2 SYNOPSIS

Name of the Sponsor:	**Test Product:**
BenevolentAI Bio Limited	▪ **Name of Finished Product:** Bavisant selective H3 antagonist (bavisant) ▪ **Name of Active Ingredient:** Bavisant dihydrochloride monohydrate

Title of the Study:

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.

Protocol ID:

Study Number: BB2001-201b
ClinicalTrials.gov ID: NCT03194217
EudraCT No: 2017-000877-35

NUMBER OF STUDY CENTERS AND COUNTRIES:

50 sites across Europe and the United States of America (US)

REFERENCES:

None

STUDY PERIOD:

Study Initiation Date (First Subject In):	31 October 2017
Study Completion Date (Last Subject Completed):	28 May 2019

PHASE OF DEVELOPMENT: IIb

BACKGROUND AND RATIONALE FOR THE STUDY:

EDS is a core non-motor symptom of PD with a significant impact on patients' quality of life and function. Pathological sleepiness is present in 20-50% of PD with a narcolepsy-like phenotype in 15-50% of these patients. Effective and safe agents for treatment of PD-related EDS are urgently needed because drugs tested for EDS management to date (e.g. modafinil) have not shown conclusive efficacy and have tolerability issues. Histamine H3 receptor antagonists may hold promise for the treatment of EDS associated with neurological disorders such as PD, narcolepsy, and obstructive sleep apnea. One H3 receptor antagonist, pitolisant, has been reported to have beneficial effects on EDS in PD.

Bavisant is a potent H3 receptor antagonist that promoted wakefulness and attention, reduced sleepiness, and increased cognitive performance in animal models. The purpose of this phase IIb, dose-finding, placebo-controlled study was to evaluate the effectiveness and safety of different doses of bavisant (0.5, 1.0, and 3.0 mg/day) vs. placebo for the treatment of EDS associated with PD during 6 weeks of active treatment and 4 weeks of safety follow-up.

OBJECTIVES:

Primary objective:

To assess the efficacy of bavisant compared to placebo on EDS in PD after a 6-week treatment period.

Secondary objective:

To assess the efficacy and safety of bavisant compared to placebo after 2 weeks and 6 weeks of treatment. The efficacy assessments included EDS, motor control, and depression assessments.

Exploratory objectives:

Exploratory objectives included the assessment of free living activity in subjects on bavisant compared to placebo after 6 weeks of treatment using a wrist-worn actigraphy device and pharmacogenomics analysis.

METHODOLOGY:

This was a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled, phase IIb, dose-finding study to evaluate the efficacy and safety of different doses of bavisant in the treatment of EDS in PD.

Eligible subjects were randomly allocated at a ratio of 1:1:1:1 to bavisant at doses of 0.5, 1.0, or 3.0 mg/d or placebo. Randomization was stratified by region (USA, Western Europe, Eastern Europe) and by whether or not the site performed polysomnography and the Maintenance of Wakefulness Test (MWT).

After providing informed consent, subjects who met the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria for PD entered a screening period (up to 3 weeks) followed by a baseline (BL) period (up to 1 week). Inclusion and exclusion criteria were assessed to determine subject eligibility during the screening and BL periods prior to randomization, including assessment of suicide risk in accordance with the US Food and Drug Administration Guidance for Industry on Suicidal Ideation and Behavior.

A 6-week treatment period with randomized, blinded investigational medicinal product (IMP) was initiated after confirmation of eligibility. A safety follow-up visit was scheduled 4 weeks after completion of the treatment period.

No interim analysis was planned or performed for this study.

NUMBER OF SUBJECTS:

Planned: Approximately 230 subjects were planned for enrollment with an expected early withdrawal rate of around 15%, which could allow 200 completed subjects (50 completed subjects per treatment group).

Actual: 248 subjects were randomized.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Men and women aged 50 to 80 years old with a previous diagnosis of PD of minimum 3 months who had moderate or severe EDS indicated by an Epworth Sleepiness Scale (ESS) score >12 and stable nocturnal sleep hygiene practices and no depression, active suicidal ideation, or any unstable significant medical condition were included.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS:

Bavisant in doses of 0.5, 1.0, and 3.0 mg.

Route of administration: Per oral (PO).

Frequency of administration: Once daily (QD)

Batch numbers: D017B (for bavisant 0.5 mg)
D018B (for bavisant 1.0 mg)
D019B (for bavisant 3.0 mg)

DURATION OF TREATMENT

6 weeks

CONTROL PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBERS:

Placebo (Dose: NA).

Route of administration: PO.

Frequency of administration: QD.

Batch number: D016B

ENDPOINTS:

Primary endpoint: Mean absolute change of bavisant treatment groups in the ESS score from BL to the end of the 6-week treatment period, assessed as both the intragroup change compared to BL, and the intergroup change compared to placebo

Secondary endpoints:

- Efficacy in EDS:
  - Mean absolute change in the ESS score from BL to the end of the 2-week treatment period
  - ESS clinical response:
    - First approach: ESS score absolute decrease from BL of at least 3.0 points after 2 and 6 weeks of treatment
    - Second approach: ESS score ≤10 points after 2 and 6 weeks of treatment
    - Third approach: Either ESS ≤10 points after 2 and 6 weeks of treatment or ESS score absolute decrease from BL of at least 3.0 points after 2 and 6 weeks of treatment
  - Mean relative change in the ESS score from BL baseline to the end of the 2-week and 6-week treatment periods
  - Mean absolute change in the Scales for Outcome in Parkinson's Disease-Sleep (SCOPA-Sleep) score from BL to the end of the 2-week and 6-week treatment periods
  - Mean absolute change in the Parkinson's Disease Sleep Scale (PDSS-2) score from BL to the end of the 2-week and 6-week treatment periods
  - Mean absolute change in the MWT score from BL to the end of the 6-week treatment period

- Mean absolute change in the Polysomnography parameters from BL to the end of the 6-week treatment period

- Efficacy in PD:
  - Mean absolute change in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor control) score from BL to the end of the 2-week and 6-week treatment periods
  - Mean absolute change in the Hamilton Depression Rating Scale (HAM-D) score mean absolute change from BL to the end of the 2-week and 6- week treatment periods and safety follow-up
  - Mean absolute change in the Montreal Cognitive Assessment (MoCA) score from BL to the end of the 6-week treatment period
  - Mean absolute change in the Fatigue Severity Scale (FSS) score from BL to the end of the 6-week treatment period

Exploratory endpoints (proposed for exploratory analysis but not analyzed)**:**

- Efficacy of bavisant compared to placebo after the 6-week treatment period of free living activity assessed by means of wrist-worn actigraphy GENEActiv® (descriptive statistics of values at BL, endpoint, and change from baseline for each of continuous triaxial accelerometry measurements by treatment group)
- Pharmacogenomic analysis to identify genetic reasons why certain people responded differently to bavisant, to find out more information about how bavisant worked, and to generate information needed for research, development, and regulatory approval of tests to predict response to bavisant, and to identify variations in genes related to the biological target of bavisant

Safety endpoints:

- Incidence of adverse events (AEs), serious AEs (SAEs), serious and related AEs, and AEs of special interest (AESIs) such as headache, nausea, and insomnia
- Incidence of suicidal ideation (Columbia-Suicide Severity Rating Scale [(C-SSRS] findings) from BL to the end of the 2-week and 6-week treatment periods and the safety follow-up
- Incidence of positive psychotic symptoms (Brief Psychiatric Rating Scale Positive Subscale [BPRS+] findings) from BL to the end of the 2-week and 6-week treatment periods and the safety follow-up
- Incidence of physical examination, vital signs, and laboratory tests (hematology and biochemistry) changes from normal to abnormal.
- Incidence of cardiovascular safety findings (blood pressure, heart rate, electrocardiogram [ECG], including QT/QTc intervals).
- Incidence of eye examination findings

STATISTICAL METHODS:

The statistical analysis was performed using SAS® version 9.4. Statistical significance was assessed as two-sided P value < 0.05.

Primary endpoint analysis:

An analysis of covariance (ANCOVA) model was used for the primary analysis with the baseline ESS as a covariate and the region and treatment as factors. Least-squared absolute mean changes and SEs were presented by treatment group together with the difference in LS means between each dose and placebo, the associated 95% confidence intervals (CIs) and 2-sided P values.

Several sensitivity analyses were performed for the primary endpoint: (i) A mixed-effect model repeated measures analysis was applied to simultaneously include 2-week and 6-week data. (ii) The dose response was explored using a multiple comparison modelling approach. (iii) The primary endpoint data were ranked and an ANCOVA model identical to that used in the primary analysis was applied to the ranked values; this analysis was designed to cope with any observed non-normality of the primary endpoint data.

The primary analysis and sensitivity analyses were performed in the intent-to-treat (ITT) population and supportive analyses in the per-protocol (PP) population.

Secondary endpoints analysis:

Similar methods of analysis were used for all secondary endpoints based on a mean absolute or a mean relative change (including mean changes in ESS, SCOPA-Sleep, PDSS, MWT, UPDRS Part III, HAM-D, MoCA, and FSS scores and polysomnography parameters) in the ITT population.

The percentage of subjects who showed ESS clinical response was summarized and compared between groups by means of a Chi-square test (or Fisher's exact test, as applicable) in both the ITT and PP populations. Percentages were expressed with their 95% Cis calculated with the binomial exact method. Differences in proportions between each dose and placebo were presented along with the associated 95% CIs and 2 sided P values.

Safety endpoint analysis:

Incidences of AEs, AESIs, SAEs, serious and related AEs were summarized as overall events, related events, and events by intensity. AEs that were classified as possible, probable, or definite were considered treatment-related events.

Laboratory tests results, vital signs, physical and ophthalmological examination findings ECG parameters, and C-SSRS and BPRS+ results were summarized by treatment group.

SUMMARY OF RESULTS AND CONCLUSIONS:

Subjects were recruited over approximately 18 months (October 2017 to April 2019).

A total 364 subjects were screened, 248 were randomized (116 [32%] screening failures, mainly due to selection criteria) of which 244 received double-blind medication. Eleven of the treated subjects withdrew early (4.5%), 8 (3.2%) of them because of AEs.

The safety and ITT populations comprised 244 subjects. A total of 41 subjects (17%) had a major protocol deviation, so 203 subjects (83%) were included in the PP population.

Demographic and baseline characteristics:

Baseline demographic and disease characteristics were similar among the 4 treatment groups in the safety and PP populations.

Subjects had a mean age of 66.9 (standard deviation: 6.97) years; 66% of subjects were at least 65 years old. Approximately twice as many men as women were enrolled. Most of them were Caucasian. Subjects were recruited in Western Europe (42%), Eastern Europe (39%), and the US (19%).

Subjects had a median of 5.0 years since their PD diagnosis and median of 25.0 months since EDS diagnosis. Medical history included 57% of subjects with cataracts, 21% of subjects with depressive disorders, 12% with lens therapeutic procedures, and 5% with anxiety symptoms.

Standard anti-Parkinsonian medication remained stable during the study: 82% of subjects with dopa or dopa derivatives, 67% with dopamine agonists, 42% with monoamine oxidase B inhibitors and 13% with adamantine derivatives.

Thirteen subjects took prohibited medications during the study.

Pill count reported in the diary was used to assess the mean compliance with IMP which was between 90% and 110% in 93.4% of the subjects.

Mean IMP exposure was similar in all treatment groups (40 to 42 days) with slightly lower rates in the active groups than in the placebo group reflecting the higher withdrawal rates in these groups.

Efficacy:

No differences in mean absolute change in ESS score between any dose of bavisant and placebo (primary efficacy endpoint) were seen at Week 6 in the primary analysis in the ITT population. The MCP-mod, rank, and MMRM sensitivity analyses of the primary endpoint were consistent with the primary analysis and analysis in the PP population, showing no clear dose response or differences between the doses and placebo. Analysis of ESS score at Week 2 showed similar results to the analysis at Week 6. The relative change in ESS score showed no difference between the bavisant doses and placebo at either Week 2 or Week 6 except for a greater reduction in the 3.0 mg/d dose group than in the placebo group at Week 2 (P = 0.026). No difference in clinical response rate between any of the bavisant doses and placebo was seen for any of the 3 criteria evaluated.

No consistent pattern of difference between any dose of bavisant and placebo was seen for absolute changes in SCOPA, HAM-D, PDSS-2, MWT, UPDRS Part III, MoCA, or FSS scores or in any of the 10 polysomnography parameters assessed. Although some efficacy endpoints showed a difference between a bavisant dose group and the placebo group in mean absolute change from BL with nominal P values < 0.05 for a single group

or at a single time point, these differences did not affect the assessment of lack of efficacy for bavisant at doses of 0.5, 1.0, and 3.0 mg/d in treatment of EDS in PD.

Safety:

- Overall AE incidence was higher in the bavisant groups (53% with 0.5 mg/d, 60% with 1.0 mg/d, and 45% with 3.0 mg/d) than in the placebo group (37%).
- For treatment-emergent AEs (TEAEs) only, incidences were: 52% with 0.5 mg/d, 57% with 1.0 mg/d, and 44% with 3.0 mg/d compared to 30% with placebo.
- No AE had a fatal outcome, and only 3 of the TEAEs were serious: cholecystectomy in a subject in the placebo group and constipation and muscular weakness in 1 subject each in the bavisant 3.0 mg/d group. None of these events were considered related to IMP.
- Related TEAEs had a higher incidence in the bavisant groups (25% with 0.5 mg/d, 32% with 1.0 mg/d, and 28% with 3.0 mg/d) than in the placebo group (12%).
- Eight subjects discontinued the study due to AEs, all of them in the bavisant dose groups. The respective AEs (one per discontinued subject) were agitation and nightmare in the 0.5 mg/d group; pruritus, initial insomnia and diarrhoea in the 1.0 mg/d group; and nightmare, nausea and muscular weakness in the 3.0 mg/d group.
- Incidence of AESIs in subjects who received bavisant was approximately 3 times as high as in the placebo group and increased with increasing bavisant dose. Initial insomnia (4%) was the most frequently reported AESI with bavisant at any dose, followed by middle insomnia (2%), headache (2%), and insomnia (2%). Insomnia events were commonest in the 3.0 mg/d group.
- Analysis of data and AEs pertaining to laboratory tests, vital signs, physical examination and ECG did not reveal any concerns.
- Four subjects had a positive response for suicidal ideation on the C-SSRS before the first administration of IMP (bavisant), and 1 subject in the bavisant 0.5 mg/d group had a positive response for suicidal ideation on the C-SSRS at Week 2.
- Baseline BPRS+ was similar among groups and did not change significantly during the course of the study.

Conclusions:

- Bavisant at doses of 0.5, 1.0 and 3.0 mg/d was not effective in the treatment of PD patients with EDS.
- The higher incidence of AESIs in all bavisant groups and the prevalence of insomnia in the 3.0 mg/d group suggests that these doses are pharmacologically active.
- The safety profile exhibited by bavisant was similar to that seen in earlier studies of treatment of attention deficit hyperactivity disorder, with no fatal events, a low incidence of SAEs and AESIs, and no clinically relevant changes in incidence of suicidal ideation or positive psychotic symptoms. These findings are notable in this elderly population with a neurodegenerative disease and a higher prevalence of comorbidities.

Date and Version of This Report:

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