



## Clinical trial results:

**Response to gabapentin enacarbil in two groups of RLS patients:  
Previously exposed to long-term treatment with dopaminergic agents  
versus dopaminergic treatment-naïve patients.**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-005111-16 |
| Trial protocol           | ES             |
| Global end of trial date | 30 June 2017   |

### Results information

|                                   |                                               |
|-----------------------------------|-----------------------------------------------|
| Result version number             | v1 (current)                                  |
| This version publication date     | 12 June 2022                                  |
| First version publication date    | 12 June 2022                                  |
| Summary attachment (see zip file) | Final Report signed (Final Report signed.pdf) |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | XP-IIT-0029 |
|-----------------------|-------------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |                                                                                                            |
|------------------------------|------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Sleep Research Institute                                                                                   |
| Sponsor organisation address | Calle Padre Damián 44, Madrid, Spain, 28036                                                                |
| Public contact               | Alejandro Gómez Laguna, Sleep Research Institute, +34 913454129, aglaguna@iis.es                           |
| Scientific contact           | Dr. Diego García-Borreguero Díaz-Varela, Sleep Research Institute, +34 913454129, dgb.investigation@iis.es |

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                       | 01 September 2017 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 30 June 2017      |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 30 June 2017      |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To compare the IRLS response to a two-week treatment with gabapentin enacarbil (600 mg/d) as judged by the clinical impression of the investigator in two groups of RLS patients:

-A group of treatment-naïve RLS patients

vs.

- a similar group of patients previously treated with dopaminergics for at least 90% of the time during the last five years.

Protection of trial subjects:

Given the short period of treatment with placebo, no specific protection measures were needed.

Subjects that could not tolerate any of both treatment conditions were allowed to discontinue the trial at any time point.

Background therapy:

Subjects included in the study were stratified into those that had been treated for at least 5 years with dopaminergic agents and those that had not.

Evidence for comparator:

All patients were treated according to a double-blind crossover design with either gabapentin enacarbil (GBPen) or placebo. GBPen is approved for the treatment of RLS in the USA and in other non-European countries (Japan, etc.)

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 01 March 2015 |
| 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 | Spain: 40 |
| Worldwide total number of subjects   | 40        |
| EEA total number of subjects         | 40        |

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)                     | 30 |
| From 65 to 84 years                      | 10 |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Subjects had to meet all inclusion and exclusion criteria as pointed out in the study protocol:

Patients were randomly contacted out of the database of our Institute and screened for eligibility.

### Pre-assignment period milestones

|                            |    |
|----------------------------|----|
| Number of subjects started | 40 |
|----------------------------|----|

|                              |    |
|------------------------------|----|
| Number of subjects completed | 39 |
|------------------------------|----|

### Pre-assignment subject non-completion reasons

|                            |                                                  |
|----------------------------|--------------------------------------------------|
| Reason: Number of subjects | due to the severity of symptoms during the sc: 1 |
|----------------------------|--------------------------------------------------|

### Period 1

|                |                                |
|----------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
|----------------|--------------------------------|

|                              |     |
|------------------------------|-----|
| Is this the baseline period? | Yes |
|------------------------------|-----|

|                   |                         |
|-------------------|-------------------------|
| Allocation method | Randomised - controlled |
|-------------------|-------------------------|

|               |              |
|---------------|--------------|
| Blinding used | Double blind |
|---------------|--------------|

|               |                                                               |
|---------------|---------------------------------------------------------------|
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |
|---------------|---------------------------------------------------------------|

Blinding implementation details:

Blinding was completed before receiving the drug at the study site; manufactured placebo capsules were equal in aspect, size, color and taste to the active compound.

### Arms

|                              |    |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

|           |                      |
|-----------|----------------------|
| Arm title | Gabapentin enacarbil |
|-----------|----------------------|

Arm description: -

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Gabapentine enacarbryl |
|----------------------------------------|------------------------|

|                                        |  |
|----------------------------------------|--|
| Investigational medicinal product code |  |
|----------------------------------------|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |               |
|----------------------|---------------|
| Pharmaceutical forms | Capsule, hard |
|----------------------|---------------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

Oral intake of 600 mg of Gabapentine enacarbryl at 19:00

|           |         |
|-----------|---------|
| Arm title | Placebo |
|-----------|---------|

Arm description: -

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|                                        |         |
|----------------------------------------|---------|
| Investigational medicinal product name | Placebo |
|----------------------------------------|---------|

|                                        |  |
|----------------------------------------|--|
| Investigational medicinal product code |  |
|----------------------------------------|--|

|            |  |
|------------|--|
| Other name |  |
|------------|--|

|                      |               |
|----------------------|---------------|
| Pharmaceutical forms | Capsule, hard |
|----------------------|---------------|

|                          |          |
|--------------------------|----------|
| Routes of administration | Oral use |
|--------------------------|----------|

Dosage and administration details:

oral intake of placebo at 19:00

| <b>Number of subjects in period 1</b> | Gabapentin<br>enacarbil | Placebo |
|---------------------------------------|-------------------------|---------|
| Started                               | 39                      | 39      |
| Completed                             | 38                      | 39      |
| Not completed                         | 1                       | 0       |
| patient decision                      | 1                       | -       |

## Baseline characteristics

### Reporting groups

Reporting group title

Overall trial

Reporting group description: -

| Reporting group values                                | Overall trial | Total |  |
|-------------------------------------------------------|---------------|-------|--|
| Number of subjects                                    | 40            | 40    |  |
| Age categorical                                       |               |       |  |
| Units: Subjects                                       |               |       |  |
| In utero                                              | 0             | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                                  | 0             | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0             | 0     |  |
| Children (2-11 years)                                 | 0             | 0     |  |
| Adolescents (12-17 years)                             | 0             | 0     |  |
| Adults (18-64 years)                                  | 30            | 30    |  |
| From 65-84 years                                      | 10            | 10    |  |
| 85 years and over                                     | 0             | 0     |  |
| Gender categorical                                    |               |       |  |
| Units: Subjects                                       |               |       |  |
| Female                                                | 23            | 23    |  |
| Male                                                  | 17            | 17    |  |

## End points

### End points reporting groups

|                                |                      |
|--------------------------------|----------------------|
| Reporting group title          | Gabapentin enacarbil |
| Reporting group description: - |                      |
| Reporting group title          | Placebo              |
| Reporting group description: - |                      |

**Primary: The primary objective of this study is to compare the therapeutic response of two types of RLS populations (previous long-term dopaminergic treatment vs treatment naïve) to a 2 week treatment period with gabapentin enacarbil by means of the IRLS.**

|                 |                                                                                                                                                                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | The primary objective of this study is to compare the therapeutic response of two types of RLS populations (previous long-term dopaminergic treatment vs treatment naïve) to a 2 week treatment period with gabapentin enacarbil by means of the IRLS. |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The primary objective of this study is to compare the therapeutic response of two types of RLS populations (previous long-term dopaminergic treatment vs treatment naïve) to a 2 week treatment period with gabapentin enacarbil by means of the International Restless Legs Scale (IRLS). Change in IRLS-Total Score from baseline (Visit BL) to week 2 (V2) will be analyzed using Analysis of Covariance (ANCOVA) with the change score as the dependent variable and the independent variables of treatment and baseline (Visit BL) IRLS-Total Score. Assumptions for the ANCOVA model will be checked using plots of predicted values versus residuals as well as plots of the baseline score versus change score for each treatment (note that the small sample size limits the usefulness of a treatment by baseline interaction term for the model).

|                                                                                                                 |         |
|-----------------------------------------------------------------------------------------------------------------|---------|
| End point type                                                                                                  | Primary |
| End point timeframe:                                                                                            |         |
| Difference in change on the IRLS scale (difference between week 2 and baseline) between both groups of patients |         |

| End point values            | Gabapentin enacarbil | Placebo         |  |  |
|-----------------------------|----------------------|-----------------|--|--|
| Subject group type          | Reporting group      | Reporting group |  |  |
| Number of subjects analysed | 19                   | 20              |  |  |
| Units: IRLS scale           |                      |                 |  |  |
| change in IRLS scale        | 19                   | 20              |  |  |

|                                   |            |
|-----------------------------------|------------|
| <b>Attachments (see zip file)</b> | Charts.pdf |
|-----------------------------------|------------|

### Statistical analyses

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

Statistical analysis description:

The primary objective of this study is to compare the therapeutic response of two types of RLS populations (previous long-term dopaminergic treatment vs treatment naïve) to a 2 week treatment

period with gabapentin enacarbil by means of the International Restless Legs Scale (IRLS).

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Comparison groups                       | Gabapentin enacarbil v Placebo |
| Number of subjects included in analysis | 39                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | < 0.05 <sup>[1]</sup>          |
| Method                                  | Wilcoxon (Mann-Whitney)        |
| Parameter estimate                      | Mean difference (final values) |
| Variability estimate                    | Standard deviation             |
| Dispersion value                        | 1.315                          |

Notes:

[1] - We hypothesized that patients never treated before with dopaminergics (Group A) would benefit significantly more from a two-week treatment with gabapentin enacarbil (vs. a two-week treatment with placebo) than patients dopaminergics treated

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

A maximum period of 24 hours, from the date on which the adverse event is known.

Adverse event reporting additional description:

Adverse events were summarized by treatment and severity. Adverse events were coded using standardized methods. Vital signs were summarized for each visit at which they are collected. Rates of concomitant medication use were summarized using WHO-coding.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |            |
|-----------------|------------|
| Dictionary name | WHO-coding |
|-----------------|------------|

|                    |      |
|--------------------|------|
| Dictionary version | 2014 |
|--------------------|------|

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Gabapentin enacarbil |
|-----------------------|----------------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Gabapentin enacarbil | Placebo        |  |
|---------------------------------------------------|----------------------|----------------|--|
| Total subjects affected by serious adverse events |                      |                |  |
| subjects affected / exposed                       | 0 / 19 (0.00%)       | 0 / 20 (0.00%) |  |
| number of deaths (all causes)                     | 0                    | 0              |  |
| number of deaths resulting from adverse events    | 0                    | 0              |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events                            | Gabapentin enacarbil | Placebo         |  |
|-------------------------------------------------------|----------------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                      |                 |  |
| subjects affected / exposed                           | 9 / 19 (47.37%)      | 5 / 20 (25.00%) |  |
| Nervous system disorders                              |                      |                 |  |
| Ataxia                                                |                      |                 |  |
| subjects affected / exposed                           | 6 / 19 (31.58%)      | 5 / 20 (25.00%) |  |
| occurrences (all)                                     | 6                    | 5               |  |
| Headache                                              |                      |                 |  |
| subjects affected / exposed                           | 4 / 19 (21.05%)      | 3 / 20 (15.00%) |  |
| occurrences (all)                                     | 4                    | 3               |  |
| Dizziness                                             |                      |                 |  |

|                                                                                                                                                                                                                                                                                                                      |                                                                                                        |                                                                                                      |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                     | 3 / 19 (15.79%)<br>3                                                                                   | 0 / 20 (0.00%)<br>0                                                                                  |  |
| General disorders and administration<br>site conditions<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                             | 1 / 19 (5.26%)<br>1                                                                                    | 1 / 20 (5.00%)<br>1                                                                                  |  |
| Eye disorders<br>conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                  | 1 / 19 (5.26%)<br>1                                                                                    | 1 / 20 (5.00%)<br>1                                                                                  |  |
| Gastrointestinal disorders<br>Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry mouth<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Reflux gastritis<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1<br><br>3 / 19 (15.79%)<br>3<br><br>2 / 19 (10.53%)<br>2<br><br>1 / 19 (5.26%)<br>0 | 1 / 20 (5.00%)<br>1<br><br>0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>1 / 20 (5.00%)<br>0 |  |
| Dyspepsia                                                                                                                                                                                                                                                                                                            | Additional description: Stomach ache                                                                   |                                                                                                      |  |
| subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                     | 1 / 19 (5.26%)<br>1                                                                                    | 1 / 20 (5.00%)<br>1                                                                                  |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                 | 1 / 19 (5.26%)<br>1                                                                                    | 1 / 20 (5.00%)<br>1                                                                                  |  |
| Endocrine disorders<br>Fluid retention<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                           | 2 / 19 (10.53%)<br>2                                                                                   | 0 / 20 (0.00%)<br>0                                                                                  |  |
| Musculoskeletal and connective tissue<br>disorders                                                                                                                                                                                                                                                                   |                                                                                                        |                                                                                                      |  |

|                                                                                             |                                                               |                      |                     |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------|----------------------|---------------------|
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                              | Additional description: Retroesternal Pain                    |                      |                     |
|                                                                                             | 1 / 19 (5.26%)<br>1                                           | 1 / 20 (5.00%)<br>1  |                     |
| Product issues<br>Lethargy<br>subjects affected / exposed<br>occurrences (all)              | Additional description: Drowsiness                            |                      |                     |
|                                                                                             | 9 / 19 (47.37%)<br>9                                          | 4 / 20 (20.00%)<br>4 |                     |
| Infections and infestations<br>Rhinitis<br>subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2                                          | 1 / 20 (5.00%)<br>1  |                     |
|                                                                                             | Infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1  | 1 / 20 (5.00%)<br>1 |

## 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