

**Clinical trial results:****Efficacy and safety of BF2.649 in the treatment of Excessive Daytime Sleepiness in patients with Obstructive Sleep Apnoea syndrome (OSA), refusing the nasal continuous positive airway pressure (nCPAP) therapy****Summary**

EudraCT number	2009-017251-94
Trial protocol	DE BE ES FI SE DK BG
Global end of trial date	07 May 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 09-09
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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:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 July 2013
Global end of trial reached?	Yes
Global end of trial date	07 May 2014
Was the trial ended prematurely?	No

Notes:

## 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 phase, to treat the excessive diurnal sleepiness in patients with moderate to severe Obstructive Sleep Apnoea (OSA) refusing the nasal Continuous Positive Airway Pressure (nCPAP) therapy.

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	06 October 2011
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	North Macedonia: 71
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 137
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 10
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Serbia: 22
Worldwide total number of subjects	268
EEA total number of subjects	175

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)	236
From 65 to 84 years	32
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, 268 patients (89.9%) 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 / 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 / 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	201	67
Completed	190	65
Not completed	11	2
Consent withdrawn by subject	6	1
Adverse event, non-fatal	3	1
Lost to follow-up	2	-

## 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	201	67	268
Age categorical			
Units: Subjects			
Adults (18-64 years)	178	58	236
65 years and over	23	9	32
Age continuous			
Units: years			
arithmetic mean	51.9	52.1	
standard deviation	± 10.6	± 11.0	-
Gender categorical			
Units: Subjects			
Female	50	16	66
Male	151	51	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	201	67		
Units: Score				
arithmetic mean (full range (min-max))	-6.3 (-18.5 to 5.0)	-3.6 (-19.0 to 9.5)		

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	For the ITT Population this model showed a statistically significant treatment effect of -2.8 (95% CI: [-4.0;-1.5]) (p<0.001). This indicated a statistically significant difference between the two treatment groups in reduction of 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	268
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

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### Secondary: Epworth Response (R1)

End point title	Epworth Response (R1)
End point description: Reaching an absolute value of the ESS inferior to 11 in 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	201	67		
Units: percent				
number (confidence interval 95%)	67.2 (60.2 to 73.6)	44.8 (32.6 to 57.4)		

### Statistical analyses

No statistical analyses for this end point

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### 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 ITT population	
End point type	Secondary
End point timeframe: From beginning of treatment to end of double-blind (treatment and placebo arms)	

<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	201	67		
Units: percent				
number (confidence interval 95%)	80.6 (74.4 to 85.8)	53.7 (41.1 to 66.0)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pichot Fatigue Scale

End point title	Pichot Fatigue Scale
End point description:	EndThe 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. It was measured in the ITT population.
End point type	Secondary
End point timeframe:	This scale was measured at V2 to V6 (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	201	67		
Units: Score				
arithmetic mean (standard deviation)	-3.6 (± 5.6)	-1.0 (± 6.3)		

### 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	201	67		
Units: percent				
number (confidence interval 95%)	84.2 (78.2 to 89.1)	56.3 (43.3 to 68.6)		

### **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).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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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.

<b>Serious adverse events</b>	Double-blind - BF2.649 Treatment	Double-blind - Placebo Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 200 (1.00%)	0 / 67 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 200 (0.50%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 200 (0.50%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	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	39 / 200 (19.50%)	17 / 67 (25.37%)	

Investigations Weight decreased subjects affected / exposed occurrences (all)	0 / 200 (0.00%) 0	2 / 67 (2.99%) 2	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	17 / 200 (8.50%) 19	8 / 67 (11.94%) 9	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	4 / 200 (2.00%) 4	2 / 67 (2.99%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	5 / 200 (2.50%) 5	1 / 67 (1.49%) 1	
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	11 / 200 (5.50%) 11	2 / 67 (2.99%) 2	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	2 / 67 (2.99%) 2	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 200 (0.50%) 1	2 / 67 (2.99%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 April 2011	Amendment 1: Addition of the amphetamine-like withdrawal symptom questionnaire to be completed 3 days after V6 for the subjects who terminate the study by the placebo wash out period and minor modification of the sleep diary (non-substantial modification) and update of the Investigator's Brochure with preclinical data (substantial modification).
05 October 2011	Amendment 2: Rules to assess the primary endpoint (ESS) were modified (substantial modification): The baseline ESS to be taken in consideration is the ESS score at V2 instead of the mean of ESS values at V1 and V2, since the patients had to stop their previous medication at V1. For the sleep diary, the possibility was foreseen to collect data electronically via telephone (3 first days of the week before the next visit) if the patient accepts. Patients who preferred the paper solution could still use it. These patients were to complete a paper diary during 3 days prior to the next visit (non substantial modification).

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported