



## 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
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##### 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
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Number of subjects completed	39
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### Pre-assignment subject non-completion reasons

Reason: Number of subjects	due to the severity of symptoms during the sc: 1
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### Period 1

Period 1 title	Overall trial (overall period)
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Is this the baseline period?	Yes
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Allocation method	Randomised - controlled
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Blinding used	Double blind
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Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
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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
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Arm title	Gabapentin enacarbil
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Arm description: -

Arm type	Active comparator
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Investigational medicinal product name	Gabapentine enacarbryl
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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Dosage and administration details:

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

Arm title	Placebo
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Arm description: -

Arm type	Placebo
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Investigational medicinal product name	Placebo
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Capsule, hard
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Routes of administration	Oral use
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Dosage and administration details:

oral intake of placebo at 19:00

<b>Number of subjects in period 1</b>	Gabapentin 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 (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 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.
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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
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### Statistical analyses

<b>Statistical analysis title</b>	Data analysis
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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
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### Dictionary used

Dictionary name	WHO-coding
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Dictionary version	2014
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### Reporting groups

Reporting group title	Gabapentin enacarbil
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Reporting group description: -

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

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