



## 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<br>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:

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**Results analysis stage**

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|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 20 June 2007 |
| Is this the analysis of the primary completion data? | No           |

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

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Notes:

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**General information about the trial**

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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              |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 390 |
| Worldwide total number of subjects   | 390                |
| EEA total number of subjects         | 0                  |

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Notes:

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**Subjects enrolled per age group**

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|                                           |     |
|-------------------------------------------|-----|
| 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   |

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## 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

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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<br>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<br>Units: Years     |            |       |  |
| arithmetic mean                             | 36.6       |       |  |
| standard deviation                          | ± 17.87    | -     |  |
| Title for Gender<br>Units: subjects         |            |       |  |
| Female                                      | 235        | 235   |  |
| Male                                        | 155        | 155   |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                           |                                                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| Reporting group title                                                                                                                                                                                                     | Topiramate                                               |
| Reporting group description:<br>Topiramate                                                                                                                                                                                |                                                          |
| Subject analysis set title                                                                                                                                                                                                | TOPAMAX Treated Subjects With 1-3 Seizures               |
| Subject analysis set type                                                                                                                                                                                                 | Sub-group analysis                                       |
| Subject analysis set description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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

|                                         |                                                                                                 |
|-----------------------------------------|-------------------------------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | 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 |                                               |

| <b>End point values</b>     | 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<br>Treated<br>Subjects With<br>1-3 Seizures<br>(ITT) | TOPAMAX<br>Treated<br>Subjects with<br>More Than 3<br>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 ( $\pm$<br>3.222)                                     | 61.461 ( $\pm$<br>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 <sup>[1]</sup>       |  |  |  |
| Units: Incidence of seizure          |                          |  |  |  |
| arithmetic mean (standard deviation) |                          |  |  |  |
| Baseline (n=351)                     | 6.04 ( $\pm$<br>38.538)  |  |  |  |
| Day 168 (n=231)                      | -1.19 ( $\pm$<br>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 %

| <b>Non-serious adverse events</b>                     | 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<br>occurrences (all) | 40 / 390 (10.26%)<br>50 |  |  |
| Metabolism and nutrition disorders               |                         |  |  |
| Anorexia                                         |                         |  |  |
| subjects affected / exposed<br>occurrences (all) | 44 / 390 (11.28%)<br>46 |  |  |
| Weight Decrease                                  |                         |  |  |
| subjects affected / exposed<br>occurrences (all) | 29 / 390 (7.44%)<br>30  |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported