Clinical trial results:
TOPAMAX (Topiramate) Initiated as Monotherapy in Epilepsy (TIME): A Multicenter, Outpatient, Open-label, Study to Evaluate the Dosing, Effectiveness and Safety of TOPAMAX® as Monotherapy in the Treatment of Epilepsy in Clinical Practice

Summary

EudraCT number	2015-001223-23
Trial protocol	Outside EU/EEA
Global end of trial date	20 June 2007

Results information

Result version number	v2 (current)
This version publication date	23 June 2016
First version publication date	31 July 2015
Version creation reason	• Correction of full data set Review of data

Trial information

Trial identification

Sponsor protocol code	CAPSS-311

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00266604
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johnson & Johnson Pharmaceutical Research and Development.
Sponsor organisation address	Archimedesweg 29, Leiden, Netherlands, 2333CM
Public contact	Clinical Registry Group-JB BV, Clinical Registry Group-JB BV, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group-JB BV, Clinical Registry Group-JB BV, 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	20 June 2007
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to identify subject characteristics (such as baseline seizure frequency) that were predict of effective doses of topiramate initiated as monotherapy in epilepsy. Topiramate is an anti-epileptic drug that is approved for the treatment of epilepsy in adults and children 2 years of age and above.

Protection of trial subjects:

Safety and tolerability evaluations for this study included monitoring of adverse events and clinical laboratory tests (liver function and electrolytes). Urine pregnancy tests were performed on women of childbearing potential.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2006
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	United States: 390
Worldwide total number of subjects	390
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)	13
Adolescents (12-17 years)	58
Adults (18-64 years)	284
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this study, 407 subjects were enrolled; 390 subjects were in the safety population, 378 were in the intent-to treat (ITT) population, 244 were in the modified intent-to-treat (mITT) population and 213 were in the mITT population on TOPAMAX monotherapy at the end of the trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Topiramate

Arm description:

Topiramate

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

Dosage and administration details:

Topiramate 400 milligram (mg) tablet orally once daily up to Week 24.

Number of subjects in period 1	Topiramate
Started	390
Completed	230
Not completed	160
Consent withdrawn by subject	21
Adverse event, non-fatal	63
Other	28
Adverse event, serious non-fatal	5
Lost to follow-up	43

Baseline characteristics

Reporting groups	
Reporting group title	Topiramate
Reporting group description:	
Topiramate	

Reporting group values	Topiramate	Total	
Number of subjects	390	390	
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	13	13	
Adolescents (12-17 years)	58	58	
Adults (18-64 years)	284	284	
From 65 to 84 years	35	35	
85 years and over	0	0	
Title for AgeContinuous			
Units: Years			
arithmetic mean	36.6		
standard deviation	± 17.87	-	
Title for Gender			
Units: subjects			
Female	235	235	
Male	155	155	

End points

End points reporting groups

Reporting group title	Topiramate
Reporting group description: Topiramate	
Subject analysis set title	TOPAMAX Treated Subjects With 1-3 Seizures
Subject analysis set type	Sub-group analysis
Subject analysis set description: TOPAMAX Treated Subjects with 1-3 Seizures in Last 3 Months Prior to Baseline.	
Subject analysis set title	TOPAMAX Treated Subjects With More Than 3 Seizures
Subject analysis set type	Sub-group analysis
Subject analysis set description: TOPAMAX Treated Subjects with More Than (>) 3 Seizures in Last 3 Months Prior to Baseline.	
Subject analysis set title	TOPAMAX Treated Subjects With 1-3 Seizures (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) defined as all subjects who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment, unless otherwise specified.	
Subject analysis set title	TOPAMAX Treated Subjects with More Than 3 Seizures (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT defined as all subjects who received at least 1 dose of study medication and had at least 1 post-baseline efficacy assessment, unless otherwise specified.	

Primary: Number of Subjects With Stabilized Topiramate Dose

End point title	Number of Subjects With Stabilized Topiramate Dose
End point description: Subjects were compared for the mean stabilized Topiramate dose during the last 28 days of treatment between Subjects Reporting 1 to 3 seizures versus subjects reporting more than 3 seizures. The analysis was performed on modified intent-to-treat (mITT) population which included subjects who were treated for at least 12 weeks, that had reached a stabilized dose during the last 28 days of the study, and were on topiramate monotherapy at the end of the trial.	
End point type	Primary
End point timeframe: Baseline up to Last 28 days of study treatment	

End point values	TOPAMAX Treated Subjects With 1-3 Seizures	TOPAMAX Treated Subjects With More Than 3 Seizures		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	78		
Units: subjects	147	66		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	TOPAMAX Treated Subjects With 1-3 Seizures v TOPAMAX Treated Subjects With More Than 3 Seizures
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0025
Method	ANOVA

Secondary: Percentage of Subjects Remaining Seizure Free

End point title	Percentage of Subjects Remaining Seizure Free
End point description:	

End point type	Secondary
End point timeframe:	
Day 28, 56, 84 and 168	

End point values	TOPAMAX Treated Subjects With 1-3 Seizures (ITT)	TOPAMAX Treated Subjects with More Than 3 Seizures (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	251	127		
Units: subjects				
Day 28	184	45		
Day 56	131	31		
Day 84	127	25		
Day 168	100	16		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to stabilized dose

End point title	Time to stabilized dose
End point description:	

End point type	Secondary
End point timeframe:	
Baseline up to Day 168	

End point values	TOPAMAX Treated Subjects With 1-3 Seizures (ITT)	TOPAMAX Treated Subjects with More Than 3 Seizures (ITT)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	251	127		
Units: Days				
arithmetic mean (standard error)	50.701 (± 3.222)	61.461 (± 4.274)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Incidence of Seizure

End point title	Change From Baseline in Incidence of Seizure

End point description:

End point type	Secondary

End point timeframe:

Baseline and Day 168

End point values	Topiramate			
Subject group type	Reporting group			
Number of subjects analysed	351[1]			
Units: Incidence of seizure				
arithmetic mean (standard deviation)				
Baseline (n=351)	6.04 (± 38.538)			
Day 168 (n=231)	-1.19 (± 36.651)			

Notes:

[1] - Here 'N' = number of subjects analyzed for this endpoint and 'n' = analyzed at specific timepoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	WHOART
Dictionary version	0.0
Reporting groups	
Reporting group title	Topiramate
Reporting group description:	
Topiramate	

Serious adverse events	Topiramate		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 390 (5.13%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm Nos			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombophlebitis Deep			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Convulsions			

subjects affected / exposed	4 / 390 (1.03%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Convulsions Grand Mal			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tremor			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Embolism Pulmonary			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection Viral			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Injury				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Hyperacusis				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pleural Effusion				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Purpura				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stevens Johnson Syndrome				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urticaria				

subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hysteria			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Bladder Calculus			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Calculus			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Renal Failure Acute			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Oedema Periorbital			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Topiramate		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	248 / 390 (63.59%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	43 / 390 (11.03%)		
occurrences (all)	47		
Headache			
subjects affected / exposed	37 / 390 (9.49%)		
occurrences (all)	47		
Hypoaesthesia			
subjects affected / exposed	38 / 390 (9.74%)		
occurrences (all)	46		
Language Problems			
subjects affected / exposed	16 / 390 (4.10%)		
occurrences (all)	17		
Paraesthesia			
subjects affected / exposed	99 / 390 (25.38%)		
occurrences (all)	133		
Taste Perversion			
subjects affected / exposed	21 / 390 (5.38%)		
occurrences (all)	23		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	47 / 390 (12.05%)		
occurrences (all)	56		
Eye disorders			
Vision Abnormal			
subjects affected / exposed	14 / 390 (3.59%)		
occurrences (all)	14		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 390 (3.08%)		
occurrences (all)	14		
Nausea			
subjects affected / exposed	20 / 390 (5.13%)		
occurrences (all)	21		

Respiratory, thoracic and mediastinal disorders			
Upper Resp Tract Infection			
subjects affected / exposed	15 / 390 (3.85%)		
occurrences (all)	16		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	18 / 390 (4.62%)		
occurrences (all)	22		
Confusion			
subjects affected / exposed	21 / 390 (5.38%)		
occurrences (all)	21		
Depression			
subjects affected / exposed	15 / 390 (3.85%)		
occurrences (all)	20		
Difficulty with Concentration/Attention			
subjects affected / exposed	25 / 390 (6.41%)		
occurrences (all)	27		
Difficulty with Memory Nos			
subjects affected / exposed	32 / 390 (8.21%)		
occurrences (all)	34		
Emotional Lability			
subjects affected / exposed	13 / 390 (3.33%)		
occurrences (all)	14		
Insomnia			
subjects affected / exposed	22 / 390 (5.64%)		
occurrences (all)	23		
Mood Problems			
subjects affected / exposed	24 / 390 (6.15%)		
occurrences (all)	27		
Nervousness			
subjects affected / exposed	14 / 390 (3.59%)		
occurrences (all)	15		
Psychomotor Slowing			
subjects affected / exposed	12 / 390 (3.08%)		
occurrences (all)	15		
Somnolence			

subjects affected / exposed occurrences (all)	40 / 390 (10.26%) 50		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Weight Decrease subjects affected / exposed occurrences (all)	 44 / 390 (11.28%) 46 29 / 390 (7.44%) 30		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported