# Clinical trial results:
# Dose finding phase IIb study of Bavisant to evaluate its safety and efficacy in treatment of excessive daytime sleepiness (EDS) in Parkinson's Disease (PD). CASPAR study.

## Summary

| | |
|---|---|
| EudraCT number | 2017-000877-35 |
| Trial protocol | CZ ES GB DE IT |
| Global end of trial date | 28 May 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 27 August 2021 |
| First version publication date | 27 August 2021 |
| Summary attachment (see zip file) | BB-2001-201b_Synopsis_v1.0_23Apr2020 (BB-2001-201b_Synopsis_v1.0_23Apr2020.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | BB-2001-201b |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03194217 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | BenevolentAI Bio Limited |
| Sponsor organisation address | 4-8 Maple Street, London, United Kingdom, W1T 5HD |
| Public contact | Chief Scientific Officer, BenevolentAI Bio, +44 2037819360, anne.phelan@benevolent.ai |
| Scientific contact | Chief Scientific Officer, BenevolentAI Bio, +44 2037819360, anne.phelan@benevolent.ai |

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 | 09 September 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of Bavisant compared to placebo on excessive daytime sleepiness (EDS) in Parkinson's Disease (PD) after a 6-week treatment period.

Protection of trial subjects:

Suicide risk was assessed by C-SSRS before and after treatment administration at all study visits (including follow-up) in accordance with FDA Guidance for Industry on Suicidal Ideation and Behavior. BPRS+ was used to monitor psychotic symptoms and HAM-D to monitor depression at all study visits (including follow-up). These assessments were included because subjects with PD are at a higher risk of psychosis and depression than the general population.

Vital signs (including blood pressure and heart rate) were assessed at all study visits (including follow-up) because subjects with PD commonly exhibit orthostatism and other cardiovascular changes.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 31 October 2017 |
| 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 | Poland: 74 |
| Country: Number of subjects enrolled | Spain: 44 |
| Country: Number of subjects enrolled | United Kingdom: 6 |
| Country: Number of subjects enrolled | Czechia: 21 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Italy: 36 |
| Country: Number of subjects enrolled | United States: 47 |
| Worldwide total number of subjects | 244 |
| EEA total number of subjects | 197 |

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) | 84 |
| From 65 to 84 years | 160 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

230 subjects were planned for enrollment. 248 subjects were randomised, of which 244 received the double-blind medication. The randomization followed a centralized method, and was stratified by region (US, Western Europe, Eastern Europe) and by whether or not the site performed polysonmography and maintenance of wakefulness test (MWT).

### Pre-assignment

Screening details:

A total of 364 subjects were screened. 116 were screening failures and 248 were randomised.
4 out of the 248 did not receive the study medication.
The 244 that received the study medication satisfied the inclusion/exclusion criteria prior to entry in the study.

### Period 1

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

Blinding implementation details:

IMP administration was blinded; the randomization schedule and the allocation to treatment groups were not known by the investigator, the sponsor, or any other person involved in the conduct of the study, except in the case of an emergency if knowledge of the IMP was necessary to provide optimal treatment to the subject. Bavisant and placebo tablets had identical appearance.
Prior consent from sponsor/representative was required where possible before emergency unblinding by the investigator.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Bavisant (0.5mg) |

Arm description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bavisant |
| Investigational medicinal product code | BEN2001 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets containing bavisant dihydrochloride monohydrate equivalent to 0.5 mg of bavisant.

Dosage: Once daily administration

| | |
|---|---|
| **Arm title** | Bavisant (1.0mg) |

Arm description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bavisant |
| Investigational medicinal product code | BEN2001 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets containing bavisant dihydrochloride monohydrate equivalent to 1.0 mg of bavisant.

Dosage: Once daily administration

| | |
|---|---|
| **Arm title** | Bavisant (3.0mg) |

Arm description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bavisant |
| Investigational medicinal product code | BEN2001 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablets containing bavisant dihydrochloride monohydrate equivalent to 3.0 mg of bavisant.

Dosage: Once daily administration

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| | |
|---|---|
| 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:

Matching placebo  tablets to the IMP.

Dosage: Once daily administration

| **Number of subjects in period 1** | Bavisant (0.5mg) | Bavisant (1.0mg) | Bavisant (3.0mg) |
|---|---|---|---|
| Started | 60 | 60 | 64 |
| Completed | 57 | 56 | 60 |
| Not completed | 3 | 4 | 4 |
| Selection criteria | - | - | 1 |
| Patient decision | 1 | 1 | - |
| Adverse event, non-fatal | 2 | 3 | 3 |

| **Number of subjects in period 1** | Placebo |
|---|---|
| Started | 60 |
| Completed | 60 |
| Not completed | 0 |
| Selection criteria | - |
| Patient decision | - |
| Adverse event, non-fatal | - |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Study |
|---|---|

Reporting group description: -

| Reporting group values | Overall Study | Total | |
|---|---|---|---|
| Number of subjects | 244 | 244 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 84 | 84 | |
| From 65-84 years | 160 | 160 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 81 | 81 | |
| Male | 163 | 163 | |

### Subject analysis sets

| Subject analysis set title | Efficacy |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Efficacy Set consisted of all patients in the intent-to-treat (ITT) population and supportive analyses in the per-protocol (PP) population.

| Reporting group values | Efficacy | | |
|---|---|---|---|
| Number of subjects | 244 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | 84 | | |
| From 65-84 years | 160 | | |
| 85 years and over | | | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 81 | | |
| Male | 163 | | |

## End points

### End points reporting groups

| Reporting group title | Bavisant (0.5mg) |
|---|---|

Reporting group description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| Reporting group title | Bavisant (1.0mg) |
|---|---|

Reporting group description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| Reporting group title | Bavisant (3.0mg) |
|---|---|

Reporting group description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

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

Reporting group description:

Subjects were randomly allocated to 1 of 4 treatment groups at a ratio of 1:1:1:1 to one of the following IMPs:
- Bavisant 0.5 mg tablets
- Bavisant 1.0 mg tablets
- Bavisant 3.0 mg tablets
- Placebo tablets

| Subject analysis set title | Efficacy |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Efficacy Set consisted of all patients in the intent-to-treat (ITT) population and supportive analyses in the per-protocol (PP) population.

### Primary: Efficacy: Mean Absolute Change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 6-week treatment period

| End point title | Efficacy: Mean Absolute Change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 6-week treatment period |
|---|---|

End point description:

Mean Absolute Change in Epworth Sleepiness Scale Score from Baseline to the End of the 6-week Treatment Period (Analysis of Covariance Model, Multiple Imputation) (Intent-to-Treat Population)

| End point type | Primary |
|---|---|

End point timeframe:

From baseline to the end of the 6-week treatment period.

| End point values | Bavisant (0.5mg) | Bavisant (1.0mg) | Bavisant (3.0mg) | Placebo |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 60 | 64 | 60 |
| Units: Epworth Sleepiness Scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline Mean | 15.50 (± 2.17) | 15.60 (± 2.51) | 15.44 (± 2.46) | 15.75 (± 2.53) |
| 6-week Mean | 10.86 (± 4.57) | 12.05 (± 4.54) | 10.87 (± 3.97) | 11.37 (± 5.09) |
| Absolute change from baseline Mean | -4.66 (± 3.80) | -3.49 (± 4.31) | -4.62 (± 3.68) | -4.38 (± 4.23) |

## Statistical analyses

| Statistical analysis title | Primary Endpoint Analysis (0.5mg) |
|---|---|
| Comparison groups | Bavisant (0.5mg) v Placebo |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 [1] |
| Method | ANCOVA |
| Parameter estimate | Least-squared Mean |
| Point estimate | -4.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.64 |
| upper limit | -3.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.51 |

Notes:

[1] - Statistical significance was assessed as two-sided P value < 0.05

| Statistical analysis title | Primary Endpoint Analysis (1.0mg) |
|---|---|
| Comparison groups | Bavisant (1.0mg) v Placebo |
| Number of subjects included in analysis | 120 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 [2] |
| Method | ANCOVA |
| Parameter estimate | Least-squared Mean |
| Point estimate | -3.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.46 |
| upper limit | -2.46 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.51 |

Notes:
[2] - Statistical significance was assessed as two-sided P value < 0.05

| **Statistical analysis title** | Primary Endpoint Analysis (3.0mg) |
|---|---|
| Comparison groups | Bavisant (3.0mg) v Placebo |
| Number of subjects included in analysis | 124 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 [3] |
| Method | ANCOVA |
| Parameter estimate | Least-squared Mean |
| Point estimate | -4.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.72 |
| upper limit | -3.75 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5 |

Notes:
[3] - Statistical significance was assessed as two-sided P value < 0.05

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: From baseline to the 4-week follow-up period (post-dose). | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

| Reporting groups | |
|---|---|
| Reporting group title | Related Treatment-emergent Adverse Events |
| Reporting group description: Total for all participants randomised in the study | |
| Reporting group title | Subjects affected by SAEs |
| Reporting group description: Total for all participants randomised for the study | |

| Serious adverse events | Related Treatment-emergent Adverse Events | Subjects affected by SAEs | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 3 / 244 (1.23%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Surgical and medical procedures | | | |
| Cholecystectomy | Additional description: assessed as unrelated to the IMP, occuring in the placebo group | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | Additional description: Occured in the 3.0mg treatment group and considered unrelated to the IMP by the investigator | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | Additional description: Occured in the 3.0mg group and was considered unrelated to the IMP by the investigator | | |
| subjects affected / exposed | 0 / 244 (0.00%) | 1 / 244 (0.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 1 %

| **Non-serious adverse events** | Related Treatment-emergent Adverse Events | Subjects affected by SAEs | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 244 (18.85%) | 0 / 244 (0.00%) | |
| Investigations | | | |
| Blood triglycerides increased | | | |
| subjects affected / exposed | 5 / 244 (2.05%) | 0 / 244 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Tremor | | | |
| subjects affected / exposed | 2 / 244 (0.82%) | 0 / 244 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Somnolence | | | |
| subjects affected / exposed | 4 / 244 (1.64%) | 0 / 244 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Eye disorders | | | |
| Cataract nuclear | | | |
| subjects affected / exposed | 2 / 244 (0.82%) | 0 / 244 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 244 (2.87%) | 0 / 244 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Dry mouth | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Initial insomnia | | | |
| subjects affected / exposed | 9 / 244 (3.69%) | 0 / 244 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Middle insomnia | | | |
| subjects affected / exposed | 5 / 244 (2.05%) | 0 / 244 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nightmare | | | |
| subjects affected / exposed | 3 / 244 (1.23%) | 0 / 244 (0.00%) | |
| occurrences (all) | 3 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The secondary endpoints were not reported however, the synopsis (which includes description of the study endpoints) has been included as part of this CSR.

Notes: