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 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 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 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 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: