



## Clinical trial results:

### DOUBLE BLIND RANDOMIZED STUDY TO ASSESS THE EFFICACY OF BF2.649

### COMPARED TO PLACEBO IN ADD-ON TO SODIUM OXYBATE IN THE TREATMENT OF NARCOLEPTIC PATIENTS WITH RESIDUAL EXCESSIVE DAYTIME SLEEPINESS (EDS) DURING 8 WEEKS.

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2011-000084-27 |
| Trial protocol           | DE ES FI       |
| Global end of trial date | 12 August 2014 |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 21 July 2016 |
| First version publication date | 21 July 2016 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | P10-01/BF2.649 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01789398 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bioprojet  |
| Sponsor organisation address | 9 rue Rameau , Paris, France, 75005                            |
| Public contact               | Bioprojet clinical department , Bioprojet, +33 01 47 03 66 33, |
| Scientific contact           | Bioprojet clinical department , Bioprojet, +33 01 47 03 66 33, |

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 September 2015 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 12 August 2014    |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 12 August 2014    |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To show relevant beneficial effect of BF2.649 on EDS compared to placebo in add on to sodium oxybate in narcoleptic patients with residual EDS.

To characterize the efficacy of BF2.649 compared to placebo in showing an incremental improvement to the situation achieved by the use of sodium oxybate particularly in terms of a reduction of EDS as measured by the ESS scale. In addition the change in the average number of cataplexy attacks per week was assessed.

Protection of trial subjects:

Tolerability as measured by Treatment Emergent Adverse Events (TEAE), changes in physical examination and vital signs.

Background therapy:

The study treatment is compared to placebo in add-on to sodium oxybate.

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 20 September 2012 |
| 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 | Spain: 6    |
| Country: Number of subjects enrolled | Finland: 10 |
| Country: Number of subjects enrolled | France: 4   |
| Country: Number of subjects enrolled | Germany: 12 |
| Country: Number of subjects enrolled | Italy: 16   |
| Worldwide total number of subjects   | 48          |
| EEA total number of subjects         | 48          |

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          | 0 |

|                           |    |
|---------------------------|----|
| months)                   |    |
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 45 |
| From 65 to 84 years       | 3  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Main inclusion criteria:

Diagnosis of narcolepsy (ICSD-2)

Patients complaining of residual EDS

Main non-inclusion criteria:

Untreated sleep apnea disorder

### Pre-assignment

Screening details:

Study duration for each patient: 12 weeks (1 week of wash-out + 2 weeks for baseline + 8 weeks under double blind study treatment + 1 week for study treatment wash-out).

Selected : 51 patients

Full Analysis Set (FAS): 48 patients

Intent To Treat set (ITT): 46 patients

Per Protocol Set: 45 patients

### Pre-assignment period milestones

|                              |                   |
|------------------------------|-------------------|
| Number of subjects started   | 51 <sup>[1]</sup> |
| Number of subjects completed | 48                |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Not met entry criteria: 2                  |
| Reason: Number of subjects | Not willing to participate in the study: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 51 subjects were screened. 48 subjects were enrolled.

There was 3 screen failures

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Overall trial (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 |

Blinding implementation details:

Active treatments and placebo were manufactured according to random code list. No distinction was performed regarding the final batch number.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Placebo

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

Dosage and administration details:

Placebo

|  |              |
|--|--------------|
| <b>Arm title</b>                       | BF2.649      |
| Arm description:<br>BF2.649            |              |
| Arm type                               | Experimental |
| Investigational medicinal product name | BF2.649      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Buccal use   |

Dosage and administration details:

Uptitration: 5 the 10mg

Stable dose: 10; 20 or 40 mg

| <b>Number of subjects in period 1</b> | Placebo | BF2.649 |
|---------------------------------------|---------|---------|
| Started                               | 22      | 26      |
| Completed                             | 20      | 26      |
| Not completed                         | 2       | 0       |
| Protocol deviation                    | 1       | -       |
| Lack of efficacy                      | 1       | -       |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title                   | Placebo |
| Reporting group description:<br>Placebo |         |
| Reporting group title                   | BF2.649 |
| Reporting group description:<br>BF2.649 |         |

| Reporting group values                                | Placebo | BF2.649 | Total |
|---|---------|---------|-------|
| Number of subjects                                    | 22      | 26      | 48    |
| Age categorical                                       |         |         |       |
| Units: Subjects                                       |         |         |       |
| In utero  |         |         | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |         |         | 0     |
| Newborns (0-27 days)                                  |         |         | 0     |
| Infants and toddlers (28 days-23<br>months)           |         |         | 0     |
| Children (2-11 years)                                 |         |         | 0     |
| Adolescents (12-17 years)                             |         |         | 0     |
| Adults (18-64 years)                                  |         |         | 0     |
| From 65-84 years                                      |         |         | 0     |
| 85 years and over                                     |         |         | 0     |
| Age continuous  |         |         |       |
| FAS and Total safety population (N=48)                |         |         |       |
| Units: years  |         |         |       |
| arithmetic mean                                       | 42.7    | 42.57   |       |
| standard deviation                                    | ± 12.01 | ± 12.92 | -     |
| Gender categorical                                    |         |         |       |
| FAS and Safety population (N=48)                      |         |         |       |
| Units: Subjects                                       |         |         |       |
| Female  | 7       | 7       | 14    |
| Male  | 15      | 19      | 34    |

### Subject analysis sets

|  |                           |
|--|---------------------------|
| Subject analysis set title                                   | Full Analysis Set (FAS)   |
| Subject analysis set type                                    | Full analysis             |
| Subject analysis set description:<br>Full Analysis Set (FAS) |                           |
| Subject analysis set title                                   | Safety Set                |
| Subject analysis set type                                    | Per protocol              |
| Subject analysis set description:<br>Safety Set              |                           |
| Subject analysis set title                                   | Intent To Treat set (ITT) |
| Subject analysis set type                                    | Intention-to-treat        |

## Subject analysis set description:

## Intent To Treat set (ITT)

|                            |                  |
|----------------------------|------------------|
| Subject analysis set title | Per Protocol Set |
| Subject analysis set type  | Per protocol     |

## Subject analysis set description:

## Per Protocol Set

| Reporting group values  | Full Analysis Set (FAS) | Safety Set | Intent To Treat set (ITT) |
|---|-------------------------|------------|---------------------------|
| Number of subjects  | 48                      | 48         | 46                        |
| Age categorical   |                         |            |                           |
| Units: Subjects   |                         |            |                           |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                         |            |                           |
| Age continuous  |                         |            |                           |
| FAS and Total safety population (N=48)  |                         |            |                           |
| Units: years  |                         |            |                           |
| arithmetic mean   | 42.63                   | 42.63      |                           |
| standard deviation  | ± 12.38                 | ± 12.38    | ±                         |
| Gender categorical  |                         |            |                           |
| FAS and Safety population (N=48)  |                         |            |                           |
| Units: Subjects   |                         |            |                           |
| Female  | 14                      | 14         |                           |
| Male  | 34                      | 34         |                           |

| Reporting group values  | Per Protocol Set |  |  |
|---|------------------|--|--|
| Number of subjects  | 45               |  |  |
| Age categorical   |                  |  |  |
| Units: Subjects   |                  |  |  |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                  |  |  |
| Age continuous  |                  |  |  |
| FAS and Total safety population (N=48)  |                  |  |  |
| Units: years  |                  |  |  |

|                    |   |  |  |
|--------------------|---|--|--|
| arithmetic mean    |   |  |  |
| standard deviation | ± |  |  |

|                                  |  |  |  |
|----------------------------------|--|--|--|
| Gender categorical               |  |  |  |
| FAS and Safety population (N=48) |  |  |  |
| Units: Subjects                  |  |  |  |
| Female                           |  |  |  |
| Male                             |  |  |  |



## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Placebo                   |
| Reporting group description:<br>Placebo                        |                           |
| Reporting group title  | BF2.649                   |
| Reporting group description:<br>BF2.649                        |                           |
| Subject analysis set title                                     | Full Analysis Set (FAS)   |
| Subject analysis set type                                      | Full analysis             |
| Subject analysis set description:<br>Full Analysis Set (FAS)   |                           |
| Subject analysis set title                                     | Safety Set                |
| Subject analysis set type                                      | Per protocol              |
| Subject analysis set description:<br>Safety Set                |                           |
| Subject analysis set title                                     | Intent To Treat set (ITT) |
| Subject analysis set type                                      | Intention-to-treat        |
| Subject analysis set description:<br>Intent To Treat set (ITT) |                           |
| Subject analysis set title                                     | Per Protocol Set          |
| Subject analysis set type                                      | Per protocol              |
| Subject analysis set description:<br>Per Protocol Set          |                           |

### Primary: Epworth Sleepiness Scale

|                        |   |
|------------------------|---|
| End point title        | Epworth Sleepiness Scale <sup>[1]</sup> |
| End point description: |   |

|  |         |
|--|---------|
| End point type   | Primary |
| End point timeframe:<br>Change from baseline.<br>Baseline (Mean of pre-treatment measures at V1 and V2), End of double-blind phase (Mean of post-treatment measures at V5 and V6). |         |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not specified.

| End point values            | Placebo         | BF2.649         | Intent To Treat set (ITT) |  |
|-----------------------------|-----------------|-----------------|---------------------------|--|
| Subject group type          | Reporting group | Reporting group | Subject analysis set      |  |
| Number of subjects analysed | 20              | 26              | 46                        |  |
| Units: N-P ANCOVA           |                 |                 |                           |  |
| number (not applicable)     | -2.08           | -2.6            | -2.37                     |  |

## Statistical analyses



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Throughout the study

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | BF2.649 |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                            | Placebo        | BF2.649        |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 22 (0.00%) | 0 / 26 (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: 5 %

| Non-serious adverse events                            | Placebo        | BF2.649         |  |
|---|----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                |                 |  |
| subjects affected / exposed                           | 2 / 22 (9.09%) | 6 / 26 (23.08%) |  |
| Nervous system disorders                              |                |                 |  |
| Headache  |                |                 |  |
| subjects affected / exposed                           | 2 / 22 (9.09%) | 6 / 26 (23.08%) |  |
| occurrences (all)                                     | 3              | 9               |  |
| Dizziness   |                |                 |  |
| subjects affected / exposed                           | 0 / 22 (0.00%) | 1 / 26 (3.85%)  |  |
| occurrences (all)                                     | 0              | 1               |  |
| General disorders and administration site conditions  |                |                 |  |
| Gastrointestinal disorder                             |                |                 |  |
| subjects affected / exposed                           | 0 / 22 (0.00%) | 1 / 26 (3.85%)  |  |
| occurrences (all)                                     | 0              | 1               |  |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 December 2011 | Adding of 3 weeks of follow-up [1 extra week (at baseline period) & 2 weeks at the end of study to assess the occurrence or not of withdrawal symptoms]. Patient diary recorded and collected during all the study duration.  |
| 05 April 2012    | Adding of 2 visits: a screening visit V0, three weeks prior to the study treatment randomization for patient under psychotropic medication and a control treatment visit at V7 to ensure patient monitoring. Reducing to one week the withdrawal assessment period and providing placebo to all patients during that period. Eliminating SART assessment. Eliminating BF2.649 plasma dosage. Adding an ECG at visit V4. |
| 10 December 2012 | Increase of BF2.649 (Pitolisant) dose up to 40 mg per day.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported