



## Clinical trial results:

**BF2.649 in patients with Obstructive Sleep Apnoea syndrome (OSA), and treated by nasal Continuous Positive Airway Pressure (nCPAP), but still complaining of Excessive Daytime Sleepiness (EDS).**

### Summary

EudraCT number	2009-017248-14
Trial protocol	DE BE ES FI SE DK BG
Global end of trial date	22 March 2014

### Results information

Result version number	v1 (current)
This version publication date	02 March 2022
First version publication date	02 March 2022

### Trial information

#### Trial identification

Sponsor protocol code	P 09-08
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	20 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2013
Global end of trial reached?	Yes
Global end of trial date	22 March 2014
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The first objective of this study was to demonstrate the efficacy and safety of BF2.649 given at 5-, 10-, or 20 mg per day versus placebo, during 12 weeks for the double blind period, for the treatment of the excessive diurnal sleepiness in patients with moderate to severe Obstructive Sleep Apnoea (OSA) who experience residual sleepiness despite regular nasal Continuous Positive Airway Pressure (nCPAP) use.

Protection of trial subjects:

In order to avoid useless patient exposure, 2 futility analyses were planned when 60 and 120 patients had completed the double-blind phase of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Bulgaria: 110
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Finland: 21
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	North Macedonia: 13
Worldwide total number of subjects	244
EEA total number of subjects	231

Notes:

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**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)	215
From 65 to 84 years	29
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

During the screening visit, the investigator checked the inclusion and exclusion criteria and performed all required screening assessments. From this visit, a 14-day wash-out period started.

298 patients were screened for inclusion. Of those, 244 patients (81.9%) were eligible for entry into the study

### 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	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

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

Arm description:

12-week double-blind period starting with an escalating dose period with BF2.649 given at 5-, 10-, or 20 mg per day, followed by treatment with the selected dose.

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

Dosage and administration details:

1 capsule per day, containing ¼, ½, or one 20 mg tablet of BF2.649

<b>Arm title</b>	Placebo Arm (Double-blind)
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Arm description:

12-week double-blind period with placebo.

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

Dosage and administration details:

1 capsule per day, containing placebo (lactose)

<b>Number of subjects in period 1</b>	<b>BF2.649 Treatment Arm (Double-blind)</b>	<b>Placebo Arm (Double-blind)</b>
Started	183	61
Completed	174	58
Not completed	9	3
Consent withdrawn by subject	3	1
Adverse event, non-fatal	4	2
Lost to follow-up	1	-
Protocol deviation	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	BF2.649 Treatment Arm (Double-blind)
Reporting group description: 12-week double-blind period starting with an escalating dose period with BF2.649 given at 5-, 10-, or 20 mg per day, followed by treatment with the selected dose.	
Reporting group title	Placebo Arm (Double-blind)
Reporting group description: 12-week double-blind period with placebo.	

Reporting group values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)	Total
Number of subjects	183	61	244
Age categorical Units: Subjects			
Adults (18-64 years)	159	56	215
65 years and over	24	5	29
Age continuous Units: years			
arithmetic mean	53.8	51.0	
standard deviation	± 10.5	± 10.6	-
Gender categorical Units: Subjects			
Female	34	8	42
Male	149	53	202

## End points

### End points reporting groups

Reporting group title	BF2.649 Treatment Arm (Double-blind)
Reporting group description: 12-week double-blind period starting with an escalating dose period with BF2.649 given at 5-, 10-, or 20 mg per day, followed by treatment with the selected dose.	
Reporting group title	Placebo Arm (Double-blind)
Reporting group description: 12-week double-blind period with placebo.	

### Primary: Epworth Sleepiness Scale (ESS) - Double-blind period

End point title	Epworth Sleepiness Scale (ESS) - Double-blind period
End point description: ESS score measured persistent daytime sleepiness or sleep propensity for adult patients in ITT (Intention-to-treat) 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 baseline and end of 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	183	61		
Units: Score				
arithmetic mean (full range (min-max))	-5.52 (-18.5 to 3.0)	-2.75 (-16.0 to 8.0)		

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: For the ITT Population this model showed a statistically significant treatment effect ( $p < 0.001$ ), with a least squares mean estimate of the difference between the 2 treatment groups of -2.6 (95% CI: [-3.9; -1.4]). This shows a statistically significant effect of pitolisant compared to placebo in reducing excessive daytime sleepiness in patients with OSA.	
Comparison groups	BF2.649 Treatment Arm (Double-blind) v Placebo Arm (Double-blind)

Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

### Secondary: Epworth Response (R1)

End point title	Epworth Response (R1)
End point description:	Reaching an absolute value of the ESS inferior to 11 in the ITT population.
End point type	Secondary
End point timeframe:	From beginning of treatment to end of double-blind (treatment and placebo arms).

End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	61		
Units: percent				
number (confidence interval 95%)	56.3 (48.8 to 63.6)	42.6 (30.0 to 55.9)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Epworth Response (R2)

End point title	Epworth Response (R2)
End point description:	Either reaching an absolute ESS inferior to 11 or an improvement from baseline of at least 3 in the ITT population.
End point type	Secondary
End point timeframe:	From beginning of treatment to end of double-blind (treatment and placebo arms).



End point values	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	61		
Units: percent				
number (confidence interval 95%)	71.0 (63.9 to 77.5)	54.1 (40.8 to 66.9)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pichot Fatigue Scale

End point title	Pichot Fatigue Scale
End point description: The Pichot questionnaire was a practical 24-item self-rating account with three homogeneous subscales of 8 items each which measure depressive mood, asthenia-fatigue, and anxiety parameters, respectively. A score > 22 indicates excessive fatigue. This endpoint was measured in the ITT population	
End point type	Secondary
End point timeframe: This test was performed at V2 and Visits 6 (end of 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	183	61		
Units: Score				
arithmetic mean (standard deviation)	-3.8 (± 5.6)	-2.9 (± 5.9)		

## 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 CGI was a 3-item observer-rated scale which measures illness severity (CGI-S), global improvement or change (CGI-C), and therapeutic response. The CGI was measured in the ITT population.	
End point type	Secondary
End point timeframe: The CGI-S (illness severity) was performed at V1 and V2, CGI-C (global improvement or change) at V6, V7 (end of double-blind period).	

<b>End point values</b>	BF2.649 Treatment Arm (Double-blind)	Placebo Arm (Double-blind)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	183	61		
Units: percent				
number (confidence interval 95%)	78.0 (71.1 to 84.0)	53.4 (39.9 to 66.7)		

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The period of observation for the double-blind period extended from the time the patient gave informed consent (Visit 1; D0) until one month after the last visit (Visit 7; D91).

Adverse event reporting additional description:

Frequency threshold for reporting non-serious adverse events is 2% for the Double-blind period.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	Double-blind - BF2.649 Treatment Arm
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Reporting group description:

Patients receiving BF2.649 during double-blind period.

Reporting group title	Double-blind - Placebo Arm
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Reporting group description:

Patients receiving placebo during double-blind period.

Serious adverse events	Double-blind - BF2.649 Treatment	Double-blind - Placebo Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 183 (1.09%)	0 / 61 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Irritable bowel syndrome			
subjects affected / exposed	1 / 183 (0.55%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 183 (0.55%)	0 / 61 (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 %

<b>Non-serious adverse events</b>	Double-blind - BF2.649 Treatment	Double-blind - Placebo Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 183 (42.08%)	18 / 61 (29.51%)	
Nervous system disorders			
Headache			
subjects affected / exposed	27 / 183 (14.75%)	7 / 61 (11.48%)	
occurrences (all)	28	8	
Dizziness			
subjects affected / exposed	5 / 183 (2.73%)	1 / 61 (1.64%)	
occurrences (all)	6	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 183 (3.28%)	1 / 61 (1.64%)	
occurrences (all)	6	1	
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	1 / 183 (0.55%)	2 / 61 (3.28%)	
occurrences (all)	1	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 183 (9.29%)	2 / 61 (3.28%)	
occurrences (all)	19	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 183 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	7	0	
Arthralgia			
subjects affected / exposed	4 / 183 (2.19%)	0 / 61 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 183 (2.73%)	5 / 61 (8.20%)	
occurrences (all)	5	6	
Influenza			
subjects affected / exposed	6 / 183 (3.28%)	0 / 61 (0.00%)	
occurrences (all)	7	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2011	<p>A questionnaire was added at the end of treatment to confirm the absence of amphetamine-like withdrawal symptoms. For patients who only participated in the double-blind period, the questionnaire was completed by phone three days after V6 and during V7 (last visit).</p> <p>The sleep diary to be completed in the morning was composed of eight questions, the first four were about the sleep of the previous night and the last four were about the preceding day. It was specified that a call center could join the patient to ask the questions of the diary.</p> <p>Dates of first patient in and last patient out were adjusted accordingly (FPI: 15 April 2011; LPO: 30 November 2012).</p>
06 October 2011	<p>Initially, baseline ESS score was defined as the mean of scores at V1 and V2. However, as previous treatments were discontinued at V1, it seemed fair to take V2 only into account for the baseline value.</p> <p>The modalities of completion of the sleep diary changed: it could either be in a paper or electronic (phone calls) format and had to be completed on Monday, Tuesday and Wednesday preceding the next visit in order to avoid the week-end where the patient changes his/her life rhythm.</p> <p>New participating Investigators were added.</p>

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported