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-naive 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 elegibility.

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

Number of subjects in period 1	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 naive) 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 naive) 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 naive) 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		

Attachments (see zip file)	Charts.pdf

Statistical analyses

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported