Clinical trial results:
Efficacy and Safety of Pitolisant (BF2.649) in the Treatment of Excessive Daytime Sleepiness in Patients with Obstructive Sleep Apnoea Syndrome, Treated or Not by Nasal Continuous Positive Airway Pressure, but Still Complaining of Excessive Daytime Sleepiness

Summary

EudraCT number	2015-004561-85
Trial protocol	BG
Global end of trial date	29 April 2020

Results information

Result version number	v1 (current)
This version publication date	07 May 2022
First version publication date	07 May 2022

Trial information

Trial identification

Sponsor protocol code	P1513/BF2.649

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02739568
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bioprojet Pharma
Sponsor organisation address	9, rue Rameau, Paris, France, 75002
Public contact	Clinical Development Director, Bioprojet Pharma, +33 147 03 66 33, contact@bioprojet.com
Scientific contact	Clinical Development Director, Bioprojet Pharma, +33 147 03 66 33, 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	14 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 July 2019
Global end of trial reached?	Yes
Global end of trial date	29 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to demonstrate the efficacy and safety of pitolisant given at 10, 20, or 40 mg per day versus placebo during 12 weeks for the Double-blind period, to treat the Excessive Daytime Sleepiness (EDS) in patients with moderate to severe Obstructive Sleep Apnea (OSA) refusing the nasal Continuous Positive Airway Pressure (nCPAP) therapy or treated by nCPAP but still complaining of EDS. The efficacy of pitolisant was assessed separately in patients treated with nCPAP and in patients without nCPAP use.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki 2008, and in compliance with the protocol and the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines, as required by the major regulatory authorities, and following all other local requirements.

Background therapy:

Patients receiving pitolisant or placebo were treated or not by Nasal Continuous Positive Airway Pressure (nCPAP)

Evidence for comparator: -

Actual start date of recruitment	07 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 325
Country: Number of subjects enrolled	North Macedonia: 36
Worldwide total number of subjects	361
EEA total number of subjects	325

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)	361
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 389 patients were screened, and a total of 361 patients were randomized to pitolisant (242 patients) or placebo (119 patients).

Period 1

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

Blinding implementation details:

Both the patient and the Investigator were blind during the Double-blind period. To make sure that the prescribed dose was appropriately administered to the patient to comply with the study conduct, tablets of pitolisant 5 mg and matching placebo, as well as tablets of pitolisant 20 mg and matching placebo, had the same mass, color, shape, and size.

Arms

Are arms mutually exclusive?	Yes
Arm title	BF2.649 Treatment Arm (Double-blind)

Arm description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by pitolisant.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Arm type	Experimental
Investigational medicinal product name	Pitolisant hydrochloride
Investigational medicinal product code	BF2.649
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients under pitolisant were to take, in the morning during breakfast with a glass of water, either:
o Low dose 10 mg: two 5 mg tablets;
o Medium dose 20 mg: one 20 mg tablet;
o High dose 40 mg: two 20 mg tablets;
The therapeutic units were prescribed to patients according to an individual treatment program and the posology was determined during the dose adjustment phase according to tolerance. The high dose of 40 mg (two 20 mg tablets) was the planned stable dose for the duration of the study, depending on tolerance.

Arm title	Placebo Arm (Double-blind)

Arm description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by placebo.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

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:

Same dosage and administration as BF2.649 but with placebo.

Number of subjects in period 1	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)
Started	242	119
Completed	239	117
Not completed	3	2
Adverse event, non-fatal	-	1
Other reason	1	-
Lost to follow-up	1	1
Changing position towards nCPAP therapy	1	-

Baseline characteristics

Reporting groups

Reporting group title	BF2.649 Treatment Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by pitolisant.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Reporting group title	Placebo Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by placebo.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Reporting group values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)	Total
Number of subjects	242	119	361
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	242	119	361
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	52.3	52.6	
standard deviation	± 9.8	± 10.6	-
Gender categorical Units: Subjects			
Female	66	29	95
Male	176	90	266

Subject analysis sets

Subject analysis set title	nCPAP use + BF2.649
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) treated by Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received pitolisant.

Subject analysis set title	nCPAP use + placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) treated by Nasal Continuous Positive Airway Pressure

(nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received placebo.

Subject analysis set title	No nCPAP use + BF2.649
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) refusing Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received pitolisant.

Subject analysis set title	No nCPAP use + placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) refusing Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received placebo.

Reporting group values	nCPAP use + BF2.649	nCPAP use + placebo	No nCPAP use + BF2.649
Number of subjects	121	58	121
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	121	58	121
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	No nCPAP use + placebo		
Number of subjects	61		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	61		
From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	BF2.649 Treatment Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by pitolisant.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Reporting group title	Placebo Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by placebo.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Subject analysis set title	nCPAP use + BF2.649
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) treated by Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received pitolisant.

Subject analysis set title	nCPAP use + placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) treated by Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received placebo.

Subject analysis set title	No nCPAP use + BF2.649
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) refusing Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received pitolisant.

Subject analysis set title	No nCPAP use + placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Obstructive Sleep Apnea (OSA) refusing Nasal Continuous Positive Airway Pressure (nCPAP) but still complaining of Excessive Daytime Sleepiness (EDS) who received placebo.

Primary: Epworth Sleepiness Scale (ESS)

End point title	Epworth Sleepiness Scale (ESS)

End point description:

The primary efficacy endpoint was the change of the ESS score between the baseline and the end of the Double-blind period. ESS score measured persistent daytime sleepiness or sleep propensity for adult patients in the Full Analysis Set (FAS) population. The ESS score was the sum of the eight sub-scores and can range from 0 to 24 with higher scores representing greater sleepiness. A score greater than 10 was considered as abnormal sleepiness.

End point type	Primary

End point timeframe:

Between the baseline (V2) and the end of the Double-blind period (mean between V5 and V6)

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)	nCPAP use + BF2.649	nCPAP use + placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	242	119	121	58
Units: score				
arithmetic mean (confidence interval 95%)	-4.66 (-5.05 to -4.27)	-1.83 (-2.84 to -0.82)	-5.00 (-5.54 to -4.46)	-1.89 (-3.49 to -0.28)

End point values	No nCPAP use + BF2.649	No nCPAP use + placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	121	61		
Units: score				
arithmetic mean (confidence interval 95%)	-4.31 (-4.87 to -3.75)	-1.78 (-3.08 to -0.48)		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

The primary analysis on the final ESS score demonstrated a statistically significantly greater reduction in final ESS with pitolisant than with placebo, with a least square (LS) mean difference of -2.6 (95% CI [-3.4; -1.8]; $p < 0.001$). The sensitivity analyses confirmed this result and showed no statistically significant effect of nCPAP use and no treatment nCPAP interaction.

Comparison groups	BF2.649 Treatment Arm (Double-blind) v Placebo Arm (Double-blind)
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Pichot Fatigue Scale

End point title	Pichot Fatigue Scale

End point description:

The asthenia-fatigue scale used in this study, consists of eight questions scored progressively from "0" (not at all) to "4" (extremely) in the following situations (score min 0- score max 32). A score > 22 indicates excessive fatigue. This endpoint was measured in the Full Analysis Set (FAS) population.

End point type	Secondary

End point timeframe:

The Pichot Fatigue Scale was evaluated at V2, V6, and V7 (for the double-blind period).

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	239	117		
Units: score				
arithmetic mean (confidence interval 95%)	-2.2 (-2.8 to -1.7)	-0.1 (-1.2 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression (CGI)

End point title	Clinical Global Impression (CGI)

End point description:

The clinical global impression (CGI) is a 3-item observer rated scale which measures illness severity (CGI of illness severity, CGI-S), global improvement or change (CGI-C), and therapeutic response. CGI-S was evaluated at V1 and V2, and CGI-C was evaluated at V6 and V7 (for the Double-blind period). This endpoint was measured in the Full Analysis Set (FAS) population.

End point type	Secondary

End point timeframe:

CGI was evaluated at baseline (V1 and V2) and at the end of the Double-blind period (V6 and V7).

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	92		
Units: % Patients with CGI-C improvement at V6				
number (confidence interval 95%)	92.5 (88.4 to 95.5)	78.6 (70.1 to 85.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Therapy Response R1

End point title	Therapy Response R1

End point description:

Therapy response R1 is the % of patients with an absolute value of the ESS score ≤10 at the end of the Double-blind period. This endpoint was measured in the Full Analysis Set (FAS) population.

End point type	Secondary

End point timeframe:

From baseline to the end of the Double-blind period.

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	119		
Units: Percentage of patients				
number (confidence interval 95%)	51.7 (45.2 to 58.1)	37.8 (29.1 to 47.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Therapy Response R2

End point title	Therapy Response R2

End point description:

Therapy response R2 is the % of patients with an absolute value of the ESS score ≤10 or a value of ≤-3 for the difference between DBF LOCF (Double-Blind Period Final Value, Last Observation Carried Forward) ESS and baseline (V2) ESS. This endpoint was measured in the Full Analysis Set (FAS) population.

End point type	Secondary

End point timeframe:

From baseline to the end of the Double-Blind period.

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	242	119		
Units: Percentage of patients				
number (confidence interval 95%)	71.1 (64.9 to 76.7)	56.3 (46.9 to 65.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation of AEs extended from the time the patient gave informed consent (V1) until 1 month after the last visit (V7). The occurrence of any AE was monitored at each visit and at each phone contact (Ph1, Ph2, and Ph3).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	BF2.649 Treatment Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by pitolisant.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Reporting group title	Placebo Arm (Double-blind)

Reporting group description:

Patients with OSA (obstructive sleep apnea) refusing the nCPAP therapy or treated by nCPAP but still complaining of EDS, treated by placebo.
Treatment was initiated by an individual escalating dose phase over 2 weeks, followed by a dose adjustment phase and a stable dose phase for 9 weeks until the end of the Double-blind period (V6).

Serious adverse events	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 241 (0.41%)	0 / 119 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	Additional description: Infectious exacerbation of COPD		
subjects affected / exposed	1 / 241 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 241 (11.20%)	12 / 119 (10.08%)	

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 15 / 241 (6.22%) 16	 9 / 119 (7.56%) 9	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 12 / 241 (4.98%) 12	 3 / 119 (2.52%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2018	The aim of the protocol amendment was to strengthen and enhance the level of evidence of the study by assessing the efficacy and safety of pitolisant separately in patients using nCPAP and in those refusing nCPAP as therapy for OSA.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported