# 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 |

**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 | 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:

## 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:

## 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:

### 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 |
| **Arm title** | 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

| | |
|---|---|
| **Arm title** | Placebo Arm (Double-blind) |

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)

| **Number of subjects in period 1** | BF2.649 Treatment Arm (Double-blind) | Placebo Arm (Double-blind) |
|---|---|---|
| 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<br>Units: Subjects | | | |
| Adults (18-64 years) | 159 | 56 | 215 |
| 65 years and over | 24 | 5 | 29 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 53.8 | 51.0 | |
| standard deviation | ± 10.5 | ± 10.6 | - |
| Gender categorical<br>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.<br>The ESS score was the sum of the eight sub-scores and can range from 0 to 24 with higher scores representing greater sleepiness.<br>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).

| 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%) | 78.0 (71.1 to 84.0) | 53.4 (39.9 to 66.7) | | |

## Statistical analyses

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Double-blind - BF2.649 Treatment Arm |

Reporting group description:

Patients receiving BF2.649 during double-blind period.

| | |
|---|---|
| Reporting group title | Double-blind - Placebo Arm |

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 %

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 06 April 2011 | 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).<br>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.<br>Dates of first patient in and last patient out were adjusted accordingly (FPI: 15 April 2011; LPO: 30 November 2012). |
| 06 October 2011 | 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.<br>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.<br>New participating Investigators were added. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported