Clinical trial results:
A Multiple Dose Pharmacokinetic Open-Label Study of Pregabalin (Lyrica) in Healthy Lactating Women

Summary

EudraCT number	2012-003197-57
Trial protocol	BE
Global end of trial date	16 August 2013

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	11 July 2015

Trial information

Trial identification

Sponsor protocol code	A0081181

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01727791
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	03 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine pregabalin drug concentrations in human breast milk and estimate the infant daily dose that would result from pregabalin secretion in breast milk.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2012
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	Belgium: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was conducted in Belgium from 13 Dec 2012 to 16 Aug 2013.

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	Pregabalin

Arm description:

Subjects received pregabalin immediate release (IR) capsules over 12 hour dosing intervals on Day 1, Day 2 and Day 3.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Lyrica
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Subjects received pregabalin 150 milligram (mg) capsules every 12 hour beginning on Day 1 (evening), Day 2 (morning and evening) and Day 3 (morning).

Number of subjects in period 1	Pregabalin
Started	10
Completed	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Subjects received pregabalin immediate release (IR) capsules at 12 hours dosing interval on Day 1, Day 2 and Day 3.	

Reporting group values	Overall Study	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	31.7		
standard deviation	± 4.5	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	0	0	

End points

End points reporting groups

Reporting group title	Pregabalin

Reporting group description:

Subjects received pregabalin immediate release (IR) capsules over 12 hour dosing intervals on Day 1, Day 2 and Day 3.

Primary: Area Under the Curve from Time Zero to End of Dosing Interval (AUCtau)

End point title	Area Under the Curve from Time Zero to End of Dosing Interval (AUCtau)[1]

End point description:

Area under concentration-time profile from time 0 to tau (AUCtau), where tau was the dosing interval of 12 hours. The pharmacokinetic (PK) parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: microgram*hour per milliliter(mcg*hr/mL)				
geometric mean (geometric coefficient of variation)	32.5 (± 24)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Plasma Concentration (Cmax)

End point title	Maximum Observed Plasma Concentration (Cmax)[2]

End point description:

Cmax was the peak concentration in plasma post Day 3 dose. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12, 18, 24 hours post-dose on Day 3

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	4.67 (± 18)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Plasma Concentration (Tmax)

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax)[3]

End point description:

Tmax was the time to peak concentration in plasma post Day 3 dose. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12, 18, 24 hours post-dose on Day 3

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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hr				
median (full range (min-max))	2.01 (1 to 3)			

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Half-Life (t1/2)

End point title	Plasma Half-Life (t1/2)[4]

End point description:

Plasma decay half-life (t1/2) was the time for the plasma concentration to decrease by one-half. The t1/2 is based on the terminal elimination phase time points from this timeframe. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12, 18, 24 hours post-dose on Day 3

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12, 18, 24 hours post-dose on Day 3

Notes:

[6] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	1.246 (± 36)			

Statistical analyses

No statistical analyses for this end point

Primary: Apparent Oral Clearance (CL/F)

End point title	Apparent Oral Clearance (CL/F)[7]

End point description:

Apparent oral clearance (CL/F) was calculated by dividing dose by the AUCtau,
where tau was the dosing interval of 12 hours. Clearance of a drug is a measure of the rate at which a drug is metabolized or eliminated by normal biological processes. Clearance obtained after oral dose (apparent oral clearance) is influenced by the fraction of the dose absorbed. Drug clearance is a quantitative measure of the rate at which a drug substance is removed from the blood. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6,10, 12 hours post-dose on Day 3

Notes:

[7] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: milliliter/minute (mL/min)				
geometric mean (geometric coefficient of variation)	76.9 (± 24)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Curve from Time Zero to End of Dosing Interval for Breast Milk (AUCtau [breast milk])

End point title	Area Under the Curve from Time Zero to End of Dosing Interval for Breast Milk (AUCtau [breast milk])[8]

End point description:

AUCtau (breast milk) was the area under the curve for breast milk, from time 0 to tau (AUCtau), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[8] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg*hr/mL				
geometric mean (geometric coefficient of variation)	24.64 (± 27)			

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Concentration in Breast Milk (Cmax [breast milk])

End point title	Maximum Observed Concentration in Breast Milk (Cmax [breast milk])[9]

End point description:

Cmax (breast milk) was the maximum observed concentration in breast milk post Day 3 dose. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 40 and 40 to 48 hours post-dose on Day 3

Notes:

[9] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)	2.474 (± 30)			

Statistical analyses

No statistical analyses for this end point

Primary: Time to Reach Maximum Observed Breast Milk Concentration (Tmax [breast milk])

End point title	Time to Reach Maximum Observed Breast Milk Concentration (Tmax [breast milk])[10]

End point description:

Tmax (breast milk) was time of the maximum observed breast milk concentration Day 3 post dose. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 40 and 40 to 48 hours post-dose on Day 3

Notes:

[10] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hr				
median (full range (min-max))	4.63 (3.08 to 6.16)			

Statistical analyses

No statistical analyses for this end point

Primary: Terminal Half-Life for Breast Milk (t1/2 [breast milk])

End point title	Terminal Half-Life for Breast Milk (t1/2 [breast milk])[11]

End point description:

The terminal half-life for breast milk (t1/2 [breast milk]) was the time measured for breast milk concentration to decrease by one-half. For the first 5 subjects enrolled under protocol amendment dated: 18 Sep 2012, breast milk was collected up to 24 hours after Day 3 dosing over the following time intervals: 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24 hours. Terminal half-life was determined over those points characterizing the elimination phase. For the remaining 5 subjects, there were 3 additional collection intervals (24 to 32, 32 to 40, 40 to 48 hours) for characterizing the terminal elimination phase. The t1/2 (breast milk) is based on the terminal elimination phase time points from this timeframe. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 40 and 40 to 48 hours post-dose on Day 3

Notes:

[11] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hr				
arithmetic mean (standard deviation)	8.117 (± 3.0871)			

Statistical analyses

No statistical analyses for this end point

Primary: Amount Excreted in Breast Milk Over the Dosing Interval tau (Aetaubm)

End point title	Amount Excreted in Breast Milk Over the Dosing Interval tau (Aetaubm)[12]

End point description:

Aetaubm was the amount excreted in breast milk over the dosing interval tau (12 hours). It was calculated as the sum of (breast milk concentration * sample volume) for each collection interval from 0 to 12 hours post-dose, where tau was the dosing interval of 12 hours. Sample volume was based on ratio of volume weight and density. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[12] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg				
geometric mean (geometric coefficient of variation)	286.9 (± 60)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Dose Excreted in Breast Milk During the Dosing Interval tau (Aetaubm percent)

End point title	Percentage of Dose Excreted in Breast Milk During the Dosing Interval tau (Aetaubm percent)[13]

End point description:

Percentage of dose excreted in breast milk during the dosing interval tau (Aetaubm percent) was calculated by using the formula: 100*(Aetaubm
[sum of {breast milk concentration * sample volume} for each collection interval from 0 to
12 hours post-dose] divided by dose), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[13] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of dose				
geometric mean (geometric coefficient of variation)	0.1913 (± 60)			

Statistical analyses

No statistical analyses for this end point

Primary: Breast Milk Clearance (CLbm)

End point title	Breast Milk Clearance (CLbm)[14]

End point description:

Breast milk clearance (CLbm) was calculated by dividing Aetaubm (sum of [breast milk concentration * sample volume] for each collection interval from 0 to 12 hours post--dose) by plasma AUCtau, where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Plasma: Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3.
Breast milk: Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[14] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mL/min				
geometric mean (geometric coefficient of variation)	0.1473 (± 60)			

Statistical analyses

No statistical analyses for this end point

Primary: Amount Recovered in Urine During the Dosing Interval tau (Aetauurine)

End point title	Amount Recovered in Urine During the Dosing Interval tau (Aetauurine)[15]

End point description:

Aetauurine was the amount excreted in urine over the dosing interval tau (12 hours). It was calculated as the sum of (urine concentration * sample volume) for each collection interval from 0 to 12 hours post-dose, where tau was the dosing interval of 12 hours. Here, sample volume was based on the ratio of volume weight and density. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8 and 8 to 12 hours post-dose on Day 3

Notes:

[15] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mg				
geometric mean (geometric coefficient of variation)	133.1 (± 12)			

Statistical analyses

No statistical analyses for this end point

Primary: Percent of Dose Recovered in Urine During the Dosing Interval tau (Aetauurine percent)

End point title	Percent of Dose Recovered in Urine During the Dosing Interval tau (Aetauurine percent)[16]

End point description:

Percent of dose recovered in urine during the dosing interval tau (Aetauurine percent) was calculated as 100*(Aetau [sum of {urine concentration * sample volume} for each collection interval from 0 to 12 hours post-dose] divided by the dose), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8 and 8 to 12 hours post-dose on Day 3

Notes:

[16] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of dose				
geometric mean (geometric coefficient of variation)	88.6 (± 12)			

Statistical analyses

No statistical analyses for this end point

Primary: Renal Clearance (CLr)

End point title	Renal Clearance (CLr)[17]

End point description:

Renal clearance (CLr) was the volume of plasma from which the drug was completely removed by the kidney in a given amount of time. It was calculated by dividing Aetauurine (sum of [urine concentration * sample volume] for each collection interval from 0 to 12 hours post-dose) with the plasma AUCtau, where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Plasma: Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3.
Urine: Pre-dose on Day 3; 0 to 2, 2 to 4, 4 to 8 and 8 to 12 hours post-dose on Day 3

Notes:

[17] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mL/min				
geometric mean (geometric coefficient of variation)	68.16 (± 24)			

Statistical analyses

No statistical analyses for this end point

Primary: Daily Amount of Pregabalin Excreted in Breast Milk (Ae24bm)

End point title	Daily Amount of Pregabalin Excreted in Breast Milk

End point description:

Ae24bm was the daily amount of pregabalin excreted in breast milk. It was calculated by the formula: 2 * Aetaubm (sum of [breast milk concentration * sample volume] for each collection interval from 0 to

12 hours post--dose), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre--dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[18] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg				
arithmetic mean (full range (min-max))	664.6 (270 to 1720)			

Statistical analyses

No statistical analyses for this end point

Primary: Milk to Plasma Ratio for AUCtau (MPAUCtau)

End point title	Milk to Plasma Ratio for AUCtau (MPAUCtau)[19]

End point description:

MPAUCtau was the ratio of AUCtau (breast milk) to AUCtau (plasma), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Plasma: Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3.
Breast milk: Pre--dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[19] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ratio				
arithmetic mean (full range (min-max))	0.769 (0.493 to 0.956)			

Statistical analyses

No statistical analyses for this end point

Primary: Milk to Plasma Ratio for Maximum Observed Concentration (MPCmax)

End point title	Milk to Plasma Ratio for Maximum Observed Concentration (MPCmax)[20]

End point description:

Milk to plasma ratio for maximum observed concentration (MPCmax) was calculated as the ratio of Cmax (breast milk) to Cmax (plasma). The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Plasma: Pre--dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12, 18, 24 hours post--dose on Day 3.
Breast milk: Pre-dose on Day 3;
0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 32, 32 to 40 and 40 to 48 hours post--dose on Day 3.

Notes:

[20] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ratio				
arithmetic mean (full range (min-max))	0.5413 (0.335 to 0.755)			

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight Normalized Infant Dose (BWNID)

End point title	Body Weight Normalized Infant Dose (BWNID)[21]

End point description:

Body weight normalized infant dose (BWNID) of pregabalin was the dose that an infant received from breast-feeding and was calculated from the milk to plasma AUCtau ratio multiplied by the average maternal plasma pregabalin concentration (Cav) multiplied by the standardized milk consumption for an infant (150 milliliter/kilogram/day [mL/kg/day]), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Plasma: Pre-dose on Day 3; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3.
Breast milk: Pre--dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post-dose on Day 3

Notes:

[21] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/kg/day				
arithmetic mean (full range (min-max))	317.3 (202 to 458)			

Statistical analyses

No statistical analyses for this end point

Primary: Body Weight Normalized Maternal Dose (BWNMD)

End point title	Body Weight Normalized Maternal Dose (BWNMD)[22]

End point description:

Body weight normalized maternal dose (BWNMD) was calculated as the maternal dose in microgram per day (mcg/day) divided by maternal weight in kilogram (kg) at screening. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose to 24 hours post-dose on Day 3

Notes:

[22] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/kg/day				
arithmetic mean (full range (min-max))	4343.6 (3444 to 5676)			

Statistical analyses

No statistical analyses for this end point

Primary: Infant Dose Expressed as Percentage of Body Weight Normalized Maternal Dose (BWNIDPCM)

End point title	Infant Dose Expressed as Percentage of Body Weight Normalized Maternal Dose (BWNIDPCM)[23]

End point description:

Infant dose expressed as percentage of body weight normalized maternal dose (BWNIDPCM) was the relative infant dose (relative to maternal dose) calculated by the formula: 100 * BWNID (Body Weight Normalized Infant Dose) / Body Weight Normalized Maternal Dose (BWNMD), where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre-dose to 24 hours post-dose on Day 3

Notes:

[23] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: percentage of dose				
arithmetic mean (full range (min-max))	7.341 (4.43 to 9.78)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment -Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment -Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)[24]

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life--threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment--emergent are events between first dose of study drug and up to 28 days after last dose that were absent before treatment or that worsened relative to pretreatment state. Safety analysis included all subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug

Notes:

[24] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects was				

End point title	Number of Subjects with Laboratory Abnormalities[25]

End point description:

Following parameters were analyzed for laboratory examination: hematology: (hemoglobin, hematocrit, red blood cell count, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelets, white blood cell count, lymphocytes, total neutrophils, basophils, eosinophils, monocytes); liver function (bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total protein, albumin); renal function (blood urea nitrogen, creatinine, uric acid); electrolytes (sodium, potassium, chloride, calcium, bicarbonate); clinical chemistry (glucose); urinalysis (urine pH, glucose, ketones, protein, urine blood/hemoglobin, nitrite). Safety analysis included all subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug

Notes:

[25] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects	4			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Clinically Significant Change From Baseline in Vital Signs

End point title	Number of Subjects With Clinically Significant Change From Baseline in Vital Signs[26]

End point description:

Following parameters were analyzed for examination of vital signs: electrocardiogram (ECG), systolic and diastolic blood pressure, temperature, pulse rate, respiratory rate, radial pulse and body temperature. Safety analysis included all subjects who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug

Notes:

[26] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Average Breast Milk Concentration During the Dosing Interval (Cav)

End point title	Average Breast Milk Concentration During the Dosing Interval (Cav)[27]

End point description:

Average breast milk concentration during the dosing interval (Cav) was calculated by dividing AUCtau (breast milk) with tau, where tau was the dosing interval of 12 hours. The PK parameter analysis population included subjects who received study medication and had at least 1 of the PK parameters of primary interest.

End point type	Primary

End point timeframe:

Pre--dose on Day 3; 0 to 2, 2 to 4, 4 to 8, 8 to 12 hours post--dose on Day 3

Notes:

[27] - 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: Only descriptive data was planned to be reported for this endpoint.

End point values	Pregabalin			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: mcg/mL				
arithmetic mean (full range (min-max))	2.116 (1.34 to 3.06)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to 28 days after last dose of study drug	
Adverse event reporting additional description:	
The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one subject and as non-serious in another subject, or one subject may have experienced both a serious and non-serious event during the study.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Pregabalin
Reporting group description:	
Subjects received pregabalin immediate release (IR) capsules at 12 hours dosing interval on Day 1, Day 2 and Day 3.	

Serious adverse events	Pregabalin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Pregabalin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 10 (60.00%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Restless legs syndrome			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2012	1. Added breast milk expression tests, Columbia Suicidality Severity Rating Scale (C-SSRS) and the Nursing Mother Questionnaire at both pre and post dosing. 2. Updated the urine analysis section which reflected the 12 hour intervals (0-2, 2-4, 4-8 and 8-12 hours post Day 3) on which urine samples were assayed. 3. Subject were observed for a minimum of 3 hours by the qualified Clinic personnel, in case they took doses at home.
22 February 2013	1. Adverse events and concomitant medications were monitored up to 48 hours post-dose Day 3 (on Day 4 and Day 5). 2. Post-amendment dated: 18 Sep 2012, breast milk was collected up to 48 hours after Day 3 dosing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported