Clinical trial results:
Randomized double blind parallel groups sequential, placebo controlled, trial assessing the efficacy and safety of BP1.4979 in Resteless Legs Syndrome (RLS).

Summary

EudraCT number	2013-004884-30
Trial protocol	FR
Global end of trial date	17 March 2020

Results information

Result version number	v1 (current)
This version publication date	25 June 2022
First version publication date	25 June 2022

Trial information

Trial identification

Sponsor protocol code	P13-04/BP1.4979

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345953
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bioprojet Pharma
Sponsor organisation address	9 rue Rameau, Paris, France, 75002
Public contact	Bioprojet clinical departement, Bioprojet Pharma, 0033 147036633, contact@bioprojet.com
Scientific contact	Bioprojet clinical departement, Bioprojet Pharma, 0033 147036633, contact@bioprojet.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2020
Global end of trial reached?	Yes
Global end of trial date	17 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess in RLS patients the efficacy and the safety profile of BP1.4979 15 mg BID.

Protection of trial subjects:

The study was conducted in accordance with the Ethical principles stated in the Declaration of Helsinki (Tokyo, October 2013) and the French law n° 2004-806, August 9th, 2004 relative to public health law as well as the May 1996 International Council on Harmonisation(ICH) Guidelines. The study was also conducted in accordance with International Guidelines on Good Clinical Practices (GCP) and Standard Operating Procedures (SOP) for clinical investigation and documentation in force at Bioprojet Pharma. The study was monitored by Bioprojet Pharma who regularly checked compliance with the protocol, compared selected key data in the CRF with its source data, and verified Drug Accountability and Informed Consent signatures.

Background therapy:

Patients had to stop any medication prescribed for the treatment of their Restless Legs Syndrome (RLS), any drug associated with the development or the worsening of their RLS (e.g., antidepressants, antipsychotics and dopamine antagonists, etc..) and any other medication that may have caused sedation or negatively impacted with the study drug activity (e.g., sedatives, hypnotics, steroids).

Evidence for comparator: -

Actual start date of recruitment	06 February 2018
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	France: 29
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	15
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in France from February 2018 until mid of March 2020.

Pre-assignment

Screening details:

A total of 67 patients were screened. Twenty-nine (29) out of the 67 were randomized to receive either the activie drug, BP1.4979 (13 patients) or the placebo (19 patients).

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	29

Period 1

Period 1 title	Double-blind 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:

The placebo tablets were identical in appearance to the BP1.4979 tablets, and patients / investigators / site staff / other contributors remained blinded to the treatment randomization code.

Arms

Are arms mutually exclusive?	Yes
Arm title	BP1.4979 treatment arm (Double-blind)

Arm description:

Patients with Restless Legs Syndrome (RLS) were treated with BP1.4979 15 mg tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).

Arm type	Experimental
Investigational medicinal product name	BP1.4979
Investigational medicinal product code	BP1.4979
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take 2 tablets of 15 mg BP1.4979 per day: one during lunch and one in the evening during dinner with a glass of water from randomization until end of Double-Blind period.

Arm title	Placebo arm (Double-Blind)

Arm description:

Patients with Restless Legs Syndrome (RLS) were treated with placebo tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take 2 tablets of placebo per day: one during lunch and one in the evening during

dinner with a glass of water from randomization until end of Double-Blind period.

Number of subjects in period 1	BP1.4979 treatment arm (Double-blind)	Placebo arm (Double-Blind)
Started	13	16
Completed	13	15
Not completed	0	1
Lack of efficacy	-	1

Period 2	
Period 2 title	Single-Blind
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Arm title	Placebo arm (Single-Blind)

Arm description:

Patients who completed the Double-Blind period were to continue in the study for a 1-week single-blind period under placebo treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients were to take 2 tablets of placebo per day: one during lunch and one in the evening during dinner with a glass of water for one week from the end of Double-Blind period until the end of study.

Number of subjects in period 2	Placebo arm (Single-Blind)
Started	28
Completed	28

Baseline characteristics

Reporting groups	
Reporting group title	BP1.4979 treatment arm (Double-blind)
Reporting group description:	
Patients with Restless Legs Syndrome (RLS) were treated with BP1.4979 15 mg tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).	
Reporting group title	Placebo arm (Double-Blind)
Reporting group description:	
Patients with Restless Legs Syndrome (RLS) were treated with placebo tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).	

Reporting group values	BP1.4979 treatment arm (Double-blind)	Placebo arm (Double-Blind)	Total
Number of subjects	13	16	29
Age categorical Units: Subjects			
Adults (18-64 years)	7	8	15
From 65-84 years	6	8	14
Age continuous Units: years			
arithmetic mean	59.27	58.20	
standard deviation	± 13.63	± 17.52	-
Gender categorical Units: Subjects			
Female	5	8	13
Male	8	8	16

End points

End points reporting groups

Reporting group title	BP1.4979 treatment arm (Double-blind)
Reporting group description:	
Patients with Restless Legs Syndrome (RLS) were treated with BP1.4979 15 mg tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).	
Reporting group title	Placebo arm (Double-Blind)
Reporting group description:	
Patients with Restless Legs Syndrome (RLS) were treated with placebo tablets twice a day from randomization until end of the Double-Blind period (i.e., for 2 weeks).	
Reporting group title	Placebo arm (Single-Blind)
Reporting group description:	
Patients who completed the Double-Blind period were to continue in the study for a 1-week single-blind period under placebo treatment.	

Primary: PLMS index (Periodic Limb Movements per hour of Sleep)

End point title	PLMS index (Periodic Limb Movements per hour of Sleep)
End point description:	
The PLMS index (Periodic Limb Movements per hour of Sleep) was evaluated by polysomnography (PSG) at baseline (i.e., prior to randomization) and at the end of the double-blind period. The change in PLMS index from baseline to the end of the double-blind period was measured in the ITT population.	
End point type	Primary
End point timeframe:	
The PLMS index was evaluated at baseline (prior to randomization) and at the end of the Double-Blind period (i.e., V2 and V3).	

End point values	BP1.4979 treatment arm (Double-blind)	Placebo arm (Double-Blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: Number of leg movements per hour				
arithmetic mean (standard deviation)				
PLMS index	-19.57 (± 12.62)	-9.01 (± 18.01)		

Statistical analyses

Statistical analysis title	Adjusted treatment effect
Comparison groups	BP1.4979 treatment arm (Double-blind) v Placebo arm (Double-Blind)

Number of subjects included in analysis	29
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.19

Secondary: IRLSRS (International Restless Legs Syndrome Rating Scale) score

End point title	IRLSRS (International Restless Legs Syndrome Rating Scale) score

End point description:

The IRLSRS is a 10-question scale on RLS symptoms, each rated from 0 (none) to 4 (very severe). An overall score of 31-40 points was classified as very severe, 21-30 points as severe, 11-20 points as moderate, 1-10 points as mild, and 0 points as none.
The IRLSRS score was evaluated at baseline (i.e., prior to randomization) and the end of the Double-Blind period. The change in International Restless Legs Syndrome Rating Scale (IRLSRS) score from baseline to the end of the Double-Blind period was measured in the ITT population.

End point type	Secondary

End point timeframe:

The IRLSRS score was evaluated at baseline (prior to randomization) and at the end of the Double-Blind period (i.e., V2 and V3).

End point values	BP1.4979 treatment arm (Double-blind)	Placebo arm (Double-Blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	16		
Units: Score				
arithmetic mean (standard deviation)				
IRLSRS score	-7.46 (± 8.66)	-4.56 (± 5.69)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of reporting AEs extended from the time the patient gave informed consent until the last follow-up visit of the patient.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	BP1.4979 Treatment Arm
Reporting group description: -	
Reporting group title	Placebo Treatment Arm

Reporting group description: -

Serious adverse events	BP1.4979 Treatment Arm	Placebo Treatment Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 16 (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: 2 %

Non-serious adverse events	BP1.4979 Treatment Arm	Placebo Treatment Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 13 (30.77%)	8 / 16 (50.00%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	2 / 13 (15.38%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	0 / 13 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Balance disorder			
subjects affected / exposed	0 / 13 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
General disorders and administration			

site conditions Fatigue subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	1 / 16 (6.25%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 16 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 16 (0.00%) 0	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	2 / 16 (12.50%) 2	
Infections and infestations Bonchitis subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0 0 / 13 (0.00%) 0	1 / 16 (6.25%) 1 1 / 16 (6.25%) 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? Yes

Date	Interruption	Restart date
17 March 2020	From June 2019, it was apparent that the recruitment of the trial was difficult, mainly due to the necessity of hospitalizing patients for polysomnography needed for reporting the main PLMS score. For one year, the recruitment did not increase, and from March 2020, the COVID-19 crisis annihilated any hope for further accrual. It was decided to anticipate the statistical analysis of the second GST look at the current sample size (n=29). Consecutively to the second look, a premature stop of the study was decided for significant result of the main endpoint by Bioprojet Pharma on 29 April 2020.	-

Notes:

Limitations and caveats

None reported