			
subjects affected / exposed	5 / 13 (38.46%)	3 / 10 (30.00%)	4 / 20 (20.00%)
occurrences (all)	11	9	7

Non-serious adverse events	Topiramate (TPM) 5 mg/kg/day		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Extrasystoles Supraventricular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Vasospasm			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Pregnancy, puerperium and perinatal conditions			
Autism Infantile			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Atrial Septal Defect			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		
Congenital Anomaly Nos			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Microcephaly			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Psychomotor Development Impaired			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Adverse Event Nos			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Allergy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Drug Level Increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Fever			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	17		
Infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Injury			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infection Viral			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Otitis Media			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Asthma				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Bronchitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Bronchospasm				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	4			
Coughing				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	3			
Dyspnoea				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Pharyngitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Pneumothorax				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Respiratory Disorder				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Rhinitis				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	7			
Sinusitis				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			
Stridor				
subjects affected / exposed	0 / 12 (0.00%)			
occurrences (all)	0			

Upper Resp Tract Infection subjects affected / exposed occurrences (all)	6 / 12 (50.00%) 16		
Psychiatric disorders Anorexia subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Nervousness subjects affected / exposed occurrences (all) Somnolence subjects affected / exposed occurrences (all)	 4 / 12 (33.33%) 7 1 / 12 (8.33%) 2 2 / 12 (16.67%) 2 5 / 12 (41.67%) 9		
Cardiac disorders Hypertension subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 4		
Nervous system disorders Ataxia subjects affected / exposed occurrences (all) Convulsions Aggravated subjects affected / exposed occurrences (all) Coordination Abnormal subjects affected / exposed occurrences (all) Hypertonia subjects affected / exposed occurrences (all) Hypotonia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 1 / 12 (8.33%) 2 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Granulocytopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Leucopenia			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eye disorders			
Vision Abnormal			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	13		
Eructation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastro-Intestinal Disorder Nos			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Melaena			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tooth Discolouration			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Stomatitis Ulcerative			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tooth Disorder			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	9		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Gamma-Gt Increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
SGOT Increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Hepatic Function Abnormal			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
SGPT Increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Dermatitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Dermatitis Contact			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Rash Maculo-Papular			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Seborrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Skin Discolouration			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin Dry			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Sweating Decreased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Albuminuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Bladder Calculus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Hydronephrosis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

Nephropathy Toxic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Oliguria subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Renal Calculus subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Urine Abnormal subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2			
Urinary Tract Infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2			
Metabolism and nutrition disorders Alkalosis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2			
Acidosis subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 9			
Calcinosis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Dehydration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1			
Hyperchloraemia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0			
Hyperammonaemia subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 8			
Hyperkalaemia				

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
LDH Increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Phosphatase Alkaline Increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weight Decrease			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2005	The overall reason for the amendment was to modify the timing of dosing, scheduling and time of admission to the study site on pharmacokinetic(s) (PK) visit days, and use of intravenous catheterization for PK assessments.
04 May 2006	The overall reason for the amendment was to incorporate feedback from investigators and regulatory authorities. Liberalization and clarification of enrollment criteria and laboratory alert parameters were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported