



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.

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|--|---------------|
| 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 standard deviation | 31.7 ± 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

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: 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) | 5.624 (\pm 0.65656) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Average Plasma Concentration During the Dosing Interval (Cav)

| | |
|-----------------|--|
| End point title | Average Plasma Concentration During the Dosing Interval (Cav) ^[5] |
|-----------------|--|

End point description:

Average plasma concentration during the dosing interval (Cav) was calculated by dividing AUC_{tau} (plasma) 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; 0.5, 1, 2, 3, 4, 6, 10, 12 hours post-dose on Day 3

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: 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) | 2.709 (\pm 24) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Minimum Observed Plasma Trough Concentration (Cmin)

| | |
|-----------------|--|
| End point title | Minimum Observed Plasma Trough Concentration (Cmin) ^[6] |
|-----------------|--|

End point description:

Cmin was the minimum observed plasma concentration of a drug after 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:

[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 (\pm 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 AUC_{tau}, 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 (\pm 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.

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|----------------|---------|
| 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: $100 \times (\text{Aetaubm} / [\text{sum of \{breast milk concentration * sample volume\} for each collection interval from 0 to 12 hours post-dose} / \text{dose}])$, 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 (\pm 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 (\pm 60) | | | |

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Amount Recovered in Urine During the Dosing Interval tau (Aetaaurine) ^[15] |
|-----------------|---|

End point description:

Aetaaurine 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 (Aetaaurine percent)

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

End point description:

Percent of dose recovered in urine during the dosing interval tau (Aetaaurine percent) was calculated as $100 \times (\text{Aetau} [\text{sum of } \{\text{urine concentration} \times \text{sample volume}\} \text{ for each collection interval from 0 to 12 hours post-dose}] \text{ divided by the dose})$, 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 (\pm 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 Aetaurine (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 (\pm 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: $100 * \text{BWNID} (\text{Body Weight Normalized Infant Dose}) / \text{Body Weight Normalized Maternal Dose (BWNMD)}$, 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 | | | | |
| AE | 8 | | | |
| SAE | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Laboratory Abnormalities

| | |
|--|--|
| 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 AUC_{tau} (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 | | | |

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

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