Protocol No.	BB-2001-201b
EudraCT No.	2017-000877-35
Title:	Dose finding phase IIb study of Bavisant to evaluate its safety and effi**C**acy in tre**A**tment of exce**S**sive daytime slee**P**iness (EDS) in P**AR**kinson's Disease (PD). **CASPAR** study.
Study Sponsor:	BenevolentAI Bio 4-8 Maple Street W1T 5HD, London, UK Tel +44 2037 819 360 Dr. Leo James Medical Director (contract) e-mail: leo.james@benevolent.ai

Amendment History

Date	Amendment Number	Amendment Type
05 April 2017	Initial version	Not applicable
20 June 2017	01	Non-substantial
03 July 2017	02	Non-substantial
23 August 2017	03	Substantial
07 November 2018	04	Non-substantial

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Clinical Trial Protocol Approval

BB-2001-201b
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.

DR. LEO JAMES
MEDICAL DIRECTOR (CONTRACT)
BENEVOLENTAI BIO

14 NOV 2018
DATE

SIGNATURE

ADEPEJU OSHISANYA
DIRECTOR,
CLINICAL PROGRAMME LEADER
BENEVOLENTAI BIO

14 Nov 2018
DATE

SIGNATURE

EDUARDO SOBREVIELA
BIOSTATISTICIAN
LINICAL

14NOV2018
DATE

SIGNATURE

DR. CARLOS M HORTELANO
MEDICAL WRITER
LINICAL

14NOV2018
DATE

SIGNATURE

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the investigator brochure, and other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice E6.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

Signature of Investigator	Date

Investigator Name (print or type)

Investigator's Title

Name of Facility

Location of Facility (City)

REASON FOR NON SUBSTANTIAL AMENDMENT 04

This amended study protocol is prepared to update the sponsor's postal address, medical director, study statistician, and the setup arranged for the 24h emergency contact:

- BenevolentAI Bio: New postal address.
- Dr. Patrick Keohane, Chief Medical Officer, replaced by Dr. Leo James, Medical Director (contract)
- Sara Prada, Statistician, replaced by Eduardo Sobreviela, Statistician
- 24h emergency contact: Split between business hours weekdays, and non-business hours and weekends

Detailed changes are summarized in the following table:

Section	Page	Old text	New text
Heading	All	Amendment 03, Final Version 1.0	Amendment 04, Final Version 1.0
	All	23/Aug/2017	06/Nov/2018
Cover	1	BenevolentAI Bio 40 Churchway W1 1LW, London, UK Tel +44 20 3096 0720 Dr. Patrick Keohane Chief Medical Officer e-mail: patrick.keohane@benevolent.ai	BenevolentAI Bio 4-8 Maple Street W1T 5HD, London, UK Tel +44 2037 819 360 Dr. Leo James Medical Director (contract) e-mail: leo.james@benevolent.ai
Signature page	2	DR. PATRICK KEOHANE CHIEF MEDICAL OFFICER PEJU OSHISANYA SENIOR PROJECT MANAGER SARA PRADA STATISTICIAN	DR. LEO JAMES MEDICAL DIRECTOR (CONTRACT) ADEPEJU OSHISANYA DIRECTOR, CLINICAL PROGRAMME LEADER EDUARDO SOBREVIELA STATISTICIAN
Reason for non substantial amendment 04	4	<<blank>>	<<New section with details of the non substantial amendment 04>>
3.0 Table of contents	26	<<blank>>	<<updated>>

Section	Page	Old text	New text
18.1 Administrative Information – Contacts	99	24h emergency contact Linical (CRA / MM) BEN01.medical.emergency@linical.com Dr. Isabel Caballero (+34 610 134 109) Dr. Carlos Hortelano (+34 670 836 340) Dr. Patrick Keohane (+44 782 6854 866)	Emergency contact Business hours weekdays (08:00 to 16:00 CET) Linical (CRA / MM) BEN01.medical.emergency@linical.com Dr. Isabel Caballero (+34 610 134 109) Dr. Carlos Hortelano (+34 670 836 340)
18.1 Administrative Information – Contacts	99	<<blank>>	24h emergency contact Non business hours and weekends Czech Republic 296849801 +441204684560 Germany 08005891887 +441235239958 Italy 0236007792 +441228899357 Poland 124207010 +441204684450 Spain 966990007 +441204684092 United Kingdom 01242649524 +441242649524 USA 18666151825 +441204684544

REASON FOR SUBSTANTIAL AMENDMENT 03

This amended study protocol is prepared to include the requests from the FDA regarding the safety review of IND 133435 in order for the study to be considered Safe to Proceed:

- C-SSRS: Columbia-Suicide Severity Rating Scale will be assessed at all study visits (including follow-up visits where adverse events are also assessed), and not just screening and Visit 3 following the FDA Guidance for Industry – Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials[(1)].
- BPRS+ (Brief Psychiatric Rating Scale positive subscale) will be included to monitor psychotic symptoms at all study visits (including follow-up visits where adverse events are also assessed), based that patients with Parkinson's disease are known to be at higher risk of psychosis than the general population.
- HAM-D will be assessed at all study visits (including follow-up visits), and not just screening and Visit 3, based that patients with Parkinson's disease are known to be at higher risk of depression.
- Follow-up procedures are described for a positive finding on the C-SSRS, or an elevated HAM-D or psychosis scale score.
- Vital signs (including blood pressure and heart rate) will be assessed at all study visits (including follow-up visits), as patients with Parkinson's disease are known to commonly exhibit orthostatis and other cardiovascular changes.

The statistical section of the protocol has been updated to:

- Consider the intent to treat population as the main population for the efficacy analysis and the per protocol population also as a sensitivity analysis.
- Include the region as a factor for the ANCOVA model
- Include sensitivity analyses (mixed-effect model with repeated measures, MCP-Mod approach, Rank ANCOVA model.
- Consider missing data in the 6-week ESS evaluation as a treatment failure.
- Consider three regions for the stratification: USA, Western Europe, and Eastern Europe

Additionally, some text passages were clarified and errors were corrected in the study protocol corresponding to the following:

- Update on the patient reported and clinician reported outcome instruments
- Cross references were updated
- E-mail address of Linical Safety department for SAE reporting updated to BEN01.safetydesk@linical.com
- E-mail address of 24h emergency contact updated to BEN01.medical.emergency@linical.com

Detailed changes are summarized in the following table:

Section	Page	Old text	New text
Heading	All	Amendment 02, Final Version 1.0	Amendment 03, Final Version 1.0
	All	03/Jul/2017	23/Aug/2017
Reason for substantial amendment 03	4	<<blank>>	<<New section with details of the substantial amendment 03>>
Summary – Main Criteria for Inclusion	18	(3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria.	(3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria)* of minimum 3 months before informed consent date.
Summary – Main Criteria for Exclusion	19	<<blank>>	<<New criterion #3>> (3) Subjects with a need of referral to a trained mental health professional based on their suicidal ideation (C-SSRS with an answer of 'yes' to any of the 6 questions)
Summary – Main Criteria for Exclusion	19	Exclusion criteria (3) – (17)	Exclusion criteria (4) to (18)
Summary - Main Criteria for Evaluation and Analysis: Primary variable:	20	ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, and treatment as a factor. A non-parametric ANCOVA model (as rank ANCOVA model) will be implemented in case the assumptions for the previous analysis are not met. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment.	ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, region and treatment as a factor. Missing data in the 6-week ESS evaluation will be considered as a treatment failure , that is imputing the missing ESS reduction as 0. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment. As sensitivity analyses: a) A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, region, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will

Section	Page	Old text	New text
		As sensitivity analyses, both a Last Observation Carried Forward (LOCF) imputation for missing data, and a mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.	be run with an unstructured correlation matrix to model the within-subject errors. b) MCP-Mod approach will be applied to identify the most suitable dose-response curve. Further details about the curve selection and validation procedures being used will be stated in the Statistical Analysis Plan. c) Similar to the primary analysis a Rank ANCOVA will be modelled in order to provide evidence of the treatment effect in case of violation of normality assumption. d) Primary Analysis, and sensitivity analysis as described above will be performed in the Per Protocol Population.
Summary – Secondary variables	20	HAM-D (6 week), C-SSRS (6 week)	HAM-D (2-week and 6-week)
Summary – Secondary variables	20	Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, and ocular changes findings will be described for the different treatment groups and assessed as either clinically or non-clinically significant findings.	Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, ocular changes, suicidal ideation (C-SSRS) findings, and positive psychotic symptoms (BPRS+) findings will be described for the different treatment groups and assessed as either clinically or non-clinically significant findings.
3.0 Table of contents	22	<<blank>>	<<updated>>
4.0 List of abbreviations and definition of terms	27	<<blank>>	BPRS+ – Brief Psychiatric Rating Scale positive subscale
6.2.2 Secondary Endpoint(s)	33	• Mean absolute change in the depression HAM-D score from screening/baseline to the end of the the 6-week treatment period.	•Mean absolute change in the depression HAM-D score from screening/baseline to the end of the the 2-week and 6-week treatment period and safety follow-up.
6.2.2 Secondary Endpoints	33	<<blank>>	• Incidence of suicidal ideation (C-SSRS) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up • Incidence of positive psychotic

Section	Page	Old text	New text
			symptoms (BPRS+) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
7.1 Overall Study Design and Plan: Description	35	There is a 6 weeks treatment period, starting on Day 1, followed by a safety follow-up call made at least 4 weeks after completion of the treatment period. Additional unscheduled visits may be required based on the investigators' judgement at the end of study visit or at the safety phone call. For early termination, all the assessments of the treatment week 6 visit should be performed, if possible, including the safety follow-up call 4 weeks after the last IMP administration.	There is a 6 weeks treatment period, starting on Day 1, followed by a safety follow-up at least 4 weeks after completion of the treatment period. Additional unscheduled visits may be required based on the investigators' judgement at the end of study visit or at the safety follow-up. For early termination, all the assessments of the treatment week 6 visit should be performed, if possible, including the safety follow-up 4 weeks after the last IMP administration.
Figure 1	36	<<Figure 1>>	<<updated to include C-SSRS, HAM-D, and BPRS+ at screening, visit 2, visit 3, and follow-up>>
7.2 Discussion of Study Design, including the Choice of Control Groups	37	[…] have no clinical evidence of depression, cognitive impairment, or fatigue).	[…] have no clinical evidence of suicidal ideation, depression, cognitive impairment, or fatigue).
7.2 Discussion of Study Design, including the Choice of Control Groups	37	<<blank>>	[…] need of referral to a trained mental health professional based on their suicidal ideation (C-SSRS with an answer of 'yes' to any of the 6 questions), […]
7.2 Discussion of Study Design, including the Choice of Control Groups	37	The suicide risk will be assessed (C-SSRS) both before and after treatment administration following the the FDA Guidance for Industry on Suicidal Ideation and Behavior[3]	The suicide risk will be assessed (C-SSRS) before and after treatment administration at all study visits including follow-up following the the FDA Guidance for Industry on Suicidal Ideation and Behavior[1]. BPRS+ (Brief Psychiatric Rating Scale) positive subscale to monitor psychotic symptoms and HAM-D to monitor depression will be assessed at all study visits (including follow-up) based that patients with Parkinson's disease are known to be at higher risk of psychosis and depression than the general

Section	Page	Old text	New text
			population. Follow-up procedures will be described for a positive finding on the C-SSRS, or an elevated HAM-D or psychosis scale score. Vital signs (including blood pressure and heart rate) will be assessed at all study visits (including follow-up) as patients with Parkinson's disease are known to commonly exhibit orthostatis and other cardiovascular changes.
8.1 Inclusion Criteria	40	(3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria.	(3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria)* of minimum 3 months before informed consent date.
8.2 Exclusion Criteria	41	<<blank>>	<<New criterion #3>> (3) Subjects with a need of referral to a trained mental health professional based on their suicidal ideation (C-SSRS with an answer of 'yes' to any of the 6 questions)
8.2 Exclusion Criteria	41	Exclusion criteria (3) – (17)	Exclusion criteria (4) to (18)
8.3 Prior and Concomitant Therapy	42	At a minimum, the following medications will be prohibited at any time during the study (see exclusion criterion #7):	At a minimum, the following medications will be prohibited at any time during the study (see exclusion criterion #8):
8.4 Efficacy and Safety Assessments / Variables	43	<<reference to follow-up safety call>>	<<reference to follow-up visit>>
8.4.1.7 Vital signs	44	<<assessed at screening and visit 3 (day 42)>>	<<assessed at all study visits (screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up.
8.4.1.7 Vital signs	44	Blood pressure (both systolic and diastolic and heart rate) will be assessed but this is considered for this protocol as specific cardiovascular assessment (see later)	Blood pressure (both systolic and diastolic and heart rate) will be assessed at the same visits but this is considered for this protocol as specific cardiovascular assessment (see later)
8.4.1.8 Contraception and Pregnancy Avoidance	45	<<blank>>	All potential participate in this clinical trial that are of child bearing potential MUST use adequate contraception methods; this should be one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary

Section	Page	Old text	New text
			barrier method (such as condom, diaphragm) with a spermicide.
8.4.1.9 Pregnancy	46	All pregnancies from subjects on active study drug will be followed up to final outcome, using the pregnancy form.	All pregnancies from female subjects, or female partner of a male subjects on active study drug will be followed up to final outcome, using the pregnancy form.
8.4.1.15 Clinician-Reported Outcome Instruments	51	<<blank>>	<<inclusion of C-SSRS and BPRS+>>
8.4.1.15.3 HAM-D	53	<<assessed at screening and visit 3 (day 42)>>	<<assessed at all study visits (screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up.
8.4.1.15.3 HAM-D	53	<<blank>>	Subjects with a HAM-D score ≥ 17 at screening will be considered as excluded from the study. Any positive finding on the HAM-D during the study will be followed based on usual clinical practice of the participant sites.
8.4.1.15.4 C-SSRS	53	<<assessed at screening and visit 3 (day 42)>>	<<assessed at all study visits (screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up.
8.4.1.15.4 C-SSRS	54	<<blank>>	Subjects with a need of referral to a trained mental health professional based on their suicidal ideation (C-SSRS with an answer of 'yes' to any of the 6 questions) will be considered as excluded from the study. Any positive finding on the C-SSRS during the study will be followed based on usual clinical practice of the participant sites.
8.4.1.15.5 BPRS+	54	<<blank>>	<<New section describing BPRS+ and assessment at all study visits including follow-up>>
8.4.2 Study Procedures	56	<<blank>>	Screening: BPRS+ Randomisation: Vital signs Visit 2: vital signs, C-SSRS, HAM-D, BPRS+ Visit 3: BPRS+
8.4.2 Study Procedures	59	Follow-up Period (+Day 28 ±2) During the following up period the eye examination post dose on Day 42 will be conducted and a follow-up safety call will be performed 28 days after the	Follow-up Period (+Day 28 ±2) During the following up period the eye examination post dose on Day 42 will be conducted and a follow-up safety visit will be performed 28 days after the last IMP administration where the vital signs (including hear rate and

Section	Page	Old text	New text
		last IMP administration. The eye examination should be performed before the follow up safety call. Additional unscheduled visits may be arranged as needed for the management of eye examination findings and / or adverse event findings.	blood pressure), C-SSRS, HAM-D, and BPRS+ will be assessed. The eye examination should be performed before the follow up visit. Additional unscheduled visits may be arranged as needed for the management of eye examination findings and / or adverse event findings.
8.4.2 Study Procedures – Unscheduled visits	58	<<blank>>	Other scales: C-SSRS, HAM-D and BPRS+
8.4.5 Secondary Variables	60	• Mean absolute change in the depression HAM-D score from screening/baseline to the end of the the 6-week treatment period.	• Mean absolute change in the depression HAM-D score from screening/baseline to the end of the the 2-week and 6-week treatment period and safety follow-up.
8.4.7 Safety Variables	61	<<blank>>	• Incidence of suicidal ideation (C-SSRS) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up • Incidence of positive psychotic symptoms (BPRS+) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
8.6.6 Method of Assigning Subjects to Treatment Groups	65	A computer-generated randomisation scheme will be provided by Nuvisan according to Sponsor specification.	A computer-generated randomisation scheme by region will be provided by Nuvisan according to Sponsor specification.
8.6.6 Method of Assigning Subjects to Treatment Groups	65	The randomisation will be stratified by the polysomnography and the MWT assessment which will be performed to a subset of subjects (around 50%). The information on whether the subject will do the polysomnography and the MWT assessment will be collected first and the randomisation will be performed based on this information. A first block of medication according to the randomisation scheme created	The randomisation will be stratified by region, the polysomnography and the MWT assessment which will be performed to a subset of subjects (around 50%). The information on whether the subject will do the polysomnography and the MWT assessment will be collected first and the randomisation will be performed based on this information. A first block of medication according to the randomisation scheme created for the corresponding region will be provided to each site.

Section	Page	Old text	New text
		will be provided to each site.	
9.7.1 Serious Adverse Events	74	<<blank>>	The Medical Manager at Linical will review the reported documentation for any medical clarification.
9.7.1 Serious Adverse Events	74	safetydesk@linical.com	BEN01.safetydesk@linical.com
11.1. Statistical and analytical plans	77	The main population for the efficacy analysis will be the Per Protocol (PP) Population defined as all the subjects of the intent to treat population (ITT) who do not perform any major protocol deviation.	The main population for the efficacy analysis will be the intent to treat population (ITT). The per protocol population (PP) will be analysed also as a sensitivity analysis.
11.1.4 Primary Efficacy Analyses	77	ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, and treatment as a factor. A non-parametric ANCOVA model (as rank ANCOVA model) will be implemented in case the assumptions for the previous analysis are not met. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment. As sensitivity analyses, both a Last Observation Carried Forward (LOCF) imputation for missing data, and a mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, visit and treatment-by-visit interaction as well as the continuous fixed covariates of	ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, region and treatment as a factor. Missing data in the 6-week ESS evaluation will be considered as a treatment failure , that is imputing the missing ESS reduction as 0. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment. As sensitivity analyses: a) A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, region, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors. b) MCP-Mod approach will be applied to identify the most suitable dose-response curve. Further details about the curve selection and validation procedures being used will be stated in the Statistical Analysis Plan.

Section	Page	Old text	New text
		mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.	c) Similar to the primary analysis a Rank ANCOVA will be modelled in order to provide evidence of the treatment effect in case of violation of normality assumption. d) Primary Analysis, and sensitivity analysis as described above will be performed in the Per Protocol Population.
11.1.5 Secondary Efficacy Analyses	77	[…] and HAM-D (6-week), MoCA (6-week), C-SSRS (6-week), and FSS (6-week).	[…] HAM-D (2-week, 6-week and follow-up), MoCA (6-week), and FSS (6-week).
11.1.7 Safety Analyses	78	Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, and ocular changes will be described for the different treatment groups […]	Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, ocular changes, suicidal ideation (C-SSRS) findings, and positive psychotic symptoms (BPRS+) findings will be described for the different treatment groups […]
11.5 Handling of dropouts or missing data	79	As sensitivity analyses, both a Last Observation Carried Forward (LOCF) imputation for missing data, and a mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.	For the primary analysis ESS missing at 6-weeks will be inputed under the treatment failure approach. As sensitivity analyses, a mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.
11.3 Randomisation Methods	81	One single randomisation list will be performed to guarantee a ratio of 1:1:1:1 for the treatment groups.	Three regions will be defined: USA, Western Europe and Eastern Europe. Regionally randomization list will be performed to guarantee a ratio of 1:1:1:1 for the treatment groups by region.
17.0 Reference List	92	<<blank>>	<<updated>>

Section	Page	Old text	New text
18.1 Administrative Information – Contacts	96	24h emergency contact BEN01-medical-emergency@linical.com	24h emergency contact BEN01.medical.emergency@linical.com
18.10 BPRS+	119	<<blank>>	<<new appendix>>
18.11-18.15	121	<<old references 18.10 to 18.14>>	<<new references 18.11 to 18.15>>
18.15 Schedule of Assessments	139	<<blank>>	<<updated to: - include vital signs with heart rate and blood pressure at screening, V2, V3, FUP - HAM-D, C-SSRS, BPRS+ at screening, V2, V3, FUP - change follow-up call to follow-up visit>>

REASON FOR NONSUBSTANTIAL AMENDMENT 02

This amended study protocol is prepared to remove the LOCS III assessment (Lens Opacities Classification System III) from the ocular examination in the study. As this is a six week study the likelihood of observing cataract development in humans is very low and conducting the LOCS III assessment does not add value. In order to reduce the patient burden and focus on the ocular safety assessment, the LOCS III assessment is removed; but safety eye examination will remain both at Screening and during the follow-up period after the 6-week treatment period.

Additionally, some text passages were clarified and errors were corrected in the study protocol corresponding to the following:

- No data monitoring committee will be used in this study.
- Cross references were updated

Detailed changes are summarized in the following table:

Section	Page	Old text	New text
Heading	All	Amendment 01, Final Version 1.0	Amendment 02, Final Version 1.0
	All	20/Jun/2017	03/Jul/2017
Reason for nonsubstantial amendment 02	4	<<blank>>	<<New section with details of the nonsubstantial amendment 02>>
3.0 Table of contents	13	<<blank>>	<<updated>>
6.2.2 Secondary Endpoint(s)	25	Incidence of slit lamp examination findings	Incidence of eye exam findings
7.1 Overall Study Design and Plan: Description	27	<<Figure 1>>	<<updated figure to rename 'slit lamp examination' with 'eye exam'>>
8.4.1.13 Slit Lamp Examination	39	8.4.1.13 Eye Examination	<<updated section to replace 'slit lamp examination' with 'eye examination'
8.4.2 Study Procedures Screening assessments (Day -28 to Day -8)	45	Slit lamp examination and full ocular check	Eye examination
8.4.2 Study Procedures Treatment Visit 3 (Day 42 ±3)	47	Slit lamp examination and full ocular check (should be performed after the last treatment on Day 42 and before the follow up safety call)	Eye examination (should be performed after the last treatment on Day 42 and before the follow up safety call)
8.4.2 Study Procedures Follow-up Period (+Day 28 ±2)	48	During the following up period the slit lamp examination post dose on Day 42 will be conducted and a follow-up safety call will be	During the following up period the eye examination post dose on Day 42 will be conducted and a follow-up safety call will be performed 28

Section	Page	Old text	New text
		performed 28 days after the last IMP administration. The slit lamp examination should be performed before the follow up safety call. Additional unscheduled visits may be arranged as needed for the management of slit lamp examination findings and / or adverse event findings.	days after the last IMP administration. The eye examination should be performed before the follow up safety call. Additional unscheduled visits may be arranged as needed for the management of eye examination findings and / or adverse event findings.
8.4.2 Study Procedures Unscheduled Visit	48	Unscheduled visits may be arranged following investigators' judgement for Slit lamp examination, or adverse event findings identified either at the end of study or during the follow-up period.	Unscheduled visits may be arranged following investigators' judgement for eye examination, or adverse event findings identified either at the end of study or during the follow-up period.
8.4.2 Study Procedures Telephone Contacts	48	Sites will maintain telephone contacts with subjects during the study as reminders for the study logistics, including the safety slit lamp assessment during follow-up.	Sites will maintain telephone contacts with subjects during the study as reminders for the study logistics, including the safety eye examination during follow-up.
8.4.7 Safety Variables	50	Incidence of slit lamp examination findings	Incidence of eye examination findings
9.7.3 Data Monitoring Committee	64	<<blank>>	<<New section>> No data monitoring committee will be used in this study.
18.14 Schedule of Assessments	123	Slit lamp examination and ocular check	Eye examination
18.14 Schedule of Assessments	123	(1) All subjects will receive a phone-call safety follow-up from the site 28 days after last study visit performed. Additional unscheduled visits may be arranged in case of slit lamp examination, ECG, or adverse event findings.	(1) All subjects will receive a phone-call safety follow-up from the site 28 days after last study visit performed. Additional unscheduled visits may be arranged in case of eye examination, ECG, or adverse event findings.
18.14 Schedule of assessments	123	(7) The slit lamp examination should be performed after the last treatment on Day 42 and before the follow up safety call.	(7) The eye examination should be performed after the last treatment on Day 42 and before the follow up safety call.

REASON FOR NONSUBSTANTIAL AMENDMENT 01

This amended study protocol is prepared to include the Columbia-Suicide Severity Rating Scale (C-SSRS)[2, 3] following the US FDA Guidance document on the prospective assessment of occurrence of suicidal ideation and behavior in clinical trials[1], and to clarify some text passages and correct some errors in the study protocol corresponding to the following:

- Inclusion of the C-SSRS assessment both at screening and Visit 3 (week 6)
- Inclusion of the C-SSRS assessment as another secondary objective
- Insertion of a new Appendix for the C-SSRS information
- Update of the study figure to describe the C-SSRS assessment both at screening and Visit 3 (week 6)
- Update of the Schedule of assessment to include the C-SSRS assessment both at screening and Visit 3 (week 6), and a new column between Visit 2 and Visit 3 to precise the start of the GENEActive® assessment.
- Update of references with the inclusion of new references regarding the C-SSRS and the US FDA guidance document.
- Cross references were updated

Detailed changes are summarized in the following table:

Section	Page	Old text	New text
Heading	All	Final Version 1.0	Amendment 01, Final Version 1.0
	All	05/Apr/2017	20/Jun/2017
Reason for nonsubstantial amendment 01	4	<<blank>>	<<New section with details of the nonsubstantial amendment 01>>
Synopsis Secondary variables	9	<<blank>>	C-SSRS (6 week)
3.0 Table of contents	11	<<blank>>	<<updated>>
4.0 List of abbreviations and definition of terms	16	<<blank>>	C-SSRS: Columbia-Suicide Severity Rating Scale
6.2.2. Secondary Endpoint(s)	23	<<blank>>	Mean absolute change in the suicidal ideation and behaviour C-SSRS score from screening/baseline to the end of the 6-week treatment period.

Section	Page	Old text	New text
7.1 Overall Study Design and Plan: Description	24	Key inclusion / exclusion criteria will be verified to determine subject eligibility at the screening, baseline periods and prior to randomization.	Key inclusion / exclusion criteria will be verified to determine subject eligibility at the screening, baseline periods and prior to randomisation., including the suicide risk assessment following the FDA Guidance for Industry on Suicidal Ideation and Behavior[3].
Figure 1	25	<<Figure 1>>	<<New figure to update the C-SSRS assessment both at screening and Visit 3 (week 6)>>
7.2 Discussion of Study Design, including the Choice of Control Groups	26	<<blank>>	The suicide risk will be assessed (C-SSRS) both before and after treatment administration following the the FDA Guidance for Industry on Suicidal Ideation and Behavior[3].
8.4.1.15.4 Columbia-Suicide Severity Rating Scale (C-SSRS)	41	<<Blank>>	New section
8.4.1.15.5 Rater Qualification and Certification	41	8.4.1.16 Rater Qualification and Certification	8.4.1.15.5 Rater Qualification and Certification
8.4.1.15.6 Maintenance of Wakefulness Test (MWT)	42	8.4.1.17 Maintenance of Wakefulness Test (MWT)	8.4.1.15.6 Maintenance of Wakefulness Test (MWT)
8.4.1.15.7 Polysomnography	42	8.4.1.18 Polysomnography	8.4.1.15.7 Polysomnography
8.4.1.15.8 Free Living Activity	43	8.4.1.19 Free Living Activity	8.4.1.15.8 Free Living Activity
8.4.2 Study Procedures	43	<<Blank>>	<<C-SSRS included in the Screening assessments>>
8.4.2 Study Procedures	45	<<Blank>>	<<C-SSRS included in the Visit 3 (week 6) assessments>>
11.1.5 Secondary Efficacy Analyses	64	<<Blank>>	C-SSRS (6 week)
17.0 Reference List	77	<<Blank>>	<<3 new references inserted>>
18.11 Columbia-Suicide Severity Rating Scale (C-SSRS)	109	<<Blank>>	<<New appendix to describe the C-SSRS details>>
18.12 Fatigue Severity Scale (FSS)	119	18.11 Fatigue Severity Scale (FSS)	18.12 Fatigue Severity Scale (FSS)
18.14 Schedule of Assessments	121	18.13 Schedule of Assessments	18.14 Schedule of Assessments

Section	Page	Old text	New text
18.14 Schedule of Assessments	121	<<Blank>>	<<New column between Visit 2 and Visit 3 to precise the start of the GENEActive® start>> <<New row to describe the C-SSRS to be assessed both at screening and Visit 3 (week 6)>> <<Footnotes updated>>

2.0 Summary

Name of Sponsor(s): BenevolentAI Bio	**Compound:** Bavisant (H3 receptor antagonist)	
Title of Protocol: 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.		**EudraCT No.:** 2017-000877-35
Study Number: BB-2001-201b	**Phase:** 2b	
Study design: Phase IIb, randomized, double blind, parallel group, placebo controlled, multicentre, 6-week dose-finding study.		
Primary objective: To assess the efficacy of Bavisant compared to placebo after a 6-week treatment period on excessive daytime sleepiness in Parkinson's disease.		
Secondary objectives: To assess the efficacy and safety assessment of Bavisant compared to placebo after 2 weeks and 6 weeks of treatment. The efficacy assessment will include excessive daytime sleepiness, motor control and depression.		
Exploratory objectives: Exploratory objectives will include the assessment of free living activity on Bavisant compared to placebo after 6 weeks of treatment using a wrist-worn actigraphy device and pharmacogenomics analysis.		
Subject Population:		
Number of Subjects: 200 completed	**Number of sites:** Appr. 48 sites globally	
Dose Levels: 0.5, 1 and 3 mg tablets and matching placebo.	**Route of Administration:** Oral	
Duration of Treatment: Maximum 14 weeks per subject	**Period of Evaluation:** Screening of 3 weeks Baseline assessment of 1 week Treatment of 6 weeks Safety follow-up of 4 weeks after treatment	
Main Criteria for Inclusion: (1) Signed informed consent (no study-related procedures may be performed before the subject has signed the consent form). (2) Subjects of either sex aged 50 to 80 years (both inclusive and relative to Day 1). (3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria)* of minimum 3 months before informed consent date. (4) Subjects capable of understanding and complying with protocol requirements. (5) Subjects with medical history of excessive daytime sleepiness. (6) Subjects with moderate or severe excessive daytime sleepiness indicated by an Epworth Sleepiness Score (ESS) > 12 at screening . (7) Subjects with stable nocturnal sleep hygiene practices (e.g. temperature, darkness, quiet, place to lie down and stretch out) as per investigator's judgement.		

(8) Male subjects who are nonsterilized and sexually active with a female partner of childbearing potential agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 4 weeks after last dose**.
(9) Female subjects of childbearing potential who are sexually active with a nonsterilized male partner agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 4 weeks after last dose**.
(10) Subjects on stable permitted concomitant medication for at least 4 weeks before screening.

* Additional details on the UK Parkinson's disease society brain bank clinical diagnostic criteria are included in Appendix 18.2.

** Definitions and acceptable methods of contraception, and Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 8.4.1.8.

Main Criteria for Exclusion:

(1) Subjects with excessive daytime sleepiness due to conditions other than Parkinson's disease (including narcolepsy)
(2) Subjects with significant eye disease which may substantially impact the subject's mobility and ability to have eye examination conducted as per investigator's judgement.
(3) Subjects with a recent history of suicide attempt (defined as an active, interrupted or aborted attempt within the past 1 year), or reports suicidal ideation in the past 3 months as indicated by a positive response on the C-SSRS at screening visit (an answer of 'yes' to any of the 6 questions)
(4) Subjects with clinical evidence of depression with significant psychiatric comorbidities (Hamilton Rating Scale for Depression - HAM-D score ≥ 17; with or without treatment)
(5) Subjects with evidence of significant Cognitive Impairment (Montreal Cognitive Assessment - MoCA score ≤ 22 at screening)
(6) Subjects with evidence of significant fatigue (Fatigue Severity Scale - FSS ≥ 36)
(7) Subjects with high risk of sleep apnoea (Berlin questionnaire with ≥ 2 categories where the score is positive)
(8) Subjects taking any of the following prohibited medications at screening:
- Alerting agents, including r-modafinil, modafinil or methylphenidate
- Benzodiazepines
- Histamine active agents
- Hypnotics
- Cholinergics
- Skeletal muscle relaxants
- Clozapine
- Atomoxetine
- Amitriptyline
- Any other daytime medications which affect sleep

(9) Subjects with chronic oral and / or ophthalmic steroidal use
(10) Subjects with either renal or hepatic impairment defined by laboratory parameters >1.5x age-adjusted limits of normal range
- Hepatic damage: Alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, or total bilirubin
- Renal damage: Blood creatinine, blood urea nitrogen [BUN], or estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m^2

(11) Subjects with abnormal ECG time intervals at baseline including QTc (> 450 for males and > 470 for females)
(12) Subjects with known history of lung malignancy.
(13) Subjects with known history of abuse of alcohol or other addictive substances in the 6 months prior to inclusion.
(14) Subjects with known allergies or hypersensitivity to Bavisant or any of its excipients.
(15) Subjects who are pregnant or lactating.
(16) Subjects who do not wish to or cannot comply with study procedures.
(17) Subjects currently receiving, or having received within 3 months prior to enrolment into this clinical study, any investigational drug.
(18) Subjects who are study-site employees, or are immediate family members (i.e., spouse, parent, child, sibling) of a study site employee involved in conduct of this study.

Main Criteria for Evaluation and Analysis:

Primary variable:

ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, region and treatment as a factor. Missing data in the 6-week ESS evaluation will be considered as a treatment failure , that is imputing the missing ESS reduction as 0. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment.

As sensitivity analyses:

a) A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, region, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.
b) MCP-Mod approach will be applied to identify the most suitable dose-response curve. Further details about the curve selection and validation procedures being used will be stated in the Statistical Analysis Plan.
c) Similar to the primary analysis a Rank ANCOVA will be modelled in order to provide evidence of the treatment effect in case of violation of normality assumption.
d) Primary Analysis, and sensitivity analysis as described above will be performed in the Per Protocol Population.

Secondary variables:

All secondary variables assessing a mean absolute or a mean relative change will follow a similar methodology as for the primary variable; i.e., mean changes of ESS (up to 2-week treatment period), SCOPA-Sleep (up to 2-week and 6-week treatment period), PDSS-2 (2-week and 6-week), MWT (6-week), polysomnography (6-week), UPDRS Part III (2-week and 6-week), motor function assessed by the wearable tool (6-week), HAM-D (2-week and 6-week), MoCA (6-week), and FSS (6-week).

Percentage of subjects who showed ESS clinical response (defined as an ESS decrease from baseline of at least 3.0 points and/or final ESS score ≤10) after 2 and 6 weeks of treatment will be described and compared between groups by means of a Chi-square test (or Fisher's exact test according to corresponding applicability). Percentages and difference between treatments will be expressed with their 95% confidence interval calculated with a binomial exact method.

Adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), serious and related adverse events will be coded using the latest available MedDRA version and their corresponding incidences will be summarised as overall events, related events, and events by intensity. AEs will be summarised by MedDRA preferred term and system organ class (primary SOC). Summaries of AEs by preferred term and decreasing frequency and by maximum severity will also be prepared.

Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, ocular changes, suicidal ideation (C-SSRS) findings, and positive psychotic symptoms (BPRS+) findings will be

described for the different treatment groups and assessed as either clinically or non-clinically significant findings.

Exploratory variables:

The effect of Bavisant compared to placebo after the 6-week treatment period of free living activity will be assessed by means of wrist-worn actigraphy. For each set of continuous tri-axial accelerometry measurement, descriptive statistics of values at baseline, endpoint and change from baseline will be provided by treatment group.

Pharmacogenomic information will be assessed in order to identify genetic reasons why certain people respond differently to Bavisant, to find out more information about how Bavisant works, 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.

Sample size Justification: A total of approximately 200 completed subjects will be evaluated for the study (50 completed subjects per treatment group, with expected early withdrawal rate of around 15%). This sample size will be enough to confirm a statistically significant difference of at least 3.0 points in ESS between Bavisant and placebo (between treatment Δ=3.0; SD=5.0; two-side α=0.05; β=0.20; power=80%; two-sample equal-variance t-test).

Polysomnography and Maintenance of Wakefulness Test (MWT) will be performed in a minimum of 20 subjects per group (80 overall) in order to show statistically significant differences if the expected MWT absolute change from baseline differs at least in one standard deviation (effect size = 1.0).

3.0 Table of contents

Page

4.0 List of abbreviations and definition of terms

Abbreviation	Description
5-HT	Serotonin
AASM	American Association of Sleep Medicine
ASST	American Association of Sleep Technologists
ACh	Acetylcholine
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ASP	Average Sleep Propensity
AST	Aspartate Aminotransferase
BPRS	Brief Psychiatric Rating Scale
BPRS+	Brief Psychiatric Rating Scale Positive Subscale
BUN	Blood Urea Nitrogen
CM	Concomitant Medication
CNS	Central Nervous System
COMT	Catechol-O-methyl transferase
CRF/eCRF	Case Report Form / electronic CRF
CRO	Clinical Research Organisation
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
DHM	Data Handling Manual
DMC	Data Monitoring Committee
DS	Daytime Sleepiness
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalogram
eGFR	Estimated Glomerular Filtration Rate
EMG	Electromyogram
EOG	Electro-oculogram

Abbreviation	Description
EoS	End of Study Visit
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
EU	European Union
FAS	Full Analysis Set
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
GOT	Glutamate Oxaloacetic Transaminase
GPT	Glutamate Pyruvic Transaminase
HAM-D	Hamilton rating scale for depression
HIPPA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
IRB	Institutional Review Board
ISF	Investigator's Study File
ITT	Intention-to-Treat
IV	Intravenous
LOCF	Last Observation Carried Forward
LOCS III	Lens Opacities Classification System III
MAOI	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
UPDRS Part III	Unified Parkinson's Disease Rating Scale Part III
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed models for repeated measures
MoCA	Montreal Cognitive Assessment
MWT	Maintenance of Wakefulness Test
NA	Noradrenaline
NS	Night time Sleep
PD	Parkinson's Disease

Abbreviation	Description
PDSS-2	Parkinson's Disease Sleep Scale 2
PP	Per-Protocol
PTE	Pre treatment event
QT	Electrocardiogram QT interval
QTc	Electrocardiogram QT interval corrected
QTcB	Electrocardiogram QT interval corrected Bazzett's method
QTcF	Electrocardiogram QT interval corrected Fridericia's method
RR	Electrocardiogram RR interval
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
s.c.	Subcutaneous
SCOPA-Sleep	Scales for Outcome in Parkinson's Disease Sleep
SD	Standard Deviation
SL	Sleep Latency
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TMN	Tuberomammillary Nucleus
VAS	Visual Analogue Scale
WHO	World Health Organisation

5.0 Introduction

5.1. Background

Parkinson's Disease (PD) is the second most common neurological disease after Alzheimer's disease. PD affects between 150 and 200 people in every 100,000 population. Thus, some 800,000 people in Europe are estimated to have Parkinson's disease and about 75,000 new cases are diagnosed annually[(4)]. In the United States around 1 million people are living with PD with about 60,000 new cases per year[(5)].

In the DSM 5 classification of neurodegenerative conditions, diseases such as Parkinson's disease (PD), are associated with hypersomnolence. Excessive daytime sleepiness (EDS) , with or without SOREMs is recognised as a core part of the Parkinson Disease phenotype[(6)].

In the Honolulu Ageing Study, EDS was assessed in 3078 men without PD aged 71 to 93 years from 1991 to 2001. During follow-up, neurological assessment indicated that 43 men developed PD (19.9/10,000 person-years),and the authors concluded that EDS is part of the non motor spectrum of PD clinical expression and can pre date motor symptoms[(7)]. Excessive daytime sleepiness (EDS) is described as inappropriate and undesirable sleepiness during waking hours and is a common non-motor symptom in Parkinson's disease, affecting up to 50% of patients, being more prominent as the disease advances. EDS has a large impact on the quality of life of Parkinson's disease patients as well as of their caregivers, in some cases even more than the motor symptoms of the disease[(8)]. Daytime sleepiness may arise in patients with Parkinson's disease for many reasons, including poor night's sleep and drug-induced EDS, which is particularly shown as an adverse event of many dopamine agonists used for the treatment of Parkinson's disease. Dopaminergic treatment may also render a subset of Parkinson's disease patients at risk for sudden-onset sleep attacks that occur without warning and can be particularly hazardous. Leading neurologists attribute significant morbidity from EDS:

'In a well-managed patient with PD, the most common residual complaints are fatigue, lack of energy and sleepiness' (W.Ondo, US Neurologist)

'Of all my symptoms EDS is the one that gives me the most trouble in the real world' (Marshall Davidson MD – physician with PD – see http://www.dopadoc.com)

EDS can occur in patients that are untreated and may precede the onset of movement dysfunction[(9)].

Non-pharmacological approaches are the mainstay of treatment for mild to moderate EDS as pharmacological approaches have yet to provide consistent and reliable results and have significant adverse effects e.g. modafinil (Provigil) has not been shown to be consistently effective in placebo controlled double blind trials. Other agents that have been used are bupropion and psychostimulants, such as amphetamine, but there are significant side effects associated with both approaches to therapy. Therefore, there is a real unmet need for an effective, safe agent to treat EDS in PD.

The pathophysiology of EDS in PD is thought to relate to dysfunctional sleep-wake control/vigilance mechanisms due to the underlying disease pathology that involves different neuroanatomical substrates beyond the classical substrates associated with motor symptoms – the nigro-striatal pathway.

The cellular aetiology of non motor symptoms including sleep disorder is less well defined. Loss of dopamine action on neural excitability in several regions outside the striatum may be a factor, but neurons producing hypocretin (orexin) - a hypothalamic protein involved in sleep-wake regulation, food intake and reward mechanism have been shown to be reduced in PD

Fronczek et al showed a significant decrease between PD patients and controls in the number of hypocretin neurons, the hypocretin-1 concentration in post-mortem ventricular CSF and the hypocretin-1 concentrations in prefrontal cortex. The hypocretin-1 concentration in the prefrontal cortex was almost 40% lower in PD patients, while ventricular CSF levels were almost 25% reduced. The total number of hypocretin neurons was almost half compared to controls[10].

In a study by Thannikal et al of the hypothalamus of 11 PD (mean age 79 +/- 4) and 5 normal (mean age 77 +/- 3) brains, Hcrt (Hypocretin) cells were lost throughout the anterior to posterior extent of their hypothalamic distributions. The percentage loss of Hcrt cells was minimal in stage I disease (23%) and was maximal in stage V disease (62%). PD was characterized by a massive loss of Hcrt neurons, which significantly correlated with the clinical stage of PD, and authors commented that the loss of Hcrt cells may be a cause of disordered sleep symptoms of PD[11].

Extensive neuropathological studies have shown that PD affects areas of the brain that have been shown to be key in promoting wakefulness e.g. locus coeruleus, dorsal raphe, and pedunculopontine tegmental nucleus[12, 13]. The decreases in neurotransmitter function that this damage causes may underlay the EDS seen in PD with decreases in levels of acetylcholine (ACh), noradrenaline (NA), and serotonin (5-HT), all neurotransmitters important for wakefulness.

The histamine system has been a rich source of biologically important medicines such as the anti-allergic H1 antagonists and the anti-ulcer H2 antagonist medicines Tagamet and Zantac. Unlike the H1 and H2 receptors, the Histamine H3 receptor is restricted to the CNS and therefore any on-target actions against the H3 receptor in the periphery are expected to be minimal. Histaminergic neurons arise solely from the tuberomammillary nucleus (TMN) of the posterior hypothalamus and project into widespread regions of the mammalian brain and histamine has been shown to play a key role in a wide range of higher brain functions such as the sleep-wake cycle, appetite, nociception, cognition and emotion. On histaminergic neurons, the histamine H3 receptor is an auto-receptor which controls neuronal secretion of histamine, with agonists (including histamine itself) decreasing synaptic histamine and antagonist or inverse-agonist increasing synaptic levels of histamine. Histamine signals wakefulness via H1 receptors, stress responses via H1 and H2 receptors and immune regulation via H4 receptors. Additionally, on non-histaminergic neurones, the histamine H3 receptor is a heteroreceptor, where histamine acts to decrease the release of other neurotransmitters such as acetylcholine, dopamine, serotonin and GABA. H3 receptor antagonists and inverse-agonists act at these heteroreceptors to increase the release of these neurotransmitters[14, 15].

The histaminergic system fulfils a major role in the maintenance of waking. Histaminergic neurons are located exclusively in the posterior hypothalamus from where they project to most areas of the central nervous system. The histamine H3 receptors are autoreceptors damping histamine synthesis, the firing frequency of histamine neurons, and the release of histamine from axonal varicosities. It is noteworthy that this action also extends to heteroreceptors on the axons of most other neurotransmitter systems, allowing a powerful control over multiple homeostatic

functions. The particular properties and locations of histamine H3 receptors provide quite favourable attributes to make this a most promising target for pharmacological interventions of sleep and waking disorders associated with narcolepsy, Parkinson's disease, and other neuropsychiatric indications[16].

Preclinically H3 agonists cause sedation whilst H3 antagonists or inverse agonists have the opposite effect, increasing wakefulness[16]. They have also been shown to increase cognitive performance in preclinical species. A number of H3 antagonists have been taken to clinical proof of concept studies for a range of CNS disorders including those relating to excessive sleepiness such as narcolepsy and one compound, pitolisant has been studied in EDS in PD. Whilst many of the studies were negative, studies with pitolisant did produce positive results in narcolepsy, day time sleepiness associated with sleep apnoea and EDS in PD. Pitolisant has been approved by the EMA for narcolepsy with and without catalepsy and has been launched in the European Union (EU) in 2016 under the trade name Wakix.

5.2. Study Rationale

This Phase 2b study will be conducted with the aim of investigating the efficacy and safety of three fixed doses of Bavisant (0.5, 1 and 3 mg/d) compared to placebo for the treatment of excessive daytime sleepiness (EDS) in subjects with Parkinson's disease.

Pathological sleepiness is present in 20-50% of PD (as assessed by an objective measure of sleepiness like the multiple sleep latency test [MSLT], with a narcolepsy-like phenotype in 15-50% of these patients. With a subjective measure widely used to screen for EDS in PD (the Epworth Sleepiness score [ESS]), it has been shown that EDS in PD is not reflective of inadequate sleep at night but is intrinsic to the disease process and can be exacerbated by therapies given to treat the motor symptoms of the disease. Dopaminergic agonist treatment may also render Parkinson's disease patients at risk for sudden-onset sleep attacks that occur without warning and can be particularly hazardous if the patient is driving. In fact, 11-22% of PD patients experience sleepiness while driving and this correlates with higher ESS scores[17, 18]. These findings reinforce the need for early recognition and management of EDS not only to increase health-related quality of life but also to ensure patient safety.

Bavisant is a potent H3 receptor antagonist with considerable affinity for the human H3 receptor and minimal affinity for other neurotransmitters at concentrations up to 1000 times higher than its human H3 receptor affinity. In animals, Bavisant has been shown to promote wakefulness and attention, reduce sleepiness, and increase cognitive performance. There is therefore strong reason to believe that Bavisant will be effective in EDS in PD if administered at the appropriate dose(s). Bavisant has been investigated in Phase 2 for the treatment of ADHD (attention deficit hyperactivity disorder) and its efficacy was demonstrated at doses up to 30 mg/day; but this was not considered adequate to offer advantages over active comparator therapies. From a safety perspective, Bavisant was generally well tolerated with common adverse events including insomnia, abnormal dreams, headache and nausea, which were dose related.

Based on preclinical and clinical properties shown, Bavisant has been selected for testing in EDS in Parkinson's disease.

6.0 Study Objectives and Endpoints

6.1. Objectives

6.1.1 Primary Objective

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

6.1.2 Secondary Objective(s)

To assess the efficacy and safety assessment of Bavisant compared to placebo after 2 weeks and 6 weeks of treatment. The efficacy assessment will include excessive daytime sleepiness, motor control, and depression.

6.1.3 Exploratory Objective(s)

Exploratory objectives will include 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.

6.2. Endpoints

6.2.1 Primary Endpoint

The primary endpoint will be the mean absolute change of Bavisant treatment groups in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 6-week treatment period, assessed as both the intragroup change compared to baseline and intergroup change compared to placebo.

6.2.2 Secondary Endpoint(s)

Efficacy in Excessive Daytime Sleepiness (EDS):

- Mean absolute change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 2-week treatment period.
- ESS clinical response, defined as ESS absolute decrease from baseline of at least 3.0 points, after 2 and 6 weeks of treatment.
- ESS clinical response, defined as ESS $\leq$ 10 after 2 and 6 weeks of treatment.
- ESS clinical response, defined as either ESS $\leq$ 10 after 2 and 6 weeks of treatment or ESS absolute decrease from baseline of at least 3.0 points after 2 and 6 weeks of treatment.
- Mean relative change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 2-week and 6-week treatment periods (percentage of absolute decrease compared to baseline ESS).
- Mean absolute change in the Scales for Outcome in Parkinson’s Disease Sleep (SCOPA-Sleep) from baseline to the end of the 2-week and 6-week treatment period.

- Mean absolute change in the Parkinson's Disease Sleep Scale (PDSS-2) from baseline to the end of the 2-week and 6-week treatment period.
- Mean absolute change in the Maintenance of Wakefulness Test (MWT) from baseline to the end of the 6-week treatment period.
- Mean absolute change in the polysomnography from baseline to the end of the 6-week treatment period.

Efficacy in Parkinson's disease (PD):

- Mean absolute change in the UDPRS scale Part III (motor control) from baseline to the end of the 2-week and 6-week treatment period.
- Mean absolute change in the depression HAM-D score from screening/baseline to the end of the the 2-week and 6-week treatment period and safety follow-up.
- Mean absolute change in the Montreal Cognitive Assessment – MoCA score from screening/baseline to the end of the 6-week treatment period.
- Mean absolute change in the Fatigue Severity Scale – FSS score from screening/baseline to the end of the 6-week treatment period.

The safety of Bavisant compared to placebo will be assessed by the evaluation of the following:

- Incidence of Adverse Events (AEs), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESIs) such as headache, nausea and insomnia
- Incidence of suicidal ideation (C-SSRS) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
- Incidence of positive psychotic symptoms (BPRS+) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
- Incidence of physical examination, vital signs and laboratory tests findings (haematology and biochemistry)
- Incidence of cardiovascular safety findings (blood pressure, heart rate, ECG including QT/QTc)
- Incidence of eye exam findings

6.2.3 Exploratory Endpoint(s)

The efficacy of Bavisant compared to placebo after the 6-week treatment period of free living activity will be assessed by means of wrist-worn actigraphy. For each set of continuous tri-axial accelerometry measurement, descriptive statistics of values at baseline, endpoint and change from baseline will be provided by treatment group.

A pharmacogenomic analysis will be used to identify genetic reasons why certain people respond differently to Bavisant, to find out more information about how Bavisant works, 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.

7.0 Investigational Plan

7.1. Overall Study Design and Plan: Description

This phase 2b study is designed as multicentre, multinational, randomized, double blind, parallel group and placebo controlled with three doses of Bavisant (0.5, 1, and 3 mg/d) in subjects with excessive daytime sleepiness with Parkinson's disease. This study will involve approximately 230 subjects from around 48 sites globally.

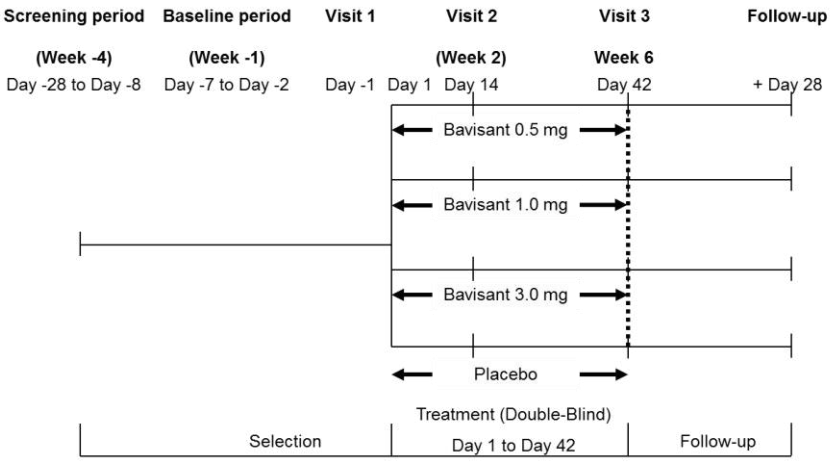
Eligible subjects will be randomly allocated at a ratio of 1:1:1:1 to either Bavisant (at doses of 0.5, 1, and 3 mg/d) or placebo.

After signing the study informed consent, subjects meeting the UK PDS Brain Banks Diagnostic Criteria for Parkinson's disease[19] (see details in Appendix 18.2) will enter a screening period (lasting up to 3 weeks) followed by a baseline period (lasting up to 1 week). Key inclusion / exclusion criteria will be verified to determine subject eligibility at the screening, baseline periods and prior to randomisation, including the suicide risk assessment following the FDA Guidance for Industry on Suicidal Ideation and Behavior[1].

There is a 6 weeks treatment period, starting on Day 1, followed by a safety follow-up at least 4 weeks after completion of the treatment period. Additional unscheduled visits may be required based on the investigators' judgement at the end of study visit or at the safety follow-up. For early termination, all the assessments of the treatment week 6 visit should be performed, if possible, including the safety follow-up 4 weeks after the last IMP administration.

A schematic of the study design is included in Figure 1 and the schedule of assessments is listed in Appendix 18.15.

Figure 1. Study figure



Inclusion / Exclusion	X	X	X			
Randomisation			X			
Laboratory tests	X				X	
Pharmacogenomic sample	X					
Eye examination	X				X	
C-SSRS	X			X	X	X
ESS	X		X	X	X	
MoCA, FSS	X				X	
HAM-D	X			X	X	X
BPRS+	X			X	X	X
SCOPA, PDSS, UPDRS			X	X	X	
MWT, polysomnography		X			X	
Free Living Activity		X			X	
Adverse Events	X	X	X	X	X	X

7.2. Discussion of Study Design, including the Choice of Control Groups

This trial is designed as a phase 2b, randomized, double blind, parallel group, placebo controlled, multicentre, 6-week dose-finding study to assess the efficacy and safety of Bavisant for the treatment of excessive daytime sleepiness in subjects with Parkinson's disease.

There is no regulatory approved pharmacological agent for the treatment of excessive daytime sleepiness and despite the use of agents such as modafinil (Provigil), which have not shown consistent and reliable effectiveness, there is still a real unmet need in the subject population. Bavisant has a unique mechanism of action and may be able to address this need.

The intention of the proposed selection criteria is to limit participation to PD subjects with moderate sleepiness and ability to complete the study assessments without any major impairment that may impact the collection of either the efficacy endpoints (should have moderate sleepiness due to PD only and no other conditions, be on stable medication without interference of concomitant medication as assessed before study participation, have no clinical evidence of suicidal ideation, depression, cognitive impairment, or fatigue) or the safety endpoints (hepatic, renal, cardiac, ophthalmological). The inclusion criteria of the planned clinical study are intended to select adult subjects (50-80 years old, both inclusive), with a previous diagnosis of Parkinson's disease (PD), and an objective assessment of at least moderate excessive daytime sleepiness

(EDS) (Epworth Sleepiness Score [ESS] > 12 at screening). Stable medication for at least 4 weeks before screening is mandatory regarding medication which may affect sleep (for example, dopaminergics, L-dopa, monoamine oxidase inhibitors, antipsychotics, or hypnotics). The exclusion criteria will exclude subjects with EDS due to conditions other than Parkinson's disease (including narcolepsy and sleep apnoea), any significant eye disease which may have an impact on a subject's mobility (which could hamper the study assessments), clinical evidence of depression (HAM-D score ≥ 17, as a certain degree of depression is shown by most of the PD subjects), positive response on the C-SSRS (an answer of 'yes' to any of the 6 questions), clinical evidence of cognitive impairment (MoCA score ≤ 22, as it could interfere with the study assessments), clinical evidence of fatigue (FSS ≥ 36, for similar reasons), any alerting medication (including r-modafinil, modafinil or methylphenidate), benzodiazepines, histamine active agents, clozapine, atomoxetine, skeletal muscle relaxants, or any other daytime medications which affect sleep (in order to avoid any selection bias). Subjects with hepatic, renal, cardiac (ECG, including QTc), or ophthalmological impairment will not be entered into the study. The suicide risk will be assessed (C-SSRS) before and after treatment administration at all study visits including follow-up following the the FDA Guidance for Industry on Suicidal Ideation and Behavior[(1)]. BPRS+ (Brief Psychiatric Rating Scale) positive subscale to monitor psychotic symptoms and HAM-D to monitor depression will be assessed at all study visits (including follow-up). These assessments are included because patients with Parkinson's disease are known to be at higher risk of psychosis and depression than the general population. Follow-up procedures for a positive finding on the C-SSRS, or an elevated HAM-D or psychosis scale score will be managed as per the standard of care at the site, including an assessment by the investigator of the need for further mental health evaluation. Vital signs (including blood pressure and heart rate) will be assessed at all study visits (including follow-up) as patients with Parkinson's disease are known to commonly exhibit orthostatis and other cardiovascular changes.

The Bavisant doses for this study have been selected based on data from previous preclinical and clinical research and are lower than the previously anticipated maximum clinical dose of 10 mg/d (for more details, please refer to the Investigator Brochure Ed. 9, 2017). Bavisant has been evaluated at dosages of 10 mg/d or lower in a total of 9 clinical trials and 481 subjects: 4 phase 1 studies in healthy adult subjects, 1 study in healthy elderly subjects, a phase 1 study in Japanese healthy adult male subjects, 2 phase 1 studies in children with ADHD, and a phase 2b study in adult subjects with ADHD. Bavisant has also been used at dosages higher than 10 mg/d in 5 clinical trials and 198 subjects: 4 phase 1 studies in healthy adult subjects and a phase 2a study in men with ADHD. No relevant safety issues are expected since the most common treatment emergent adverse events reported (at least 5%) in the Bavisant 10 mg/d group compared to placebo were: middle insomnia (27.4% vs 0%), initial insomnia (24.7% vs 6.8%), nausea (19.2% vs 1.4%), abnormal dreams (17.8% vs 0%), insomnia (15.1% vs 4.1%), dizziness (12.3% vs 0%), and dysgeusia (12.3% vs 0%). Levels of these events at 1 and 3 mg were lower than at 10mg/d.

The Epworth Sleepiness Scale (ESS) has been selected for the evaluation of the study primary endpoint because this is a well-established validated tool for assessing EDS. Normal range is between 0 and 10 (2.5 and 97.5 percentiles) which corresponds to "lower normal" (0-5) and "higher normal" (6-10). Other ranges can be interpreted as "mild excessive" (11-12), "moderate excessive" (13-15) and "severe excessive" (16-24); so in order to control the variability of the

ESS, the current study requests the categories of either "moderate excessive" or "severe excessive" ESS for the study (>12). As the ESS questionnaire is not suitable for use among people with serious cognitive impairment, correspondingly subjects with evidence of significant cognitive impairment will be excluded from the study (MoCA score ≤ 22).

The ESS, together with the Multiple Sleep Latency Test (MSLT) and the Maintenance of Wakefulness Test (MWT), are three of the most widely used tests of daytime sleepiness. Although all these three tests give results that are significantly correlated statistically, the ESS has been selected as the primary endpoint for the study as it is considered to be the most discriminating test of average of sleep propensity and sleepiness in daily life than either the MSLT or the MWT[20]. The observation of the US modafinil study group on the effects of modafinil in reducing the EDS of narcoleptics was shown more clearly in ESS than the MWT, and least by the MSLT[21]. The ESS, which is based on retrospective subjective reports, has been shown to produce more accurate results than the objective measurement made of the mean sleep latency (SL) in the MSLT or MWT. One reason is that the MSLT and MWT can each measure only one situational sleep propensity, each of which is correlated in an uncertain way with what is intended to be measured –the average of many different situational sleep propensities that reflect the activities of daily life. The ESS provides an estimate of the latter, the average sleep propensity in eight specified situations[20, 22-25]. Whatever cut-off point is used with the mean MSLT-SL it will tend either to misdiagnose a significant number of normal subjects as having EDS (false positives) or will fail to diagnose some narcoleptics or subjects with other sleep disorders as having EDS (false negatives). To do a MSLT or MWT on all subjects suspected of having EDS is difficult to justify when the ESS is a more discriminating test, is far cheaper and easier to administer with less burden on the patient. On the other hand, the ESS has a clear external validity, and this is the reason why the ESS has been already used to confirm the treatment effect (modafinil) on excessive daytime sleepiness (although not in Parkinson's disease).

The polysomnography and MWT will be performed locally by sites that have the practice parameters to develop the MWT assessment in accordance with the recommendations developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine [26]. This is key to standardise the procedure at all participating sites.

The study sample size is based on the expected Epworth Sleepiness score (ESS) change from baseline after 6 weeks of treatment. The endpoint of 6 weeks has been selected as this is a valid time frame for the ESS scale (*'Respondents to the ESS rate their chances of having dozed off or fallen asleep in particular situations in "recent times". […] intended to mean a few weeks to a few months, not a few hours or days.'*, Johns, http://epworthsleepinessscale.com/about-the-ess/). We consider the effect of Bavisant in sleepiness can be observed within 6 weeks which is a valid recall period for the ESS, and also there are results already published from clinical trials after even lower periods (2 weeks with modafinil in a crossover design in another indication[27, 28], 3 weeks with caffeine [ClinicalTrials.gov NCT00459420]). The parallel design is preferred over a crossover design which can always present a carryover effect which could bias the second period[27].

Although there is not any published agreement on the minimal clinically important difference (MCID) for the ESS, the distribution-based method of the standard error of measurement has been

previously used[22, 29-32], and that is the method chosen for this study. As there is no previous reported experience in parallel designs of the standard error of the ESS in Parkinson's disease, the assessment report of pitolisant has been used as a reference (EMA/828546/2015)[33]. The sample size of the corresponding studies, although in another indication, was calculated under the hypothesis derived from historical trials with a MCID of 3.0 and a standard deviation of 5.0[34]. This study will give the assumptions for further research which may use the distribution-based method of the standard error once there is experience with Bavisant used in EDS in PD.

As there is no previous data published on ESS which demonstrate a positive effect of ESS in excessive daytime sleepiness in Parkinson's disease, the assumptions used for the sample size calculation are based on the pitolisant EPAR with (a) a mean absolute change in the Epworth Sleepiness Scale (ESS) from baseline to the end of 6-week treatment period of at least 3.0 points and (b) a standard deviation of 5.0[34] which showed an ESS decrease between 2.5 and 2.7 at baseline.

The effect size of Bavisant in EDS is unknown. Smaller changes in ESS may be detected that may be clinically useful. In addition, although higher variability is expected in this multicentre study, variability may be lower as the selection criteria restricts a baseline ESS > 12.0 points (compared to 10.0 by other studies). Therefore, in order to confirm both the intragroup statistical decrease in daytime sleepiness together with the intergroup statistical comparison vs. placebo, a total sample size of 200 completed subjects (50 per treatment group + expected 15% of early withdrawal rate) is proposed in this planned first study. The study will be powered to detect a minimum 3.0 point difference in the ESS change from baseline compared to placebo assuming an SD range from 4.0 to 5.3 (α=0.05; β=0.20; power=80%; Δ=3.0; SD=5.0).

Finally, a placebo control group has been considered relevant for the study among other reasons because the primary endpoint is a self-reported assessment, subjective by nature. This subjectivity is controlled by intra-subject comparisons compared to baseline score, and by statistical methods (ANCOVA and MMRM models); but an additional control group with placebo could be considered as the natural progression of the EDS within a clinical trial environment. In any case, the subjects will be informed about the possibility of receiving placebo, the possible consequences and their right to withdraw from the study at any time.

8.0 Selection of study Population

The subject population will comprise male and female subjects of any race, aged between 50 and 80 years at Day 1, with a previous diagnosis of Parkinson's disease and a medical history of excessive daytime sleepiness confirmed with an Epworth Sleepiness Scale (ESS) > 12 at screening which correlates to at least moderate sleepiness ("moderate excessive" [13-15] and "severe excessive" [16-24]). Prior to any and all study-specific examinations, subjects will be informed as to the extent and nature of their study participation and will be given the opportunity to provide their written informed consent.

Approximately 48 active study sites globally will randomize a total of 230 subjects in order to have at least 200 completed subjects (50 completed subjects per treatment group, assuming an early withdrawal rate of around 15%). Recruitment will be competitive throughout all counties and sites.

Both inclusion and exclusion criteria will be assessed during the screening period and reconfirmed during the baseline period (see Section 8.1 and Section 8.2, respectively). Corresponding information should be provided in the eCRF.

8.1. Inclusion Criteria

Subjects will be eligible for inclusion into the study only if all of the following criteria are met:

(1) Signed informed consent (no study-related procedures may be performed before the subject has signed the consent form).

(2) Subjects of either sex aged 50 to 80 years (both inclusive and relative to Day 1)

(3) Subjects with previous diagnosis of Parkinson's disease (following the UK Parkinson's disease society brain bank clinical diagnostic criteria)* of minimum 3 months before informed consent date.

(4) Subjects capable of understanding and complying with protocol requirements

(5) Subjects with medical history of excessive daytime sleepiness

(6) Subjects with moderate or severe excessive daytime sleepiness indicated by an Epworth Sleepiness Score (ESS) > 12 at screening

(7) Subjects with stable nocturnal sleep hygiene practices (e.g. temperature, darkness, quiet, place to lie down and stretch out) as per investigator's judgement

(8) Male subjects who are nonsterilized and sexually active with a female partner of childbearing potential agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 4 weeks after last dose**

(9) Female subjects of childbearing potential who are sexually active with a nonsterilized male partner agree to use adequate contraception from signing of informed consent throughout the duration of the study and for 4 weeks after last dose**

(10) Subjects on stable permitted concomitant medication for at least 4 weeks before screening.

* Additional details on the UK Parkinson's disease society brain bank clinical diagnostic criteria are included in Appendix 18.2.

** Definitions and acceptable methods of contraception, and Contraception and Pregnancy Avoidance Procedure and reporting responsibilities are defined in Section 8.4.1.8.

8.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria are met:

(1) Subjects with excessive daytime sleepiness due to conditions other than Parkinson's disease (including narcolepsy)

(2) Subjects with significant eye disease which may substantially impact the subject's mobility and ability to have eye examination conducted as per investigator's judgement.

(3) Subjects with a recent history of suicide attempt (defined as an active, interrupted or aborted attempt within the past 1 year), or reports suicidal ideation in the past 3 months as indicated by a positive response on the C-SSRS at screening visit (an answer of 'yes' to any of the 6 questions)

(4) Subjects with clinical evidence of depression with significant psychiatric comorbidities (Hamilton Rating Scale for Depression – HAM-D score ≥ 17; with or without treatment)

(5) Subjects with evidence of significant Cognitive Impairment (Montreal Cognitive Assessment - MoCA score ≤ 22 at screening)

(6) Subjects with evidence of significant fatigue (Fatigue Severity Scale - FSS ≥ 36)

(7) Subjects with high risk of sleep apnoea (Berlin questionnaire with ≥ 2 categories where the score is positive)

(8) Subjects taking any of the following prohibited medications at screening:

- Alerting agents, including r-modafinil, modafinil or methylphenidate
- Benzodiazepines
- Histamine active agents
- Hypnotics
- Cholinergics
- Skeletal muscle relaxants
- Clozapine
- Atomoxetine
- Amitriptyline
- Any other daytime medications which affect sleep

(9) Subjects with chronic oral and / or ophthalmic steroidal use

(10) Subjects with either renal or hepatic impairment defined by laboratory parameters >1.5x age-adjusted limits of normal range

- Hepatic damage: Alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, or total bilirubin
- Renal damage: Blood creatinine, blood urea nitrogen [BUN], or estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73m2

(11) Subjects with abnormal ECG time intervals at baseline including QTc (> 450 for males and > 470 for females)

(12) Subjects with known history of lung malignancy.

(13) Subjects with known history of abuse of alcohol or other addictive substances in the 6 months prior to inclusion.

(14) Subjects with known allergies or hypersensitivity to Bavisant or any of its excipients.

(15) Subjects who are pregnant or lactating.

(16) Subjects who do not wish to or cannot comply with study procedures.

(17) Subjects currently receiving, or having received within 3 months prior to enrolment into this clinical study, any investigational drug.

(18) Subjects who are study-site employees, or are immediate family members (i.e., spouse, parent, child, sibling) of a study site employee involved in conduct of this study.

8.3. Prior and Concomitant Therapy

Any medication or therapy given in addition to the study medication is defined as concomitant medication/therapy (CM) and is to be thoroughly documented in the eCRF together with any previous medication administered within 4 weeks prior to the date of the informed consent signature. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by Sponsor.

At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

To the extent possible, the dose of any CM required for chronic diseases should be kept as constant as possible throughout the study. Any changes in administration of any CM must be recorded by the investigator in the relevant eCRF page.

The following primary PD medications will be permitted at any time during the study if taken as stable medication for at least 4 weeks before screening. Any treatment / dose not described in this list should be checked with the medical monitor before deciding the subject randomisation:

- Dopaminergics
- L-dopa
- Monoamine oxidase inhibitors (MAOI)
- Short-acting antipsychotics if taken in the evening
- Catechol-O-methyl transferase (COMT) inhibitors
- Amantadine if not used as an alerting agent

At a minimum, the following medications will be prohibited at any time during the study (see exclusion criterion #8):

- Alerting agents, including r-modafinil, modafinil or methylphenidate
- Benzodiazepines
- Histamine active agents
- Hypnotics
- Cholinergics
- Skeletal muscle relaxants
- Clozapine
- Atomoxetine
- Amitriptyline
- Any other daytime medications which affect sleep

Subjects must be instructed not to take any other medication, including over-the-counter products, without consulting with the investigator first; who should contact the medical monitor for questions regarding episodic use.

8.4. Efficacy and Safety Assessments / Variables

The schedule of assessments is described in the Appendix 18.15.

Subject recruitment for the study is competitive through all sites and countries. Subject data must be entered –after written informed consent is obtained– into the eCRF system as soon as possible, including demographic data. Data/results from screening and baseline should be added immediately upon availability.

Subjects not entered in the eCRF are not considered as enrolled in the study.

Study visits are categorized according to the following schedule: pre-treatment screening visit, pre-treatment baseline visits, randomisation visit 1 (day-1), treatment visit 2 (day 14 / week 2) and visit 3 (day 42 / week 6), and follow-up safety visit 4 weeks after the last IMP administration (+28 days). The activities planned for all study visits are described in this section.

8.4.1 Description of study procedures

8.4.1.1 Informed Consent

Subject Information Sheet and Informed Consent should be obtained prior to the subject entering into the study and before any study specific assessment and/or procedures are performed (see Section 12.3).

A unique subject identification number (subject number) will be assigned to each subject at the time of screening; this subject number will be used throughout the study.

8.4.1.2 Pharmacogenomic Informed Consent

A separate informed consent form pertaining to storage of the sample must be obtained prior to collecting blood samples for pharmacogenomic research for this study (see Section 12.3). The provision of consent to collect and analyse the pharmacogenomic samples is optional and independent of consent to the other aspects of the study.

8.4.1.3 Demographics

Demographic information will be collected at screening, including age, gender, race and smoking status.

8.4.1.4 Medical history and previous medication

Medical history including EDS and PD will be checked and recorded during both the screening and the baseline periods. Medical history to be obtained will include determining whether the subject has any significant conditions or diseases that stopped at or prior to Screening (time of informed consent). Ongoing conditions are considered concurrent medical conditions.

All relevant previous medication, including all ongoing medication and medication of the last 4 weeks before screening, should be recorded in the eCRF too.

8.4.1.5 Concurrent Medical Condition

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at Screening (at time of informed consent). This includes clinically significant laboratory, ECG, or physical examination abnormalities. The condition (i.e., diagnosis) should be described, and the date that the condition began should be documented

8.4.1.6 Physical examination

Complete physical examination will be performed at screening and visit 3 (day 42) or early termination. Physical examinations will consist of the following body systems: (1) general appearance; (2) extremities; (3) skin; (4) head and neck; (5) eyes, ears, nose and throat; (6) lungs and chest; (7) heart/ cardiovascular; (8) neurological; (9) abdomen / gastrointestinal; (10) liver; (11) musculoskeletal; and (12) other. Each system should be assessed as normal or abnormal and in this last case if that is clinically relevant or not.

8.4.1.7 Vital signs

Vital signs (respiratory rate, height, weight and BMI) will be assessed at all study visits (screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up. Blood pressure (both systolic and diastolic and heart rate) will be assessed at the same visits but this is considered for this protocol as specific cardiovascular assessment (see later).

8.4.1.8 Contraception and Pregnancy Avoidance

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (e.g., condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 4 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use adequate contraception. In addition they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilized males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

An acceptable method of contraception is defined as one that has no higher than a 1% failure rate. In this study, the only acceptable methods of contraception are:

Table 1. Acceptable methods of contraception

(A)Barrier methods (each time the subject has intercourse):	(B) Intrauterine devices (IUDs):	(C)Hormonal contraceptives:
1. Male condom PLUS spermicide. **2.** Cap (plus spermicidal cream or jelly) PLUS male condom and spermicide. 3. Diaphragm (plus spermicidal cream or jelly) PLUS male condom and spermicide.	1. Copper T PLUS condom or spermicide. 2. Progesterone T PLUS condom or spermicide.	1. Implants. 2. Hormone shot/injection. 3. Combined pill. 4. Minipill. 5. Patch. 6. Vaginal ring PLUS male condom and spermicide.

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the course of the study.

All potential participate in this clinical trial that are of child bearing potential MUST use adequate contraception methods; this should be one highly reliable method (such as intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide.

During the course of the study, subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures.

8.4.1.9 Pregnancy

Blood pregnancy sampling for central assessment will be obtained together with the laboratory samples at screening and at visit 3 (day 42) or early termination. A Dipstick pregnancy test to be completed before randomisation on day -1.

If any subject is found to be pregnant during the study she should be withdrawn and any sponsor-supplied drug should be immediately discontinued and returned to the study site. In addition, any pregnancies in the partner of a male subject during the study or for 4 weeks after the last dose, should also be recorded following authorisation from the subject's partner.

If the pregnancy occurs during administration of active study medication or within 4 weeks of the last dose of active study medication, the pregnancy should be reported immediately, using a pregnancy notification form.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator. Subjects randomized to placebo need not be followed.

If the female subject, or female partner of a male subject, agrees to the primary care physician being informed, the investigator should notify the primary care physician that the subject was participating in a clinical study at the time the subject/female partner of the subject became pregnant and provide details of treatment the subject received.

All pregnancies from female subjects, or female partner of a male subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

8.4.1.10 Procedure for Clinical Laboratory Samples

Blood sampling for central assessment will be obtained at screening, baseline (if there is more than 14 days between screening and baseline) and finally at visit 3 (day 42) or early termination. All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual provided to the site.

All laboratory values outside the normal range must be evaluated and assessed by the investigator for clinical relevance and in this case, they should be recorded in the eCRF as adverse events.

The clinical analyses will be performed in a central laboratory with blood volumes of around 7 mL per sampling visit (including haematology, biochemistry and pregnancy testing). Total of around 14 mL of blood will be obtained during the whole study for the central laboratory examination.

All material for blood sampling and postage to the central laboratory will be provided by the central laboratory. All samples will be labelled with the subject number, visit number, and study number. Information on site number, date of sampling, and age will be provided on an accompanying form.

The following parameters will be assessed:

- Haematology: White Blood Cells (WBC), neutrophils, lymphocytes, monocytes, eosinophils, basophils, Red Blood Cells (RBC), Haemoglobin, Haematocrit, Platelet Count.
- Biochemistry: Total protein, albumin, globulin, glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, urea nitrogen (BUN), creatinine, cholesterol, triglycerides, calcium, phosphorus, sodium, potassium, chloride. The estimated glomerular filtration rate (eGFR) will be calculated following the CKD-EPI Creatinine Equation (2009)[35, 36].

8.4.1.11 Pharmacogenomic blood sample

An additional blood sample of 11 mL will be obtained from subjects at screening (separate written informed consent) for further pharmacogenomics analysis.

All material for the pharmacogenomics blood sampling and postage to the central laboratory will be provided by the central laboratory.

When sampling of whole blood for pharmacogenomic analysis occurs, every subject must sign the pharmacogenomics informed consent/be consented in order to participate.

Two whole blood samples (3 mL per sample) for deoxyribonucleic acid (DNA) isolation will be collected during the screening period from each subject in the study.

Two whole blood ribonucleic acid (RNA) samples (2.5 mL per sample) will be collected into PAXgeneTM tubes during the screening period.

- DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets. RNA has multiple vital roles in the coding, decoding, regulation, expression of genes, and sensing and communicating responses to cellular signals. Both DNA and RNA samples may be evaluated for the genetic and expressional contribution to how the drug is broken down, or how the drug affects the body. This is called a “Pharmacogenomics research study.”

Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to Bavisant.
- Finding out more information about how Bavisant works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to Bavisant.
- Identifying variations in genes related to the biological target of Bavisant.

This information may be used, for example, to develop a better understanding of the safety and efficacy of Bavisant and other study medications, and for improving the efficiency, design and study methods of future research studies.

If necessary and feasible, a second aliquot of blood may be taken if isolation of DNA from the first sample was not successful or possible. Please refer to the Study Manual for information on sample collection and preparation.

The samples will be stored for no longer than 15 years after completion of the study. No samples will be stored for longer than permitted by the applicable law and samples will be destroyed upon notification from BenevolentAI Bio. “Stored samples” are defined as pseudo anonymised samples. Pseudonymisation is a procedure by means of which identifying data with a particular algorithm are replaced by encrypted data (the pseudonym). The algorithm can always calculate the same pseudonym for a person, by means of which information about the person, also from various sources, can be combined. Pseudonymisation distinguishes itself in this way from anonymisation, because linking information to a person, from various sources, is not possible with anonymisation. With this pseudonymisation the samples are stripped of all personal identifying information but the specifications listed below will link the samples to the clinical data collected from the sample donor, which is a usual process used in the analysis of investigational drug or related drugs:

- Study number
- Subject number
- Sampling date

Future analysis of the stored pharmacogenomics samples may be conducted as appropriate.

Detailed instructions for the handling and shipping of samples are provided in the Laboratory Manual.

8.4.1.12 Electrocardiogram, heart rate, blood pressure

A 12-lead ECG will be performed locally at screening and visit 3 (day 42) or early termination. Additional ECGs may be performed at the discretion of the investigator during follow-up. The findings and any abnormality will be recorded in the eCRF as either medical history (findings at screening) or adverse events (any further finding or change from screening). Standard ECG parameters will be recorded in the eCRF (heart rate, RR, QT, QTc following both Bazzett's and Fridericia's methods).

8.4.1.13 Eye Examination

An eye examination will be performed at screening and after study treatment completion or early termination. This will include a full ocular check (lids, conjunctiva, sclera, cornea, anterior chamber, pupil, iris, and lens) and any abnormalities will be noted. Additional eye examinations may be performed at the discretion of the investigator during follow-up. An ophthalmologist will evaluate the findings and any abnormality will be recorded in the subject clinical notes as either medical history (findings at screening) or any further finding or change from screening after completion of study treatment. A specific eye exam procedure guidance document will be prepared for the study in order to harmonize the examination..

8.4.1.14 Patient-Reported Outcome Instruments (PRO)

Subjects will complete the Epworth Sleep Scale (ESS), Scales for Outcome in Parkinson’s Disease Sleep (SCOPA-Sleep), Parkinson’s Disease Sleep Scale 2 (PDSS-2), Fatigue Severity

Scale (FSS) and the Berlin questionnaire (BQ) at the time points specified in the schedule of events (see Appendix 18.15).

8.4.1.14.1 Epworth Sleepiness Scale (ESS)

The Epworth Sleepiness Scale (ESS)[22-25] is the primary efficacy endpoint and will be assessed at all study visits: screening, baseline (day -1), visit 2 (day 14), and visit 3 (day 42) or early termination.

The ESS is a self-administered questionnaire with 8 questions rated on a 4-point scale (0-3) for the assessment of the usual chances of dozing off or falling asleep while engaged in eight different activities. Most people engage in those activities at least occasionally, although not necessarily every day. The ESS score (sum of 8 item scores) ranges from 0 to 24, where the higher score corresponds to the higher average sleep propensity (ASP) in daily life (higher daytime sleepiness). The questionnaire takes no more than 2 or 3 minutes to answer and although the original language was English for Australia, this is validated in many different languages. All those validations were performed by Mapi Research Trust (https://eprovide.mapi-trust.org/instruments/epworth-sleepiness-scale#languages).

More information on the appropriateness of the ESS as the primary study endpoint is included in Section 7.2. An ESS sample questionnaire has been included in Appendix 18.2.

8.4.1.14.2 Scales for Outcome in Parkinson's Disease Sleep (SCOPA-Sleep)

The Scales for Outcome in Parkinson's Disease (SCOPA-Sleep) is one of the secondary efficacy endpoints and will be assessed at baseline (day -1), visit 2 (day 14), and visit 3 (day 42) or early termination.

The SCOPA-Sleep is a specific PD rating scale for assessing night-time sleep (NS) and daytime sleepiness (DS) in the past month[37]. The NS subscale addresses NS problems in the past month and includes 5 items with 4 response options. Subjects have to indicate how much they were bothered by particular sleep problems, ranging from 0 (not at all) to 3 (a lot). The 5 items address sleep initiation, sleep fragmentation, sleep efficiency, sleep duration, and early wakening. The maximum score of this scale is 15, with higher scores reflecting more severe sleep problems. One additional question evaluates overall sleep quality on a 7-point scale (ranging from slept very well to slept very badly). The score on this item is not included in the score of the NS scale but is used separately as a global measure of sleep quality. The DS subscale evaluates DS in the past month and includes 6 items with 4 response options, ranging from 0 (never) to 3 (often). Subjects indicate how often they fell asleep unexpectedly, fell asleep in particular situations (while sitting peacefully, while watching TV or reading, or while talking to someone), how often they had difficulty staying awake, and whether falling asleep in the daytime was considered a problem. The maximum score is 18, with higher scores reflecting more severe sleepiness. A SCOPA-Sleep sample questionnaire has been included in Appendix 18.7.

8.4.1.14.3 Parkinson's Disease Sleep Scale (PDSS-2)

The Parkinson's Disease Sleep Scale revised version 2 (PDSS-2) is one of the secondary efficacy endpoints and will be assessed at baseline (day -1), visit 2 (day 14), and visit 3 (day 42) or early termination.

The Parkinson's Disease Sleep Scale (PDSS) is a scale for the assessment of sleep disorders in PD in the past week[6]. The scale has 15 items and subjects mark their response to each item on a 10-cm visual analogue scale (VAS). All PDSS items are focussed on nocturnal sleep, except item 15 which addresses DS. The total score is the sum of the item scores and the maximum is 150.

The Revised Version PDSS-2 was developed in order to extend the spectrum of PDSS regarding nocturnal disabilities and for an easier use for subjects as the answers are rated in 5 categories (from 0 [never] to 4 [very frequent])[38]. PDSS-2 total score ranges from 0 (no disturbance) to 60 (maximum nocturnal disturbance). The scale was originally validated in both English and German, and further language validations were performed by Mapi Research Trust (https://eprovide.mapi-trust.org/instruments/parkinson-s-disease-sleep-scale-2#languages). A PDSS-2 sample questionnaire has been included in Appendix 18.5.

8.4.1.14.4 Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) is used as one of the exclusion criteria, and will be assessed at screening and visit 3 (day 42) or early termination.

The FSS is a self-administered questionnaire with 9 items investigating the severity of fatigue in different situations during the past week. It was developed in 1989 and it is the most commonly used fatigue specific questionnaire[39] with its 9 items ranging from 1 to 7, where 1 indicates strong disagreement and 7 strong agreement, and the final score represents the mean value of the 9 items. A FSS sample questionnaire has been included in Appendix 18.12.

8.4.1.14.5 Berlin Questionnaire (BQ)

The Berlin Questionnaire (BQ) is used as one of the exclusion criteria, and will be assessed at screening only.

The BQ is a self-administered and validated questionnaire to be used as a screening tool to identify persons in the community who are at high risk for sleep apnoea[40, 41]. The questionnaire consists of 3 categories (questions 2 to 6 about snoring [category 1], questions 7 to 9 about daytime somnolence [category 2], and question 10 about hypertension and BMI [category 3]) and the risk is based on the responses to individual items and overall scores in the symptom categories (high risk is assessed with 2 or more categories where the score is positive). A BQ sample questionnaire has been included in Appendix 18.14.

8.4.1.15 Clinician-Reported Outcome Instruments

The following assessments will be performed by qualified personnel (rater) as indicated in the schedule of procedures. Rater qualification, certification and training required for any rater and/or investigator who will be administering outcomes in this study will be provided

Qualified personnel (rater) will complete the Unified Parkinson's Disease Rating Scale (UPDRS Part III), Cognitive Impairment (Montreal Cognitive Assessment – MoCA), Columbia-Suicide Severity Rating Scale (C-SSRS), Brief Psychiatric Rating Scale Positive Subscale (BPRS+), and the Hamilton Rating Scale for Depression (HAM-D) at the time points specified in the schedule of events (see Appendix 18.15).

8.4.1.15.1 Unified Parkinson's Disease Rating Scale (UPDRS Part III)

The Unified Parkinson's Disease Rating Scale Part III (UPDRS Part III) is one of the secondary efficacy endpoints and will be assessed at baseline (day -1), visit 2 (day 14), and visit 3 (day 42) or early termination. Patients will be instructed to have already taken their normally scheduled dose of anti-parkinsonian medication and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in ON (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in OFF will not be evaluated.

The UPDRS is the most widely used clinical rating scale for PD[42]. The UPDRS was originally developed in 1987, and a new version was sponsored in 2001 by the Movement Disorder Society in order to retain the strengths of the original scale, but resolving identified problems and especially incorporating a number of clinically pertinent PD-related problems poorly captured in the original version. The original four component (Parts I-IV) design was retained, but the focus of each part was changed. Part I concerns "non-motor experiences of daily living", Part II concerns "motor experiences of daily living", Part III is retained as the "motor examination", and Part IV concerns "motor complications". Rater involvement time for administering the UPDRS is estimated to require less than 15 minutes for Part III. Each question is anchored with five responses that are linked to commonly accepted clinical terms of 0 (normal), 1 (slight), 2 (mild), 3 (moderate), and 4 (severe). Part III contains 33 scores based on 18 items, several with right, left or other body distribution scores. An UPDRS Part III sample questionnaire has been included in Appendix 18.8.

8.4.1.15.2 Cognitive Impairment (Montreal Cognitive Assessment – MoCA)

The Montreal Cognitive Assessment (MoCA) is used as one of the exclusion criteria, and will be assessed at screening and visit 3 (day 42) or early termination.

The MoCA was developed as a tool to screen subjects who present with mild cognitive impairment[43]. A total of 30 items are evaluated as follows: The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes. Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point). Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points). Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each). Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the aforementioned fluency task. Finally, orientation to time and place is evaluated (6 points). The

total possible score is 30 points; a score of 26 or above is considered normal. An MoCA sample questionnaire has been included in Appendix 18.10.

8.4.1.15.3 Hamilton Rating Scale for Depression (HAM-D)

The Hamilton Depression Rating Scale (HAM-D) is one of the secondary efficacy endpoints and will be assessed at screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up visit (28 days after the last IMP administration).

The HAM-D was designed as a way of determining a patient's level of depression before, during, and after treatment[44]. Although the HAM-D form lists 21 items, the scoring is based on the first 17 (0-7 [normal], 8-13 [mild depression], 14-18 [moderate depression], 19-22 [severe depression], and ≥23 [very severe depression]). For the total sum, 8 items are scored on a 5-point scale, ranging from 0 (not present) to 4 (severe), and the remaining 9 are scored from 0 to 2. Subjects with a HAM-D score ≥ 17 at screening will be considered as excluded from the study. Patients with elevated HAM-D during the study will be managed as per the standard of care at the site, including an assessment by the investigator of the need for further mental health evaluation.

An HAM-D sample questionnaire has been included in Appendix 18.9.

8.4.1.15.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be assessed at screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up visit (28 days after the last IMP administration).

The C-SSRS supports suicide risk assessment through a series of simple, plain-language questions that anyone can ask[2, 3]. The answers help users identify whether someone is at risk for suicide, assess the severity and immediacy of that risk, and gauge the level of support that the person needs. Users of the C-SSRS tool ask people whether and when they have thought about suicide (ideation), what actions they have taken (and when) to prepare for suicide, and whether and when they attempted suicide or began a suicide attempt that was either interrupted by another person or stopped of their own volition.

Columbia University, the University of Pennsylvania, and the University of Pittsburgh — supported by the National Institute of Mental Health (NIMH) — developed the screening tool for a 2007 NIMH study of treatments to decrease suicide risk among adolescents with depression. The C-SSRS, based on more than 20 years of scientific study, filled an urgent need for suicide research and prevention: a better way to uniformly and reliably identify people who are at risk. The C-SSRS achieved accurate and comparable results by using consistent, well-defined, and science-based terminology. Just as important as its ability to identify who might attempt suicide, it was the first scale to assess the full range of a person's suicidal ideation and behavior, including intensity, frequency, and changes over time.

In 2011, the Centers for Disease Control and Prevention adopted the scale's definitions for suicidal behavior and recommended the use of the C-SSRS for data collection. In 2012, the Food and Drug Administration declared the C-SSRS the standard for measuring suicidal ideation and

behavior in clinical trials[1]. Today, the C-SSRS is used in clinical trials, public settings, and everyday situations, such as in schools, faith communities, hospitals, and the military, to identify who needs help — saving lives in 45 nations on six continents.

Subjects with a positive response on the C-SSRS (an answer of 'yes' to any of the 6 questions) will be considered as excluded from the study. Any positive finding on the C-SSRS during the study will be managed as per the standard of care at the site, including an assessment by the investigator of the need for further mental health evaluation.

A C-SSRS sample questionnaire has been included in Appendix 18.12.

8.4.1.15.5 Brief Psychiatric Rating Scale Positive Subscale (BPRS+)

The Brief Psychiatric Rating Scale Positive Subscale (BPRS+) will be assessed at screening, visit 2 (day 14), visit 3 (day 42) or early termination, and follow-up visit (28 days after the last IMP administration).

The BPRS is an instrument originally developed to characterize psychopathology and to measure change in clinical psychopharmacology research[45]. It permits the recording of severity of 18 (originally 16) distinct signs and symptoms of psychopathology such as hostility, suspiciousness, hallucination, and grandiosity, based on clinical interview of a patient. It is particularly useful in gauging the efficacy of treatment in patients who have moderate to severe psychoses, and based on the clinician's interview with the patient and observations of the patient's behaviour over the previous 2-3 days. The patient's family can also provide the behaviour report. The rater enters a number for each symptom construct that ranges from 1 (not present) to 7 (extremely severe).

Psychiatric symptoms, associated with PD itself and specifically in patients with Parkinson's psychosis, consist primarily of paranoid delusions, visual hallucinations and/or other sensory disturbances. Psychosis in PD most commonly manifests in visual hallucinations. Auditory hallucinations occur less commonly in PD psychosis (unlike hose seen in schizophrenia) and typically co-occur with visual hallucinations. Tactile, olfactory and gustatory hallucinations have also been reported in PD psychosis and also tend to co-occur with visual hallucinations, but less commonly than other forms of hallucinations. Delusions and is organized thinking are also seen in PD psychosis, although they are not as common as visual hallucinations.

While it is assumed that in this study adverse events known to occur with Bavisant will be directly assessed along with any sleep related effects, the Brief Psychiatric Rating Scale Positive Symptoms Subscale (BPRS+) would be appropriate to observe for psychiatric symptoms occurring in this study, with this population.

The BPRS+ has been used in studies of major depressive disorders[46-50] to observe for psychotic features occurring with drug treatment. It consist of 4 (Conceptual Disorganization, Suspiciousness, Hallucinatory Behaviour, and Unusual Thought Content) of the 18 domains of the full Brief Psychiatric Rating Scale and would cover those symptoms seen with Parkinson's psychosis. It could readily be taught to neurologists to perform in a reasonable amount of time during a study visit without becoming an undue burden on either the rater or the subject. The full BPRS with its 18 items would require extended time to teach and to perform without offering any clear additional benefit over the BPRS+ here.

Alternatives, such as the Positive and Negative Syndrome Scales (PANSS) have been discarded as being primarily used in schizophrenia which has psychotic features which differ from those seen with Parkinson's disease.

A BPRS+ sample questionnaire has been included in Appendix **Error! Reference source not found.**.

8.4.1.15.6 Rater Qualification and Certification

In order to ensure satisfactory training of raters and quality execution with regards to data collection, raters assigned to this study will be required to adhere to certain requirements prior to participation in the trial. All raters will be required to successfully complete the full scope of rater training requirements prior to rating any subjects in this study. The rater training and certification process will consist of verifying rater qualification via completion of a Rater Experience Survey and completion of training or certification on key scales. Raters who successfully complete requirements will be approved for participation in the study. Raters who do not meet all the qualification and training requirements may be prohibited from participating as raters on this trial.

8.4.1.15.7 Maintenance of Wakefulness Test (MWT)

The Maintenance of Wakefulness Test (MWT) is one of the secondary efficacy endpoints and will be assessed at baseline (day -7 to day -2) and visit 3 (day 42) or early termination at specific sleep centres.

The MWT is an evaluation used as a quantitative polysomnographic (PSG) measurement of daytime wakefulness/somnolence during soporific circumstances[51]. The assessment of such disorders requires a polygraphic approach in which multiple physiologic parameters are recorded. This is usually performed during the day following a night sleep with some electrodes placed on the head, around the eyes and on the chin. The test isolates subjects from outside factors that can influence their ability to fall asleep (temperature, light, noise, activity). The test consists of four sleep trials timed at 2-hourly intervals, with the first trial performed 2 to 3 hours after the normal wake time and after having eaten a light breakfast at least one hour before the first trial. During each trial, subjects will sit quietly on the bed with both back and head supported by a pillow, and subjects will be asked to look directly ahead and try to stay awake as long as they can. If they fall asleep, they will be woken up after 90 seconds and the trial will end if the subjects do not fall asleep within 40 minutes. Start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for each trial, and the mean sleep latency (the arithmetic mean in minutes of the four trials) will be recorded, considering sleep latency as the time from lights out until the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch of either 3 consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep. In between trials subjects must stay awake and stay out of bed. From midnight of the day before the test, drinks containing caffeine (tea, coffee, cola drinks, energy drinks, etc.) need to be avoided. In order to harmonize the practice parameters of the MWT, a Task Force of content experts was appointed by the American Academy of Sleep Medicine and their recommendations were developed by the Standards of Practice Committee and reviewed and approved by the Board of Directors of the American Academy of Sleep Medicine[26]. A copy of these recommendations is included in Appendix 18.4.

8.4.1.15.8 Polysomnography

The Polysomnography (PSG) is one of the secondary efficacy endpoints and will be assessed at baseline (day -7 to day -2) and visit 3 (day 42) or early termination at specific sleep centres.

The PSG is a sleep study which consists of a simultaneous recording of multiple physiologic parameters related to sleep and wakefulness and is used to evaluate abnormalities of sleep and/or wakefulness and other physiologic disorders that have an impact on or are related to sleep and/or wakefulness. For a standard test, the subject will have the electroencephalogram (EEG), the electro-oculogram (EOG), the electromyogram (EMG), and the electrocardiogram (ECG) performed. The American Association of Sleep Technologies developed the technical guideline of sleep technology for a standard polysomnography, updated July 2012[52]. A copy of this guideline is included in Appendix 18.5.

8.4.1.15.9 Free Living Activity

Approximately half (50%) of subjects participating in the clinical study will be offered an opportunity to take part in the assessment of free living activity as an exploratoty assessment. A wrist-worn actigraphy device (GENEActiv®) will be provided to these subjects and they will be required to wear the actigraphy device on their non-dominant wrist for 7 consecutive days during the baseline period (day -7 to day -1) and 7 consecutive days **before** the last dose on visit 3 (day 35 to day 42).

The wrist-worn actigraphy device (GENEActiv®) is a tri-axial accelerometer which provides an objective measure of physical activity levels. A study manual with instructions will be provided to both the investigators and the subjects.

8.4.2 Study Procedures

Screening assessments (Day -28 to Day -8)

Subjects will be screened for enrolment within 3 weeks prior to the start of baseline assessments. Subjects will be screened in accordance with predefined entrance criteria as described in Sections 8.1 and 8.2. See Section 8.5.1 for the procedure for documenting screen failures.

Procedures to be completed at screening include:

- Subject information/Informed consent signed and dated.
- Assessment of inclusion / exclusion criteria.
- Demographics
- Medical history and previous medication (prohibited as of 4 weeks before D-28)
- Concurrent medical condition
- Physical examination
- Vital signs

- For women of childbearing potential the method of contraception must be documented (as CM as applicable)
- Laboratory (haematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Pharmacogenomic blood sample
- Electrocardiogram, heart rate, blood pressure
- Eye examination
- Cognitive assessment (MoCA)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Fatigue assessment (FSS)
- Assessment of sleepiness scales: ESS
- Other scales: HAM-D, BPRS+ and Berlin Questionnaire
- Determination of subject eligibility
- Recording of adverse events

Baseline assessments (Day -7 to Day -2)

Baseline assessment will be performed after subjects have passed all the screening assessments and up to 1 week prior to the day of the 1st treatment administration (Day 1). The following procedures will be performed and documented during the Baseline period:

- Re-assessment of inclusion / exclusion criteria.
- Medical history and previous medication
- Laboratory (haematology, biochemistry), serum pregnancy test (for women of childbearing potential) if there is more than 14 days between screening and baseline.
- Maintenance of Wakefulness Test (MWT)
- Polysomnography
- Wrist-worn actigraphy (GENEActiv®) assessment 7 days continuously before the first dose on Day 1
- Recording of adverse events
- Recording of concomitant medication

Randomisation Visit 1 (Day -1)

- Re-assessment of inclusion / exclusion criteria.
- Urine dipstick for pregnancy assessment.
- Assessment of sleepiness scales: ESS, SCOPA-Sleep, PDSS-2
- Other scales: UPDRS Part III
- Wrist-worn actigraphy (GENEActiv®) assessment 7 days continuously before the first dose on Day 1
- Vital signs (including heart rate and blood pressure)
- Confirmation of subject eligibility
- Subjects will be randomised to their treatment assignments
- Study drug dispensing
- Recording of adverse events
- Recording of concomitant medication

Treatment Visit 2 (Day 14 ±2)

This visit will be performed 2 weeks after the 1st treatment administration (Day 1). The following examinations/procedures will be performed:

- Vital signs (including heart rate and blood pressure)
- Assessment of sleepiness scales: ESS, SCOPA-Sleep, PDSS-2
- Other scales: UPDRS Part III, C-SSRS, HAM-D, BPRS+
- Dispensing of double blind study medication
- Drug return and accountability
- Recording of adverse events
- Recording of concomitant medication

Treatment Visit 3 (Day 42 ±3)

This visit will be performed 6 weeks after the 1st treatment administration (Day 1). The following examinations/procedures will be performed:

- Physical examination
- Vital signs
- Laboratory (haematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram, heart rate, blood pressure
- Assessment of sleepiness scales: ESS, SCOPA-Sleep, PDSS-2
- Maintenance of Wakefulness Test (MWT)

- Polysomnography
- Cognitive assessment (MoCA)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Fatigue assessment (FSS)
- Other scales: UPDRS Part III, HAM-D and BPRS+
- Wrist-worn actigraphy assessment 7 days continuously **before** last dose (day 35 to day 42).
- Wrist-worn actigraphy device return
- Drug return and accountability
- Recording of adverse events
- Recording of concomitant medication
- Eye examination (should be performed after the last treatment on Day 42 and before the follow up safety call)

Early Termination

In case of an early termination after 1st IMP administration and before treatment at visit 3 (day 42), the same procedures planned for the treatment at visit 3 (day 42) should be performed.

Follow-up Period (+Day 28 ±2)

During the following up period the eye examination post dose on Day 42 will be conducted and a follow-up safety visit will be performed 28 days after the last IMP administration where the vital signs (including heart rate and blood pressure), C-SSRS, HAM-D, and BPRS+ will be assessed. The eye examination should be performed before the follow up visit. Additional unscheduled visits may be arranged as needed for the management of eye examination findings and / or adverse event findings.

Unscheduled Visit

Unscheduled visits may be arranged following investigators' judgement for eye examination, or adverse event findings identified either at the end of study or during the follow-up period. The examinations/procedures may include:

- Physical examination
- Vital signs
- Laboratory (haematology, biochemistry), serum pregnancy test (for women of childbearing potential)
- Electrocardiogram, heart rate, blood pressure
- Other scales: C-SSRS, HAM-D and BPRS+
- Recording of adverse events

- Recording of concomitant medication

Telephone Contacts

Sites will maintain telephone contacts with subjects during the study as reminders for the study logistics, including the safety eye examination during follow-up.

Post-Study Care

The study medication will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

8.4.3 Efficacy Variables

8.4.4 Primary Variables

The primary variable will be the mean absolute change of Bavisant treatment groups in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 6-week treatment period, assessed as both the intragroup change compared to baseline and intergroup change compared to placebo.

8.4.5 Secondary Variables

Secondary variables will assess the efficacy on both the excessive daytime sleepiness and PD concomitant conditions:

Efficacy in Excessive Daytime Sleepiness (EDS):

- Mean absolute change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 2-week treatment period.
- ESS clinical response, defined as ESS absolute decrease from baseline of at least 3.0 points, after 2 and 6 weeks of treatment.
- ESS clinical response, defined as ESS $\leq$ 10 after 2 and 6 weeks of treatment.
- ESS clinical response, defined as either ESS $\leq$ 10 after 2 and 6 weeks of treatment or ESS absolute decrease from baseline of at least 3.0 points after 2 and 6 weeks of treatment.
- Mean relative change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 2-week and 6-week treatment periods (percentage of absolute decrease compared to baseline ESS).
- Mean absolute change in the Scales for Outcome in Parkinson's Disease Sleep (SCOPA-Sleep) from screening/baseline to the end of the 2-week and 6-week treatment period.
- Mean absolute change in the Parkinson's Disease Sleep Scale (PDSS-2) from screening/baseline to the end of the 2-week and 6-week treatment period.
- Mean absolute change in the Maintenance of Wakefulness Test (MWT) from baseline to the end of the 6-week treatment period.
- Mean absolute change in the polysomnography from baseline to the end of the 6-week treatment period.

Efficacy in Parkinson's disease (PD):

- Mean absolute change in the MDS-UDPRS scale Part III (motor control) from screening/baseline to the end of the 2-week and 6-week treatment period.
- Mean absolute change in the depression HAM-D score from baseline to the end of the 2-week and 6-week treatment period and safety follow-up.
- Mean absolute change in the Montreal Cognitive Assessment – MoCA score from screening/baseline to the end of the 6-week treatment period.
- Mean absolute change in the Fatigue Severity Scale – FSS score from screening/baseline to the end of the 6-week treatment period.

8.4.6 Exploratory Variables

The effect of Bavisant compared to placebo after the 6-week treatment period of free living activity will be assessed by means of wrist-worn actigraphy. For each set of continuous tri-axial accelerometry measurement, descriptive statistics of values at baseline, endpoint and change from baseline will be provided by treatment group.

Pharmacogenomic information will be assessed in order to identify genetic reasons why certain people respond differently to Bavisant, to find out more information about how Bavisant works, 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.

8.4.7 Safety Variables

Safety variables will include:

- Incidence of Adverse Events (AEs) and Adverse Events of Special Interest (AESIs) like headache, nausea and insomnia
- Incidence of physical examination, vital signs and laboratory tests findings (haematology and biochemistry)
- Incidence of cardiovascular safety findings (blood pressure, heart rate, ECG including QT/QTc)
- Incidence of suicidal ideation (C-SSRS) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
- Incidence of positive psychotic symptoms (BPRS+) findings from screening/baseline to the end of the 2-week and the 6-week treatment period and safety follow-up
- Incidence of eye examination findings

8.5. Removal of Subjects from Therapy or Assessment

8.5.1 Screening failures

Subjects who signed the informed consent form and performed screening and/or baseline activities (either completely or partially) but were not randomized to the study are considered screening failures.

If the subject is found to be not eligible at this visit, the investigator should complete the eCRF.

The primary reason for screen failure should be recorded in the eCRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal, <specify reason>.
- Study termination.
- Other, <specify reason>.

Subject numbers assigned to subjects who fail screening should not be reused.

8.5.2 Discontinuation or Withdrawal of Individual Subjects

If a randomized subject terminates the study prematurely for any reason, all attempts should be made by the investigator to perform the procedures for the early termination visit (same as for the week 6 visit) and determine the primary reason for the termination and where possible the primary underlining reason, providing as much as detail as possible, and documenting the information on the eCRF. Randomized subjects will not be replaced.

The primary reason for discontinuation or withdrawal of the subject from the study should be noted using the following categories:

(1) Pretreatment event (PTE) or Adverse Event (AE). The subject has experienced an adverse event or pre-treatment event that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the adverse event or pre-treatment event.

(2) Noncompliance with investigational medicinal product (IMP). This includes subjects who did not take the study drug for more than 6 consecutive days.

(3) Major protocol deviation. The subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health, or a major protocol deviation occurred at the site such as the blind was broken.

(4) Withdrawal of consent. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the case report form (eCRF). Subjects may withdraw from the study at any

time at their own request without giving reasons and without any disadvantageous consequences for their subsequent medical care.

(5) Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.

(6) Subject does not fulfil randomisation criteria.

(7) Other.

In the case of study termination by the sponsor, institutional review board (IRB), independent ethics committee (IEC), or regulatory agency, reason for withdrawal should be captured as Other, Study Termination.

If the subject is found to be pregnant during the study, the subject must be withdrawn immediately. The reason for withdrawal should be "major protocol deviation" unless there was a complication of the pregnancy which led to withdrawal, in which case the reason for withdrawal should be "adverse event(s)". The procedure is described in Section 9.7.

8.6. Treatments

8.6.1 Treatments Administered

BenevolentAI Bio will supply the IMP consisting of:

- Bavisant 0.5 mg tablets
- Bavisant 1 mg tablets
- Bavisant 3 mg tablets
- Matching placebo tablets

8.6.2 Identity of Investigational Product(s)

Experimental treatment:

Product Name:	Bavisant tablets 0.5/1/3 mg
Drug substance:	Bavisant dihydrochloride monohydrate
Pharmaceutical Form:	Tablets containing Bavisant dihydrochloride monohydrate equivalent to 0.5/1/3 mg of Bavisant
Administration route:	Oral use
Dosage:	Once daily administration
Manufacturer:	Nuvisan GmbH, Wegenerstr. 13, Neu-Ulm, Germany

Control treatment:

Control substance:	Placebo
Pharmaceutical Form:	Tablets

Administration route:	Oral use
Dosage:	Once daily administration
Manufacturer:	Nuvisan GmbH, Wegenerstr. 13, Neu-Ulm, Germany

The IMP will be supplied in wallet cards. The IMP will be identifiable by a unique identification number. The wallet cards will contain a surplus of tablets to cover the treatment period and visit windows. The IMP should be stored at 25ºC; excursions permitted to 15ºC to 30ºC.

Each card of investigational medication will be labelled with pertinent study information and country-specific regulatory caution statements in country-specific language(s).

8.6.3 Dosages and Regimen

Each subject who qualifies for the study will receive wallet cards containing tablets of double-blind study medication. Subjects will receive 1 wallet card of their assigned treatment at Visit 1 (for 2 weeks treatment period) and 2 wallet cards at Visit 2 (for 4 weeks treatment period).

Subjects will be instructed to take 1 tablet orally per day at the same time in the morning, with or without food. The first dose is to be taken the day after randomisation when study medication has been dispensed to the subject.

The investigator or designee must instruct the subject to bring each of their study medication containers (wallet cards) to each clinic visit, regardless of whether the study medication cards are empty.

8.6.4 Packaging and Labelling

IMP manufacture will be performed according to Good Manufacturing Practice (GMP) standards and according to the currently valid version of the respective national laws applicable at Nuvisan, Germany. Identity and stability of the substance for the duration of the study are ensured and documented through Certificates of Analyses.

Products' labelling will show at least the following information:

- Name and address and contact phone of Sponsor and CRO.
- Trial reference code and EudraCT Number.
- Pharmaceutical dosage form, route of administration and quantity of dosage units.
- The number of the IMP, batch number and expiry date.
- The statement "for clinical trial use only".
- The statement "keep out of the reach of children".
- The medication number and the Patient Number.
- Storage conditions.
- Name, principal investigator.

If applicable, local or country specific requirements regarding labelling of the blister wallets are also to be considered.

8.6.5 Storage and Disposition of Study Drug

At each study site, the investigator is responsible for the correct storage and handling of the IMP. The IMP must be stored in a place with access limited to the investigator and/or especially authorized personnel of the local study team only, i.e. study nurse or study coordinator.

The temperature of the storage area must be monitored and documented. The investigator is required to inform the responsible monitor immediately in cases of deviation of the storage temperature from the required range (+15°C - +25°C). Furthermore adherence to the storage conditions will be checked routinely by the monitor during the on-site visits.

8.6.6 Method of Assigning Subjects to Treatment Groups

A computer-generated randomisation scheme by region will be provided by Nuvisan according to Sponsor specification.

Subjects will be randomized in order to have 200 completed subjects. At the end of the baseline period on day -1, all subjects fulfilling the inclusion and exclusion criteria will be randomly allocated to one of the 4 treatment groups at a ratio of 1:1:1:1.

Treatment group 1: Bavisant 0.5 mg tablets

Treatment group 2: Bavisant 1.0 mg tablets

Treatment group 3: Bavisant 3.0 mg tablets

Treatment group 4: Placebo tablets

The randomisation will be stratified by region and by the polysomnography and the MWT assessment which will be performed to a subset of subjects (around 50%). The information on whether the subject will do the polysomnography and the MWT assessment will be collected first and the randomisation will be performed based on this information. A first block of medication according to the randomisation scheme created will be provided to each site. Upon completion of the first block of medication, the site should request a new supply of medication. In this case, if the subject will perform both the polysomnography and the MWT assessment, the randomisation number being provided will be selected as the first available from the bottom of the randomisation list; otherwise the subject will receive the maximum available subject number. With this method (also known as down-up / up-down) the randomisation can be stratified by polysomnography/MWT assessment with one single randomisation list and so guaranteeing a similar 1:1:1:1 distribution between strata.

The randomisation number will consist of a 3-digit number which will be linked to the respective electronic case report form (eCRF) number.

At the end of the baseline period, subjects will be randomly allocated to 1 of the 4 treatment groups and given the IMP with the next available randomisation number in either ascending or descending sequence. The 3-digit randomisation number is printed on the labels of the study medication and will uniquely identify the IMP which is assigned to the subject. Each subject must

be given only the IMP carrying his or her randomisation number. The investigator will document the randomisation number in the eCRF and IMP accountability records.

The randomisation schedule will link sequential medication numbers to treatment codes. The medication numbers will be blocked to facilitate attainment of a homogeneous distribution of treatment groups.

The randomisation schedule will be kept at Nuvisan's CTS department.

The investigator must keep a subject identification list including sufficient information to link records, i.e. eCRF, eDiary, and subject files/hospital records. Furthermore, a list of all subjects screened for the study should be kept in the ISF. The identity of the study subjects (subject number, year of birth, and age at screening), date of informed consent, and date of inclusion, or the reason for non-inclusion of the subjects at screening must be recorded in this subject screening/enrolment randomisation log.

8.6.7 Blinding

Study treatments are blinded and the randomisation schedule and the allocation to treatment groups will not be known to the investigator, the sponsor, or any other person involved in the conduct of the study, except in case of an emergency if knowledge of the IMP is necessary to provide optimal treatment to the subject in an emergency situation.

For each subject, the investigator will receive an emergency envelope identified by the study code and the medication number, and containing information about the therapy regimen. In case of any subject-related event that requires unblinding (e.g. emergency), the investigator will be allowed to open the emergency envelope and find out the therapy regimen of the subject. If possible the sponsor or his responsible representative should be contacted prior to opening the envelope. Any unblinding must be documented with the date, time, and reason for unblinding and the sponsor or his responsible representative must be notified; the subject should be withdrawn from the study if medically indicated. However, such subjects may remain in the study "under observation" only.

To ensure the scientific integrity of the study, it is imperative that all emergency envelopes (open or sealed), as well as any documentation on unblinding of emergency envelope(s) be returned to the sponsor at the end of the study.

8.6.8 Treatment Adherence

The IMP will be self-administered by the subjects as once daily oral tablet in the morning. At visit 2 and visit 3, subjects will return any empty and non-used treatments providing information to study personnel regarding their compliance with study medication. Compliance will be monitored by study personnel at the site by using the source documents and will be recorded in the eCRF.

Every visit after baseline will be used for dispensing new medication and collecting used medication in order to closely promote the treatment adherence.

8.6.9 Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to the individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s).

SAEs associated with overdose should be reported according to the procedure outlined in Section 9.7.1.

In the event of drug overdose, the subject should be treated symptomatically.

8.6.10 Drug Accountability

The investigator or designee must document the receipt, dispensing, and return of IMP supplies and materials provided for this study in specific accountability forms included in the investigator's study file (ISF). The original form will be retrieved from the study site by the responsible monitor, and the investigator will retain a copy. Documentation of drug accountability for individual subjects will be captured in the eCRF.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, they should acknowledge the receipt of the shipment (by signing the bottom half of the packing list and faxing per instructions provided on the form). If there are any discrepancies between the packing list and the actual product received, Linical must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed with the drug lot/medication ID/job number used to document each dose.
- Verifying that all containers used/assigned are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

Residual medication (complete blisters) must be returned to the sponsor, who will be responsible for accountability and destruction. If the site is responsible for destruction, the process must be done once the accountability is verified by the study monitor. The investigator is not permitted to dispense any study medication to persons not taking part in the study. Non-used drug will be returned to the centre at week 2 and week 6, and compliance will be assessed as:

$$\text{Compliance (\%)} = \frac{(\text{Tablets dispensed}) - (Tablets\ returned)}{\text{Total number of days between visits}} \times 100$$

9.0 Pretreatment Events (PTEs) and Adverse Events (AEs)

9.1. Definitions

9.1.1 Adverse Event

A Pre-Treatment Event (PTE) is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

An adverse event (AE) is defined as any unfavourable and unintended sign (including a clinically significant abnormal laboratory finding), symptom or disease, temporally associated with the use of a medicinal product, regardless of its nature, intensity, seriousness, or presumed relationship (causality) to the product or experimental procedure used.

All adverse events which occur after the first study medication intake and within 4 weeks after the treatment stop date will be considered as treatment emergent adverse events (TEAEs).

Each TEAE will be evaluated for duration, intensity, and relationship to (or association with) the study treatment (or other causes). Additionally, the actions taken (e.g., administration of treatment) and the resulting outcome of the adverse event will be indicated on the eCRF. All adverse events will be followed up until resolved or as clinically required.

All subjects will be followed-up for safety reasons, including those subjects who withdraw or stop participation due to premature termination of the study, especially if the reason for withdrawal is an AE, by means of a phone call 4 weeks after the end of the study treatment.

Any AE, which remains unresolved after completion of the trial, requires detailed evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence is found.

If a worsening of any pathological condition that the subject had before the start of the study or medical problems that are present prior to the start of treatment but worsen during treatment occur, these must be considered as a new adverse event and will require a complete evaluation and the relevant explanation in the case report form.

9.1.2 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study medication or a concomitant medication.
- Be considered unfavourable by the investigator for any reason.

- PTEs/AEs caused by a study procedure (e.g., a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG parameters are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g., laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study medication) or an AE (worsening or complication occurs after start of study medication). Investigators should ensure that the event term recorded captures the change in the condition (e.g., “worsening of…”).
- If a subject has a pre-existing episodic condition (e.g., asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the episodes become more frequent, serious or severe in nature, that is, investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g., “worsening of…”).
- If a subject has a degenerative concurrent condition (e.g., cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if occurring to a greater extent to that which would be expected. Again, investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after starting administration of the study medication, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).

- If the subject experiences a worsening or complication of an AE after any change in study medication, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of…").

Changes in severity of AEs /Serious PTEs:

- If the subject experiences changes in severity of an AE/serious PTE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured appropriately as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

9.1.3 Serious Adverse Event

Serious adverse events are defined as any untoward medical occurrence that at any dose:

- result in subject's death.
- are life-threatening.
- result in permanent or significant disability/incapacity.
- cause hospital admission or prolong hospital stay.
- result in congenital anomalies or birth defects.
- medically important condition that may jeopardize the subject or may require intervention to prevent any of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias,

or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

NOTE: The term "life-threatening" in the definition of "serious" refers to any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death.

An overnight stay in the hospital that is only due to transportation, organisation or accommodation problems and without medical background does not need to be handled/documented as a SAE. Hospitalisations due to surgical procedures for pre-existing conditions that have been planned before enrolment of the subject are not considered SAEs.

9.1.4 Unexpected Adverse Event

Any adverse event, which is not described in the Reference Safety Information (RSI) of the Investigator Brochure (IB) in nature, severity or frequency is unexpected. Expectedness will be assessed in relation to the RSI of the IB. For details, please check the IB version 9, 2017.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction related to the treatment that is both unexpected and serious.

9.2. Adverse Event Severity

Severity of adverse events will be classified according to the following criteria:

Mild	Trivial adverse events, of low significance and short duration that require no special treatment, and do not substantially impair the normal life of the subject.
Moderate	Adverse events causing enough discomfort to interfere with normal life of the subject but are usually ameliorated by simple therapeutic measures.
Severe	Adverse events causing disability to work or perform the daily activities of the subject, and require systemic drug therapy or other treatment

9.3. Relationship to Study Drug

The causal relationship of an adverse event with the study medication will be established based on the following definitions:

Unrelated	There is little or no chance that the study medication caused the AE; other conditions, including concurrent illnesses, progression or expression of the disease state, or a reaction to a concomitant medication best explain the event.

Unlikely	Event of laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
Possible	A reasonable temporal association exists between the AE and treatment administration **and/or** the AE follows a known response pattern to the study drug; **but** could have been produced by other factors such as the subject clinical state, therapeutic intervention or concomitant therapy.
Probable	A reasonable temporal association exists between the AE and treatment administration **and/or** the AE follows a known response pattern to the study drug; **and** could not have been produced by other factors such as the subject clinical state, therapeutic intervention or concomitant therapy.
Definite	A definite temporal association exists between the AE and treatment administration **and/or** the AE follows a known response pattern to the study drug; **and** could not have been produced by other factors such as the subject clinical state, therapeutic intervention or concomitant therapy, **and** the event either occurs immediately following study drug administration or abates following discontinuation of study treatment and may be confirmed by reappearance on repeat exposure.

For the purpose of safety analyses, all AEs which are classified as 'Possible' or 'Probable' or 'Definite' will be considered treatment-related events.

Any subject who is withdrawn from the study because of an AE will be followed until the outcome of the event is determined, and the investigator will prepare a written summary of the event and document the available follow-up information on the eCRF.

9.4. Action Concerning Study Medication

- Drug withdrawn – a study medication is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study medication.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study medication was stopped for a reason other than the particular AE e.g., the study has been terminated, the subject died, dosing with study medication was already stopped before the onset of the AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

9.5. Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by one or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but

has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".

- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g., recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

9.6. Adverse Event Collection Period

Adverse events will be collected throughout the whole study period (screening of 3 weeks, baseline of 1 week, treatment period of 6 weeks and safety follow-up of 4 weeks).

A safety follow-up call will be performed 4 weeks after subject's discharge at the end of the treatment period. Information regarding any ongoing AEs, new AEs and SAEs and concomitant medications will be collected. Subjects who completed the treatment who cannot be contacted for this follow-up call will be considered to have completed the study. Documentation of unsuccessful follow-up phone contact, after 3 attempts, should be included in the subject's source document.

9.7. Adverse Event Reporting

All adverse events occurring during the trial must be documented in the CRF. This applies not only to those adverse events supposedly related to the study medication, but also to any undesired experience, whether or not a causal relationship is suspected.

For this, the CRF includes a specific section for collecting information related to the adverse events. In addition, for the serious adverse events, a standard Serious Adverse Event report form will be included.

9.7.1 Serious Adverse Events

All serious adverse events will be reported by the investigator to the monitor responsible for the clinical trial or to the Pharmacovigilance Manager at Linical within 24 hours after their knowledge. Such report will be made by telephone, fax or email message. The Serious Adverse Event report form, duly completed, should be made available to the Pharmacovigilance Manager at Linical within 48 hours. The Medical Manager at Linical will review the reported documentation for any medical clarification.

Address and contact phone:

Reporting time for the phone communication: 24 hours

Reporting time for the written report: 48 hours

LINICAL

All notifications calls will be made to Linical Safety department:

e-mail address: BEN01.safetydesk@linical.com

Rosa de Lima, 1-bis – EDIFICIO ALBA

28290 Las Matas (Madrid), Spain

Tel. +34 91 372 6035

Fax: +34 91 372 6074

Reporting of serious adverse events using the Serious Adverse Event report form does not exempt from the need to complete all information relating to such adverse events in the specific eCRF section.

If the serious adverse event is still active at the time of reporting or further information is obtained after the initial report, this information must be updated on a new Serious Adverse Event Report Form, clearly identifying the case in order to avoid duplicity.

9.7.2 Non Serious Adverse Events

Non-serious adverse events will be documented in the specific section for reporting in the eCRF that will be submitted to BenevolentAI Bio once the participation of the subject in the clinical trial is completed.

9.7.3 Data Monitoring Committee

No data monitoring committee will be used in this study.

10.0 Protocol Deviations

10.1. Protocol Deviations

Generally, a protocol deviation is not imperative for subject withdrawal. Before the statistical analysis begins, the protocol deviations must be taken into account for the population analysis. The mandatory withdrawal reasons will be considered as major protocol deviations. Other protocol deviations will be classified as minor protocol deviations. Additionally, the following major protocol deviations will be considered:

1) Violation of one of the inclusion/exclusion criteria after enrolment into the study.
2) Treatment incorrectly administered, or overdose.
3) Use of prohibited medication.

Any protocol deviation must be recorded in the eCRF.

10.2. Procedure for protocol amendments

Any amendment to this protocol involving a substantial change may be made as an amendment or addendum in writing. In order to be formalised, it is necessary to obtain the agreement of all the responsible people who signed the original protocol.

Amendments that can result in substantial changes in the original protocol must be submitted and approved by the IRB/IEC and the Health Authorities.

11.0 Statistical Methods and Determination of Sample Size

11.1. Statistical and analytical plans

The statistical analysis will be performed by the Department of Biostatistics of Linical, using SAS®[53] version 9.2 or later.

Statistical significance will be assessed for two-sided probability values < 0.05.

All descriptive variables will be tabulated. Quantitative variables will be described showing their number of available and missing observations, mean, median, standard deviation (SD), the range (minimum and maximum) and the first and third quartiles. Frequency and percentage will describe qualitative variables. Missing values will be tabulated with their frequency but will not be included in the calculation of percentages.

The main population for the efficacy analysis will be the intent to treat population (ITT). The per protocol population (PP) will be analysed also as a sensitivity analysis.

The main population for the safety analysis will be the safety population (SAF), defined as all the subjects who have received at least one dose of study treatment.

Full details of the statistical analysis will be given in a Statistical Analysis Plan (SAP) which will be prepared, approved and signed before the database closure, and so before the subjects' evaluability assessment.

Any deviation from the original SAP will be included and reported in the clinical study report (CSR).

11.1.1 Data Sets Analysed

The safety population (SAF) will be defined as all subjects who have received at least one dose of the study treatment.

The intent to treat population (ITT) will be defined as all subjects who have taken at least one dose of study treatment and who have available a post-baseline evaluation of the primary efficacy endpoint at screening/baseline and at week 6.

The per protocol population (PP) will be defined as all subjects in the FAS who do not experience a major protocol deviation.

11.1.2 Demographic and Other Baseline Characteristics

Baseline characteristics (gender, age, race, weight, height, body mass index, blood pressure, heart rate) for the safety population will be summarised descriptively.

Categorical data will be summarised with absolute and relative frequencies (percentage), and numerical data will be summarised with the number, mean, median, standard deviation (SD), the range (minimum and maximum), and the first and third quartiles (if applicable).

11.1.3 Efficacy Analyses

11.1.4 Primary Efficacy Analyses

ESS mean absolute change from baseline to the end of the 6-week treatment period will be analysed with an ANCOVA model, with the baseline ESS as a covariate, region and treatment as a factor. Missing data in the 6-week ESS evaluation will be considered as a treatment failure , that is imputing the missing ESS reduction as 0. Least-squared (LS) absolute mean changes will be presented by treatment group together with their corresponding 95% confidence interval. Paired-comparisons will be performed without any multiplicity adjustment.

As sensitivity analyses:

a) A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, region, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.

b) MCP-Mod approach will be applied to identify the most suitable dose-response curve. Further details about the curve selection and validation procedures being used will be stated in the Statistical Analysis Plan.

c) Similar to the primary analysis a Rank ANCOVA will be modelled in order to provide evidence of the treatment effect in case of violation of normality assumption.

d) Primary Analysis, and sensitivity analysis as described above will be performed in the Per Protocol Population.

11.1.5 Secondary Efficacy Analyses

All secondary variables assessing a mean absolute or a mean relative change will follow a similar methodology as for the primary variable; i.e., mean changes of ESS (up to 2-week treatment period), SCOPA-Sleep (up to 2-week and 6-week treatment period), PDSS-2 (2-week and 6-week), MWT (6-week), polysomnography (6-week), UPDRS Part III (2-week and 6-week), motor function assessed by the wrist worn device (6-week), HAM-D (2-week, 6-week and follow-up), MoCA (6-week), and FSS (6-week).

The percentage of subjects who showed ESS clinical response (defined as an ESS decrease from baseline of at least 3.0 points and/or final ESS score $\leq$10) after 2 and 6 weeks of treatment will be described and compared between groups by means of a Chi-square test (or Fisher's exact test according to corresponding applicability). Percentages and difference between treatments will be expressed with their 95% confidence interval calculated with a binomial exact method.

11.1.6 Exploratory Analyses

All variables obtained with the wearable tool assessing a mean absolute or a mean relative change will follow a similar methodology as for the primary variable. Categorical variables will be described and compared between groups by means of a Chi-square test (or Fisher's exact test

according to corresponding applicability). Percentages and difference between treatments will be expressed with their 95% confidence interval calculated with a binomial exact method.

Both univariate and multivariate statistical methods will be used as an exploratory pharmacogenomic analysis in order to identify genetic reasons why certain people respond differently to Bavisant, to find out more information about how Bavisant works, 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.

11.1.7 Safety Analyses

Adverse events, adverse events of special interest, serious adverse events, serious and related adverse events will be coded using the latest available MedDRA version and their corresponding incidences will be summarised as overall events, related events, and events by intensity. AEs will be summarised by MedDRA preferred term and system organ class (primary SOC). Summaries of AEs by preferred term and decreasing frequency and by maximum severity will also be prepared.

Physical examination changes, vital signs changes, laboratory tests changes, cardiovascular changes, ocular changes, suicidal ideation (C-SSRS) findings, and positive psychotic symptoms (BPRS+) findings will be described for the different treatment groups and assessed as either clinically or non-clinically significant findings.

11.1.8 Other Analyses

No other analyses are planned.

11.2. Determination of sample size

A total of 200 completed subjects will be evaluated for the study (50 completed subjects per treatment group, with expected early withdrawal rate of around 15%).

The assumptions used for the sample size calculation are a mean absolute change in the Epworth Sleepiness Scale (ESS) from baseline to the end of the 6-week treatment period of at least 3.0 points (minimum change considered as clinically relevant) and a standard deviation of 5.0 (based on a comparable study of Modafinil in a similar population recruited at one centre[32] which showed a standard deviation in the ESS between 3.5 at baseline and 4.8 at the end of the treatment period) and a reduction in ESS of 2.7 points for subjects treated with Modafinil.

The confirmation of the hypothesis of detecting a mean difference in ESS of 3.0 points vs. baseline requires a sample size of 25 subjects per group (intragroup Δ=3.0; SD=5.0; two-side α=0.05; β=0.20; power=80%; one-sample t-test).

The additional endpoint of showing a statistically significant difference of at least 3.0 points in ESS between Bavisant and. placebo requires a sample size of 50 subjects per group (between treatment Δ=3.0; SD=5.0; two-side α=0.05; β=0.20; power=80%; two-sample equal-variance t-test).

The effect size of Bavisant in EDS is unknown and smaller changes in ESS may be clinically useful according to its profile, and higher variability is expected in this multicentre study; so the sample size of 200 completed subjects (50 per treatment group) is proposed in order to cover both the confirmation of an intragroup change of at least 3.0 points vs. baseline, and the between-group difference of at least 3.0 points change vs. placebo.

The Maintenance of Wakefulness Test (MWT) will be performed in a minimum of 20 subjects per group (80 overall) in order to be enough to show statistically significant differences if the expected MWT absolute change from baseline differs at least in one standard deviation (effect size = 1.0).

11.3. Randomisation Methods

Three regions will be defined: USA, Western Europe and Eastern Europe. Regionally randomization list will be performed to guarantee a ratio of 1:1:1:1 for the treatment groups by region. As the study intends on keeping that ratio of 1:1:1:1 both in the subjects who will perform a polysomnography/MWT assessment, and in subjects who will not do that assessment, a down-up / up-down strategy will be followed in order to simplify the stratified randomisation. This way, if the subject will perform both the polysomnography and the MWT assessment, he/she will receive the lowest available subject number at the respective study site; otherwise he/she will receive the maximum available subject number.

The randomisation schedule will be generated by Nuvisan CTS following a computer-generated randomisation scheme. The randomisation schedule will link sequential medication numbers to treatment codes. The medication numbers will be blocked to facilitate attainment of a homogeneous distribution of treatment groups.

11.4. Interim Analysis

No interim evaluation of data is planned.

11.5. Handling of dropouts or missing data

For the primary analysis ESS missing at 6-weeks will be inputed under the treatment failure approach.

As sensitivity analyses, a mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random framework carried out using an adequate contrast at Week 2 or Week 6, accordingly. The model will include fixed categorical effects of treatment group, visit and treatment-by-visit interaction as well as the continuous fixed covariates of mean baseline ESS. This MMRM model will be run with an unstructured correlation matrix to model the within-subject errors.

11.6. Multiple Comparisons/ Multiplicity

No adjustments for multiplicity of assessments will be considered.

11.7. Examination of subgroups

Not applicable.

12.0 Ethics

12.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

The participating centres have their IRB/IEC (or an IRB/IEC tutoring them) established and authorised by the respective authorities, whose composition is available to them and is not shown here.

The Principal Investigator at each site is responsible for obtaining IRB/IEC approval for the final protocol, informed consent form and patient information sheet, any advertisements to recruit subjects, and documents to be handed out to the subjects at the next available meeting.

Written approval of these documents must be obtained from the committee before any subject is enrolled at a site.

When in accordance with local regulations IRB/IEC submission and interaction can be also covered by the assigned CRO.

Each investigator will also be responsible for complying with ethical standards for clinical trials as per local and European laws and regulations, during the study.

12.2. Ethical Conduct of the Study

This study will be conducted with the highest respect for the individual participants (i.e., subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki (18th World Medical Assembly, 1964) and its last revision (Fortaleza, October 2013)[54], the ICH Harmonised Tripartite Guideline for GCP and local laws and regulations of the country where the study is performed.

12.3. Subject Information and Consent

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorisation form. The informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorisation form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent

form, subject authorisation form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorisation form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorisation (if applicable) at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Before being enrolled in the clinical study, subjects must consent to participate after the nature, scope and possible consequences of the clinical study have been explained in a form understandable to them.

The investigator will provide the subject with an information form on the product and the study characteristics that should be read to and/or discussed with the subject in an understandable way. In this document, the subjects willing to consent to participate in this study will be informed of the nature, extent, design and conduct of the study and their consent will be obtained in writing prior to inclusion to the study schedule. Subjects will be given the opportunity to ask questions and will be informed of their right to withdraw from the study at any time, for any reason.

After reading the informed consent document, the subject must give consent in writing. The consent must be confirmed at the time of consent by the personally dated signature of the subject and the personally dated signature of the person conducting the informed consent discussions. A copy of the subject information sheet and the signed consent forms must be given to the subjects. The original signed consent will be retained in the investigator's site file.

The principal investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

The investigator will not include in the study any subject without previously obtaining written consent from the subject.

12.4. Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or

date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (e.g., FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorisation of the subject as part of the informed consent process.

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e., subject name, address, and other identifier fields not collected on the subject's eCRF).

12.5. Insurance Policy

BenevolentAI Bio will obtain liability insurance, in accordance with the national requirements established in the laws of the participating countries, which covers health impairments resulting from medications and/or substances/investigational products administered in the course of this study for which the subject has given his/her written informed consent to participate.

13.0 Source Documents and Case Report Form Completion

13.1. Source Documents

According to the guidelines on Good Clinical Practice, the Monitors Team must check the electronic case report form (eCRF) entries against the source documents, except for the pre-identified source data directly recorded in the eCRF.

During the study, the investigator will maintain adequate records for the study, including medical records, records detailing the progress of the study for each subject, laboratory reports, eCRFs, signed informed consent forms, drug disposition records, AE reports, and information regarding subject discontinuation and completion of the study.

The Informed Consent Form will include a statement by which the subject allows the Sponsor's duly authorised personnel, the IRB/IEC, and the regulatory authorities to have direct access to source data which supports the data on the eCRF (e.g., subject's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

The process for source data verification will be documented in the monitoring plan.

13.2. Case Report Forms

The investigator must keep a written or electronic file for each subject that participates in the clinical trial. In that file, the subjects' demographic and medical data, especially: name, birthday, gender, medical history, diseases and concomitant drug, physical examination and clinical signs, observed adverse events, etc. should be recorded. It must be possible, in any moment, to identify the subject with his/her personal file. The period that the subject participates in the clinical trial must be clearly specified. The data collection will be done using the Electronic Data Capture (EDC) market leader tool from Oracle® called InForm®. The InForm® platform has been validated according to the highest industry standards and practices. The InForm® software uses a secure web browser to provide access to clinical study data and management of the clinical study process.

All documentation will be transcribed to an electronic CRF (eCRF). Any created documentation, especially the files that would be created by the technicians, must be filed. This includes the results of laboratory tests, ECGs, etc. These documents must be identified with the subject number, date of making and study code, in order to specify clearly the subject to whom this document belongs, and to identify the participants.

The main objective is to get the most complete files of each candidate.

Any result obtained during the study development will be reported in the subject's electronic case report form, and if it is used, the serious adverse event form must be sent to BenevolentAI Bio.

The investigator will guarantee that all the documents sent to BenevolentAI Bio, including the eCRF and other type of documents, do not contain any mention to the name of the subject. It is an investigator's duty to guarantee adequate filing and storage of the study documentation after the end of the study as specified in the Guidelines for Good Clinical Practice. All the original files

must be kept as much as possible following the hospital rules, research institutes or local regulation, but for at least 25 years according to the legislation in force.

All the eCRFs must be completed in its entirety. Any correction or amendment will be corrected by the investigator and the previous value recorded in the audit trail of the EDC system along with the reason and date of the change.

The eCRF is considered an official document, and it must be available for the Health Authorities.

Additional information on the data management and quality process is included in Section 13.0 and Section 15.0.

13.3. Monitoring

Representatives of Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity. They will review study records on site and will compare them with source documents. They will also discuss the conduct of the study with the Investigator, and will verify that the facilities remain compliant with the study requirements.

14.0 Data Quality Assurance

For the purpose of ensuring compliance with the protocol, Good Clinical Practice (GCP) and applicable regulatory requirements, the sponsor's Quality Assurance department (or authorised representatives) may conduct on site audits of all aspects of the clinical study either during the study or after the study has been completed. The investigator/institution will permit study related monitoring, audits, IRB/IEC review and regulatory inspection(s) by providing direct access to source documents.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

As soon as the Investigator is notified of a future inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate at this inspection.

The confidentiality of the data verified and the anonymity of the subjects should be respected during these inspections.

The study will be conducted with an electronic case report form with a qualified single data entry performed by the investigators with controlled and restricted access. Additional information on the data management will be provided in a specific document (Data Handling Manual [DHM]). A full data validation plan will be performed and described in this DHM which should be approved before the data entry process starts.

The database quality will be assessed before the database closure; and only when the Statistical Analysis Plan (SAP) is approved and the populations are determined, the database will be locked and moved to Statistics to perform the statistical analysis and prepare the Clinical Study Report (CSR).

Additional information on the data management process is included in Section 16.0.

15.0 Practical Issues

15.1. Early Termination of the Study

The sponsor can prematurely terminate or suspend the study. Study sites will be closed upon study completion.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance.

Reasons for discontinuation of the study may include but are not limited to the following:

- The risks and benefits of the study are re assessed.
- The incidence of AEs constitutes a potential health hazard.
- New scientific data on the investigational medication do not justify a continuation of the clinical study.
- Serious and/or persistent non adherence to the protocol, GCP, and/or applicable regulatory requirements by an investigator/institution occurs.
- Subject enrolment is unsatisfactory.
- The IRB/IEC or other regulatory authority decides to terminate or suspend approval for the investigation or investigator.

Additionally, the sponsor has the right to terminate the study for any reason at any time.

If the study is prematurely terminated or suspended for any reason, the investigator has to inform the subjects and assure appropriate follow up for the subjects. The sponsor should promptly inform the investigators or institutions and the regulatory authorities of the termination or suspension and the reasons for the termination or suspension within the timeframes referred to in applicable regulations. The IRB/IEC should also be informed promptly and provided the reasons for the termination or suspension by the sponsor or by the investigator or institution as specified by the applicable regulatory requirements.

The last visit of the last patient (LPLV) indicates the end of the study and that end of study will be communicated to the IRBs/IECs and the regulatory authorities of each participating country. Last visit of the last subject at each site/country also indicates the end of the study for that site/country.

15.2. Publication Policy

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and

review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.2.1 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, BenevolentAI Bio will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study. BenevolentAI Bio contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

15.2.2 Clinical Trial Results Disclosure

BenevolentAI Bio will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by BenevolentAI Bio Policy/Standard, applicable laws and/or regulations.

16.0 Data Management Procedures

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organisation Drug Dictionary.

16.1. Review and Confirmation of Case Report Forms

Electronic case report forms will be filled directly by the investigators.

Prior to obtaining the clean file, checks of consistency of inclusion/non-inclusion criteria, clinical assessment, visit dates, compliance, concomitant treatment, adverse event, withdrawal information and efficacy evaluation will be performed.

Data query forms will be generated to the investigator in order to clarify the data inconsistencies through the source data verification.

16.2. Database production and verification

16.2.1 Data Management Plan

A validation plan is set-up according to the protocol requirements, which describes the validation rules to be applied. Actions that should be taken in case of data abnormalities are detailed. In case of missing values, out of range values, data inconsistencies or values that fail logical checks, correction forms (queries) are edited and transmitted to the investigator for clarification.

16.2.2 Database

A database will be created in order to collect all clinical and other data from the clinical trial. The data management will take place at the Data Management Department of Linical.

16.2.3 Database access

Access to the database will be restricted to the investigators, data managers and clinical monitors. Any entry in the database will be traceable through its identification and date. Audit trail of data changes will be assured.

16.2.4 Quality and consistency controls

The investigators will enter the clinical data in the electronic case report form.

Prior to obtaining the clean file, checks of consistency of inclusion/exclusion criteria, clinical assessment, visit dates, compliance, concomitant treatment, adverse event, withdrawal information and efficacy evaluation will be performed.

16.2.5 Data queries

Data query forms will be generated to the investigator in order to clarify the data inconsistencies through the source data verification.

Only then and after all detected errors, inconsistencies or doubts cleared, will the database be declared a clean file and protected accordingly.

16.2.6 Clean File

A clean file will be created and registered, to which further changes will be disallowed. A document with the eligibility of subjects will be generated.

16.2.7 Data coding

Coding will be carried out according to standard dictionaries partly by program and then validated and completed by a medical doctor according to the Linical dictionaries. The latest available version of the following dictionaries will be used:

- Concomitant treatments: WHO DRUG
- Adverse Events: MedDRA

All case report forms and data checking records will be retained as permanent records of the study.

17.0 Reference List

1. FDA - Food and Drug Administration. Guidance for Industry. Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials. Revision 1. 2012; Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm315156.htm.
2. Mundt JC, Greist JH, Jefferson JW, Federico M, Mann JJ, Posner K. Prediction of suicidal behavior in clinical research by lifetime suicidal ideation and behavior ascertained by the electronic Columbia-Suicide Severity Rating Scale. The Journal of clinical psychiatry. 2013;74(9):887-93. Epub 2013/10/11.
3. Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. The American journal of psychiatry. 2011;168(12):1266-77. Epub 2011/12/24.
4. EFPIA - European Federation of Pharmaceutical Industries and Associations. Parkinson's Disease. 2016 [December 2016]; Available from: http://www.efpia.eu/diseases/98/59/Parkinson-39-s-disease.
5. Parkinson's Disease Foundation. Statistics on Parkinson. 2016 [December 2016]; Available from: http://www.pdf.org/en/parkinson_statistics.
6. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, et al. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 2002;73(6):629-35. Epub 2002/11/20.
7. Abbott RD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology. 2005;65(9):1442-6. Epub 2005/11/09.
8. Knie B, Mitra MT, Logishetty K, Chaudhuri KR. Excessive daytime sleepiness in patients with Parkinson's disease. CNS drugs. 2011;25(3):203-12. Epub 2011/02/18.
9. Arnulf I, Leu-Semenescu S. Sleepiness in Parkinson's disease. Parkinsonism & related disorders. 2009;15 Suppl 3:S101-4. Epub 2010/01/30.
10. Fronczek R, Overeem S, Lee SY, Hegeman IM, van Pelt J, van Duinen SG, et al. Hypocretin (orexin) loss in Parkinson's disease. Brain : a journal of neurology. 2007;130(Pt 6):1577-85. Epub 2007/05/02.
11. Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. Brain : a journal of neurology. 2007;130(Pt 6):1586-95. Epub 2007/05/11.
12. Hirsch EC, Graybiel AM, Duyckaerts C, Javoy-Agid F. Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy. Proceedings of the National Academy of Sciences of the United States of America. 1987;84(16):5976-80. Epub 1987/08/01.
13. Jellinger KA. The pathology of Parkinson's disease. Advances in neurology. 2001;86:55-72. Epub 2001/09/14.
14. Gemkow MJ, Davenport AJ, Harich S, Ellenbroek BA, Cesura A, Hallett D. The histamine H3 receptor as a therapeutic drug target for CNS disorders. Drug discovery today. 2009;14(9-10):509-15. Epub 2009/05/12.
15. Passani MB, Blandina P. Histamine receptors in the CNS as targets for therapeutic intervention. Trends in pharmacological sciences. 2011;32(4):242-9. Epub 2011/02/18.

16. Lin JS, Sergeeva OA, Haas HL. Histamine H3 receptors and sleep-wake regulation. The Journal of pharmacology and experimental therapeutics. 2011;336(1):17-23. Epub 2010/09/25.
17. Brodsky MA, Godbold J, Roth T, Olanow CW. Sleepiness in Parkinson's disease: a controlled study. Movement disorders : official journal of the Movement Disorder Society. 2003;18(6):668-72. Epub 2003/06/05.
18. Meindorfner C, Korner Y, Moller JC, Stiasny-Kolster K, Oertel WH, Kruger HP. Driving in Parkinson's disease: mobility, accidents, and sudden onset of sleep at the wheel. Movement disorders : official journal of the Movement Disorder Society. 2005;20(7):832-42. Epub 2005/02/24.
19. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. Journal of neurology, neurosurgery, and psychiatry. 1992;55(3):181-4. Epub 1992/03/01.
20. Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. Journal of sleep research. 2000;9(1):5-11. Epub 2000/03/25.
21. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. US Modafinil in Narcolepsy Multicenter Study Group. Annals of neurology. 1998;43(1):88-97. Epub 1998/02/05.
22. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. Epub 1991/12/01.
23. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep. 1992;15(4):376-81. Epub 1992/08/01.
24. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest. 1993;103(1):30-6. Epub 1993/01/01.
25. Johns MW. Sleepiness in different situations measured by the Epworth Sleepiness Scale. Sleep. 1994;17(8):703-10. Epub 1994/12/01.
26. Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep. 2005;28(1):113-21. Epub 2005/02/11.
27. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2003;18(3):287-93. Epub 2003/03/07.
28. Hogl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep. 2002;25(8):905-9. Epub 2002/12/20.
29. Chen NH, Johns MW, Li HY, Chu CC, Liang SC, Shu YH, et al. Validation of a Chinese version of the Epworth sleepiness scale. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2002;11(8):817-21. Epub 2002/12/17.
30. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep & breathing = Schlaf & Atmung. 2008;12(2):161-8. Epub 2007/10/09.
31. Manni R, Politini L, Ratti MT, Tartara A. Sleepiness in obstructive sleep apnea syndrome and simple snoring evaluated by the Epworth Sleepiness Scale. Journal of sleep research. 1999;8(4):319-20. Epub 2000/01/26.

32. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. Journal of neurology, neurosurgery, and psychiatry. 2005;76(12):1636-9. Epub 2005/11/18.
33. EMA - European Medicines Agency. EMA/828546/2015 Assessment Report - Wakix2005. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002616/WC500204749.pdf.
34. Dauvilliers Y, Bassetti C, Lammers GJ, Arnulf I, Mayer G, Rodenbeck A, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. The Lancet Neurology. 2013;12(11):1068-75. Epub 2013/10/11.
35. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2010;55(4):622-7. Epub 2010/03/27.
36. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12. Epub 2009/05/06.
37. Marinus J, Visser M, van Hilten JJ, Lammers GJ, Stiggelbout AM. Assessment of sleep and sleepiness in Parkinson disease. Sleep. 2003;26(8):1049-54. Epub 2004/01/30.
38. Trenkwalder C, Kohnen R, Hogl B, Metta V, Sixel-Doring F, Frauscher B, et al. Parkinson's disease sleep scale--validation of the revised version PDSS-2. Movement disorders : official journal of the Movement Disorder Society. 2011;26(4):644-52. Epub 2011/02/12.
39. Hjollund NH, Andersen JH, Bech P. Assessment of fatigue in chronic disease: a bibliographic study of fatigue measurement scales. Health and quality of life outcomes. 2007;5:12. Epub 2007/03/01.
40. Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. Sleep & breathing = Schlaf & Atmung. 2008;12(1):39-45. Epub 2007/08/09.
41. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Annals of internal medicine. 1999;131(7):485-91. Epub 1999/10/03.
42. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Movement disorders : official journal of the Movement Disorder Society. 2008;23(15):2129-70. Epub 2008/11/26.
43. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society. 2005;53(4):695-9. Epub 2005/04/09.
44. Hamilton M. A rating scale for depression. Journal of neurology, neurosurgery, and psychiatry. 1960;23:56-62. Epub 1960/02/01.
45. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychological Reports. 1962;10:799-812.
46. DeWilde KE, Levitch CF, Murrough JW, Mathew SJ, Iosifescu DV. The promise of ketamine for treatment-resistant depression: current evidence and future directions. Annals of the New York Academy of Sciences. 2015;1345:47-58. Epub 2015/02/05.
47. Moskal JR, Burch R, Burgdorf JS, Kroes RA, Stanton PK, Disterhoft JF, et al. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces

antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. Expert opinion on investigational drugs. 2014;23(2):243-54. Epub 2013/11/21.

48. Shiroma PR, Albott CS, Johns B, Thuras P, Wels J, Lim KO. Neurocognitive performance and serial intravenous subanesthetic ketamine in treatment-resistant depression. The international journal of neuropsychopharmacology. 2014;17(11):1805-13. Epub 2014/06/26.
49. Janssen Research & Development L. A Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression (SUSTAIN-2). ClinicalTrials.gov Identifier: NCT02497287. ClinicalTrials.gov2017 [Aug2017]; Available from: https://clinicaltrials.gov/ct2/show/NCT02497287.
50. Janssen Research & Development L. Long-term Safety Study of Rapastinel as Adjunctive Therapy in Patients With Major Depressive Disorder. ClinicalTrials.gov Identifier: NCT03002077. ClinicalTrials.gov2017 [Aug2017]; Available from: https://clinicaltrials.gov/ct2/show/NCT02497287.
51. Doghramji K, Mitler MM, Sangal RB, Shapiro C, Taylor S, Walsleben J, et al. A normative study of the maintenance of wakefulness test (MWT). Electroencephalography and clinical neurophysiology. 1997;103(5):554-62. Epub 1997/12/24.
52. American Association of Sleep Technologists A. Sleep Technology: Technical Guideline. Standard Polysomnography - Updated July 20122012. Available from: https://go.aastweb.org/Resources/Guidelines/StandardPSG.pdf.
53. SAS Institute. SAS/STAT 9.2 User's Guide, Second Edition. Cary, NC: SAS Institute; 2009. Available from: http://support.sas.com/documentation/cdl/en/statug/63033/PDF/default/statug.pdf.
54. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama. 2013;310(20):2191-4. Epub 2013/10/22.

18.0 Appendices

18.1. Administrative Information - Contacts

Issue	Contact*
Serious Adverse Event Reporting	Linical (CRA / PhV Officer) (see section 9.7)
Safety Questions	Linical (CRA / PhV Officer) (see section 9.7)
Pregnancy Reporting	Linical (CRA / PhV Officer) (see section 9.7)
Unblinding	Linical (CRA / PM / BST)
Protocol Deviations	Linical (CRA / PM / BST)
Protocol Guidance	Linical (CRA / PM / MM)
Emergency contact Business hours weekdays (08:00 to 16:00 CET)	Linical (CRA / MM) BEN01.medical.emergency@linical.com Dr. Isabel Caballero (+34 610 134 109) Dr. Carlos Hortelano (+34 670 836 340)
24 emergency contact Non business hours and weekends	See table below
Insurance	Linical (CRA / PM)

Country	In Country Number	International Back Up Number
Czech Republic	296849801	+441204684560
Germany	08005891887	+441235239958
Italy	0236007792	+441228899357
Poland	124207010	+441204684450
Spain	966990007	+441204684092
United Kingdom	01242649524	+441242649524
USA	18666151825	+441204684544

* CRA (Clinical Research Associate / Study Monitor), PhV Officer (Pharmacovigilance Officer), PM (Project Manager), BST (Biostatistician), MM (Medical Manager)

Study-Related Responsibilities

Activity	Organisation
Site selection, management and monitoring	Linical / BenevolentAI Bio
Central Laboratory	LKF
Data Management	Linical
Electronic Data Capture System	Linical (Oracle Inform 6.1)
Clinical supply packaging and distribution	Nuvisan CTS
Clinical supply return	Nuvisan CTS
Rater vendor	Bracket

18.2. UK PDS Brain Bank Diagnostic Criteria for Parkinson's Disease

UK PARKINSON'S DISEASE SOCIETY BRAIN BANK CLINICAL DIAGNOSTIC CRITERIA*

Step 1. Diagnosis of Parkinsonian Syndrome

- Bradykinesia
- At least one of the following
  - Muscular rigidity
  - 4-6 Hz rest tremor
- postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction

Step 2 Exclusion criteria for Parkinson's disease

- history of repeated strokes with stepwise progression of parkinsonian features
- history of repeated head injury
- history of definite encephalitis
- oculogyric crises
- neuroleptic treatment at onset of symptoms
- more than one affected relative
- sustained remission
- strictly unilateral features after 3 years
- supranuclear gaze palsy
- cerebellar signs
- early severe autonomic involvement
- early severe dementia with disturbances of memory, language, and praxis
- Babinski sign
- presence of cerebral tumor or communication hydrocephalus on imaging study
- negative response to large doses of levodopa in absence of malabsorption
- MPTP exposure

Step 3 supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

*From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184[19].

18.3. Epworth Sleepiness Scale (ESS)

EPWORTH SLEEPINESS SCALE FORM

Instructions: Be as truthful as possible. Print the form. Read the situation in the first column; select your response from the second column; enter that number in the third column. Total all of the entries in the third column and enter the total in the last box.

Situation	Responses	Score
Sitting and Reading	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Watching Television	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting inactive in a public place, for example, a theater or a meeting	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
As a passenger in a car for an hour without a break	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Lying down to rest in the afternoon	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting and talking to someone	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
Sitting quietly after lunch when you've had no alcohol	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
In a car while stopped in traffic	0 = would never doze 1 = slight chance of dozing 2 = moderate chance of dozing 3 = high chance of dozing	
TOTAL SCORE		

 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540-545.

18.4. Maintenance of Wakefulness Test (MWT)

The Clinical Use of the MSLT and MWT – AASM Practice Parameters[26]

(Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. SLEEP 2005;28(1):113-121.)

Box 2

Recommendations for the MWT protocol

(Developed from methods of Doghramji and colleagues, A normative study of the maintenance of wakefulness test (MWT), 1997. 10

Modified by collective expert opinion using Rand/UCLA Appropriateness Method)

1. The 4-trial MWT 40-minute protocol is recommended. The MWT consists of four trials performed at two hour intervals, with the first trial beginning about 1.5 to 3 hours after the patient's usual wake-up time. This usually equates to a first trial starting at 0900 or 1000 hours.
2. Performance of a PSG prior to MWT should be decided by the clinician based on clinical circumstances.
3. Based on the Rand/UCLA Appropriateness Method, no consensus was reached regarding the use of sleep logs prior to the MWT; there are instances, based on clinical judgment, when they may be indicated.
4. The room should be maximally insulated from external light. The light source should be positioned slightly behind the subject's head such that it is just out of his/her field of vision, and should deliver an illuminance of 0.10-0.13 lux at the corneal level (a 7.5 W night light can be used, placed 1 foot off the floor and 3 feet laterally removed from the subject's head). Room temperature should be set based on the patient's comfort level. The subject should be seated in bed, with the back and head supported by a bedrest (bolster pillow) such that the neck is not uncomfortably flexed or extended.
5. The use of tobacco, caffeine and other medications by the patient before and during MWT should be addressed and decided upon by the sleep clinician before MWT. Drug screening may be indicated to ensure that sleepiness/wakefulness on the MWT is not influenced by substances other than medically prescribed drugs. Drug screening is usually performed on the morning of the MWT but its timing and the circumstances of the testing may be modified by the clinician. A light breakfast is recommended at least 1 hour prior to the first trial, and a light lunch is recommended immediately after the termination of the secondnoon trial.
6. Sleep technologists who perform the MWT should be experienced in conducting the test.
7. The conventional recording montage for the MWT includes central EEG (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electrooculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG).
8. Prior to each trial, the patient should be asked if they need to go to the bathroom or need other adjustments for comfort. Standard instructions for bio-calibrations (i.e., patient calibrations) prior to each trial include: (1) sitlie quietly with your eyes open for 30 seconds, (2) close both eyes for

30 seconds, (3) without moving your head, look to the right, then left, then right, then left, right and then left, (4) blink eyes slowly for 5 times, and (5) clench or grit your teeth tightly together.

9. Instructions to the patient consist of the following: “Please sit still and remain awake for as long as possible. Look directly ahead of you, and do not look directly at the light.” Patients are not allowed to use extraordinary measures to stay awake such as slapping the face or singing.
10. Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch.
11. Trials are ended after 40 minutes if no sleep occurs, or after unequivocal sleep, defined as three consecutive epochs of stage 1 sleep, or one epoch of any other stage of sleep.
12. The following data should be recorded: start and stop times for each trial, sleep latency, total sleep time, stages of sleep achieved for each trial, and the mean sleep latency (the arithmetic mean of the four trials).
13. Events that represent deviation from standard protocol or conditions should be documented by the sleep technologist for review by the sleep specialist.

18.5. Polysomnography (PSG)

The American Association of Sleep Technologists developed the Technical Guideline on Sleep Technology for Standard Polysomnography – Updated July 2012 [52]. The following is the summary of the technical aspects of the referred guidelines.

SUMMARY: The scope of polysomnography encompasses the monitoring of patients in a sleep facility using an array of medical equipment that is simultaneously recorded on a multi-channel analog or digital system. Sleep technologists are specially trained to perform polysomnography for the diagnosis and treatment of sleep and arousal disorders. They are part of a team under the direction of a physician who practices sleep disorders medicine. The team works in concert to ensure the proper diagnosis, appropriate management, and education for individuals that experience sleep disorders. They follow patient sensitive standards of care, which are the foundation for clinical/technical decision-making. The sleep technologist prepares for and monitors the recording, requiring expertise in normal and abnormal sleep and multiple technical and medical monitors. Much of the utility of the polysomnogram (PSG) depends on the ability to correlate specific changes or abnormalities of one physiological parameter with specific conditions defined by another parameter or parameters. Consequently, polysomnography is a significantly more powerful and complex tool than could be provided by individual or independent measurements of each variable. The sleep technologist verifies and maintains the quality of the recording and can decipher artifact from true physiological signals. The technologist can recognize when medical intervention is required and responds according to the protocols provided by the medical director. Therefore, attended polysomnography by a trained sleep technologist produces the highest quality clinical tool. The standard diagnostic PSG requires the recording and evaluation of sleep stages and arousals, respiration, limb movements, snoring, oximetry, body position, and cardiac rhythm disturbances. The resulting documentation is used to diagnose or assess the treatment of sleep disorders.

Electrode Preparation and Application

Electrodes used in polysomnography conduct biopotentials from the patient to the recording circuit. Electrodes are used to record EEG, EOG, EMG, ECG, and sometimes respiratory effort.

Electroencephalogram (EEG)

The EEG is the primary variable to document wakefulness, arousals and sleep stages during the sleep study. A single central channel referenced to an ear mastoid site (C4-M1), a single frontal channel referenced to an ear mastoid site (F4-M1) and a single occipital channel referenced to an ear mastoid site (O2-M1) is sufficient for evaluating waveforms. The mastoid is located posterior to each ear.

However, additional channels (C3-M2, F3-M2, O1-M2) are recommended to provide redundancy in case of electrode malfunction.

Electrooculogram (EOG)

The EOG recording aids the identification of sleep onset by monitoring for slow, rolling eye movements that occur with transition to Stage N1 sleep and identification of REM sleep when rapid eye movements (REMs) that occur during Stage R (REM) sleep are present in the recording.

Chin Electromyogram (EMG)

The recording of EMG activity in the chin area is used for determining the level of muscle tone, which significantly decreases during Stage R (REM) sleep and may also be reduced with sleep onset. This channel also provides supplemental information regarding patient movements and arousals and may be useful in distinguishing artifact in other channels.

Limb Movement

Additional causes of sleep disturbances that may need to be identified and treated are periodic limb movements of sleep (PLMS). These movements are often visually detectable during the monitoring process. Monitoring the anterior tibialis muscles allows for the determination of the severity of the disorder by quantifying the rate of movements as well as the correlation with EEG arousal. Limb EMG of the upper extremities may also be recorded if clinically indicated.

Electrocardiogram (ECG)

The ECG monitors the heart rhythm. A single ECG channel is sufficient for standard PSG monitoring.

Upper Airway Sound Recording

Detecting snore bursts can be a valuable supplemental tool for determining and verifying the nature of arousals. There are several commercially available devices but snoring is typically measured with a snore microphone or sound transducer.

Respiration (Measures of Airflow and Respiratory Effort)

Airflow and respiratory effort channels are utilized during the standard PSG to monitor respiration specifically for the detection of apneas, hypopneas, RERA's and other sleep related breathing events. RERA is an acronym for Respiratory Effort Related Arousal. It is important to record at least three respiratory parameters: nasal/oral airflow, thoracic effort and abdominal effort.

Blood Oxygenation (Oxygen Saturation - SpO2)

The diagnosis of obstructive sleep apnea during the standard PSG requires the continuous monitoring and display of blood oxygen saturation levels to provide crucial information about the severity of the sleep related breathing disorder. Pulse oximeters are generally built in to or can be easily interfaced with the PSG acquisition equipment. It is necessary to carefully evaluate the pulse oximeter for use in the sleep facility for sampling rate and analog output to interface with the polygraph. The output on the oximeter must be through a DC amplifier and the signal must be displayed simultaneously with other pertinent PSG variables. In modern PSG systems oximetry is integrated as a DC channel in the system amplifier. The polygraph DC amplifier requires calibration and the output can be displayed linearly or numerically, depending on the acquisition system. Whichever method is used to record pulse oximetry, the device must be capable of a signal averaging time of 3 seconds or less.

Capnography

Capnography can be used to measure the patient's carbon dioxide (CO2) level.

Body Position

Many disorders such as apnea can be exacerbated by body orientation during sleep. Therefore, a valuable tool for accurate diagnosis and treatment of sleep disorders is a determination of body position on a continuous basis throughout the recording.

Behavioral Observation

The capability of observing the patient during the recording of the standard PSG is required for patient safety as well as clinical and technical assessment. The recommendation is to use audio monitoring and digital video recording that is synchronized with the PSG.

Montage Filter & Sensitivity Settings

The standard PSG recording montage should consist of the measurement of the above-defined parameters. An example of a montage is as follows:

Channel	Derivation	Sensitivity	High Filter	Low Filter	Sampling Rate
L outer canthus	E1- M2	5–7 µv/mm	35 Hz	0.3 Hz	500 Hz
R outer canthus	E2 - M2	5-7 µv/mm	35 Hz	0.3 Hz	500 Hz
Chin EMG	EMG1-EMG2- EMG3	10 µv/mm	100 Hz	10 Hz	500 Hz
Frontal EEG	F4-M1	5-7 µv/mm	35 Hz	0.3Hz	500 Hz

Channel	Derivation	Sensitivity	High Filter	Low Filter	Sampling Rate
	F3-M2				
Central EEG	C4-M1 C3-M2	5-7 µv/mm	35 Hz	0.3 Hz	500 Hz
Occipital EEG	O2-M1 O1-M2	5-7 µv/mm	35 Hz	0.3 Hz	500 Hz
Left Anterior Tibialis	LAT1 LAT2	10 µv/mm	100 Hz	10 Hz	500 Hz
Right Anterior Tibialis	RAT1 RAT2	10 µv/mm	100 Hz	10 Hz	500 Hz
ECG	ECG1 ECG2	20 µv/mm	70 Hz	0.3 Hz	500 Hz
Snore		20 µv/mm	100 Hz	10 Hz	500 Hz
Pressure Flow		20 µv/mm	15 Hz	0.1 Hz	100 Hz
Thermal Flow		20 µv/mm	15 Hz	0.1 Hz	100 Hz
Thoracic Effort Belts		10-100 µv/mm	15 Hz	0.1 Hz	100 Hz
Abdominal Effort Belts		10-100 µv/mm	15 Hz	0.1 Hz	100 Hz
CPAP	DCx		5 Hz		100 Hz
SpO2	DCx		5 Hz		25 Hz

60 Hz notch filters should not ordinarily be used in EEG or EOG, as this may conceal the presence of artifact, and the use of 60 Hz notch filters should be avoided in the EMG channels. The sleep facility director should determine the specific montage and the equipment and recording devices used.

Technical Documentation

Log

The sleep technologist should log notable events that occur during the study in chronological order. Notable events include “Lights Off”, sleep onset, “Lights On”, the sleep technologist entering or leaving the patient’s room, the patient getting out of bed, initiating or adjusting PAP or oxygen therapy, position changes, technical difficulties, environmental disturbances, and any other observation that might be helpful to the interpreting physician.

Summary

The sleep technologist should completely summarize all technical and behavioral observations at completion of the standard PSG. This can be done on a form designed by the sleep facility, within the context of the format set forth by the manufacturer of the PSG data acquisition equipment, or on a flowsheet within an electronic medical record. The summary should include comments on sleep

architecture, behavioral observations, myoclonus/limb movements, respiratory characteristics including respiratory events and desaturations, initiation of PAP, if applicable, and heart rate/ECG observations. The technologist should also add any significant medical or sleep-related information discovered during patient assessment, testing, or before discharge.

Sleep Parameters

The report summary should include the details of the analysis of sleep stage scoring as well as clinical event scoring.

Sleep Stage Parameters

Total Recording Time (TRT) is defined as the time from "lights out" to "lights on". Total Sleep Time (TST) is the total time asleep after sleep onset. To determine the how well the patient slept, the Sleep Efficiency (SE) is calculated by dividing the TST by the TRT and multiplying by 100. Sleep studies are recorded on 30 second "epochs". Sleep onset is defined as the first epoch scored as any stage other than stage W. Sleep Latency (SL) is the time from "lights out" to the sleep onset. Latencies to sleep stages are determined from sleep onset to the first epoch of that sleep stage. Wake after Sleep Onset (WASO) is the time awake after sleep onset until "lights on". To determine the percentage time spent in each of the sleep stages during the sleep study, the total minutes of the sleep stage is divided by the TST and multiplied by 100.

Clinical Event Parameters

To determine the severity of sleep disturbances, the indices of the clinical events scored are compared to normative values. The sleep technologist calculates these indexes by dividing the number of clinical events by the TST. These indices include the apnea index (AI), hypopnea index (HI), apnea/hypopnea index (AHI), periodic limb movement (PLMS) index, PLMS arousal index, Respiratory Effort Related Arousal (RERA) index, and the overall arousal index. Usually the PSG equipment will analyze the heart rate and oxygen saturation and report the mean, maximum and lowest value by TRT, TST and sleep state, i.e. stage N1, N2, N3 (NREM) and stage R (REM). The technologist is responsible for manually verifying these parameters.

Sleep Related Breathing Events

The study summary should document sleep related breathing events with respect to sleep state. Information should be provided concerning the respiratory rate while awake and asleep, the presence or absence of snoring, the presence of paradoxical breathing, the number and index of apnea and/or hypopnea events, the longest apnea and/or hypopnea event, the mean and minimum oxygen saturation. Notation should be made if sleep state or body position is related to the apnea/hypopnea index and/or desaturation. The absence or occurrence of Cheyne Stokes breathing pattern should be documented in all patients who demonstrate central apnea events.

Heart Rate/ECG Observation

The average and highest heart rate while asleep and the highest heart rate during the recording should be annotated and the summary should document bradycardia (lowest rate observed), asystole (longest pause observed), sinus tachycardia (highest rate observed), narrow complex tachycardia (highest rate observed), wide complex tachycardia (highest rate observed) and atrial fibrillation on a yes/no basis. All other arrhythmias should be documented with respect to frequency of occurrence and type. It is particularly important to describe the occurrence of heart rate changes or arrhythmias with respect to sleep state (REM, NREM) and sleep related breathing events such as O2 desaturations and apneic events.

Limb Movements

Limb movement activity is recorded from the extremities and must be evaluated in terms of frequency of occurrence and periodicity, sleep/wake status, and presence or absence of subsequent arousal. Rhythmic leg movements observed during wakefulness can indicate Restless Legs Syndrome (RLS). The sleep technologist should ask about symptoms of RLS during patient assessment (difficulty initiating sleep due to a need to move) and document any relevant patient comments as well as evidence of RLS seen prior to or during the recording.

Behavioral Observations

Any unusual or atypical behavioral events occurring during the patient's sleep and/or during wakefulness should be documented by the sleep technologist during the standard PSG. The sleep technologist should describe in detail what the behavior is and how it relates to the polysomnographic recording (i.e. nocturnal eating, enuresis, body rocking). When arousals are noted during the PSG recording, the sleep technologist should document the cause of the arousal, i.e. as the result of apneic events, limb movements, spontaneous or environmentally evoked.

18.6. Parkinson's Disease Sleep Scale (PDSS-2)

Parkinson's Disease Sleep Scale (PDSS-2)

Please rate the severity of the following based on your experiences during the past week (7 days). Please make a cross in the answer box

	Very often (This means 6 to 7 days a week)	Often (This means 4 to 5 days a week)	Sometimes (This means 2 to 3 days a week)	Occasionally (This means 1 day a week)	Never
1) Overall, did you sleep well during the last week?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2) Did you have difficulty falling asleep each night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
3) Did you have difficulty staying asleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
4) Did you have restlessness of legs or arms at nights causing disruption of sleep?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
5) Was your sleep disturbed due to an urge to move your legs or arms?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
6) Did you suffer from distressing dreams at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
7) Did you suffer from distressing hallucinations at night (seeing or hearing things that you are told do not exist)?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
8) Did you get up at night to pass urine?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
9) Did you feel uncomfortable at night because you were unable to turn around in bed or move due to immobility?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
10) Did you feel pain in your arms or legs which woke you up from sleep at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
11) Did you have muscle cramps in your arms or legs which woke you up whilst sleeping at night?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
12) Did you wake early in the morning with painful posturing of arms and legs?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
13) On waking, did you experience tremor?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
14) Did you feel tired and sleepy after waking in the morning?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0
15) Did you wake up at night due to snoring or difficulties with breathing?	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

Reproduced from Trenkwalder et al (Movement Disorders, Vol. 26, No. 4, 2011)[38]

18.7. Scales for Outcome in Parkinson's Disease Sleep (SCOPA-Sleep)

SCOPA-SLEEP SCALE

Aim of the Questionnaire

By means of this questionnaire, we would like to find out to what extent *in the past month* you have had problems with sleeping. Some of the questions are about problems with sleeping at night, such as, for example, not being able to fall asleep or not managing to sleep on. Another set of questions is about problems with sleeping *during the day*, such as dozing off (too) easily and having trouble staying awake.

First read these instructions before you answer the questions!

Place a cross in the box above the answer which best reflects your situation. If you wish to change an answer, fill in the 'wrong' box and place a cross in the correct one. If you have been using sleeping tablets, then the answer should reflect how you have slept while taking these tablets.

NS: Nighttime Sleep Problems

response options: not at all – a little – quite a bit – a lot

In the past month, …

1. … have you had trouble falling asleep when you went to bed at night?
2. … to what extent do you feel that you have woken *too often*?
3. … to what extent do you feel that you have been lying awake for *too long* at night?
4. … to what extent do you feel that you have woken up *too early* in the morning?
5. … to what extent do you feel you have had *too little* sleep at night?

Overall, how well have you slept at night during the past month?

response options: very well – well – rather well – not well but not badly - rather badly – badly - very badly

DS: Daytime Sleepiness

response options: never – sometimes – regularly – often

1. How often in the past month have you fallen asleep unexpectedly either during the day or in the evening?
2. How often in the past month have you fallen asleep while sitting peacefully?
3. How often in the past month have you fallen asleep while watching TV or reading?
4. How often in the past month have you fallen asleep while talking to someone?
5. In the past month, have you had trouble staying awake during the day or in the evening?
6. In the past month, have you experienced falling asleep during the day as a problem?

Reproduced from Marinus et al (SLEEP 2003;26(8):1049-54)[37]

18.8. Unified Parkinson's Disease Rating Scale Part III (UPDRS Part III)

III. MOTOR EXAMINATION

Speech

0-normal

1-slight loss of expression, diction,volume

2-monotone, slurred but understandable, mod. impaired

3-marked impairment, difficult to understand

4-unintelligible

Facial Expression

0-Normal

1-slight hypomymia, could be poker face

2-slight but definite abnormal diminution in expression

3-mod. hypomimia, lips parted some of time

4-masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

Tremor at Rest

+ Face

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

+ Right Upper Extremity (RUE)

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

+ LUE

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

+ RLE

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

+ LLE

0-absent

1-slight and infrequent

2-mild and present most of time

3-moderate and present most of time

4-marked and present most of time

Action or Postural Tremor

+ RUE

0-absent

1-slight, present with action

2-moderate, present with action

3-moderate present with action and posture holding

4-marked, interferes with feeding

+ LUE

0-absent

1-slight, present with action

2-moderate, present with action

3-moderate present with action and posture holding

4-marked, interferes with feeding

Rigidity

+ Neck

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ RUE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ LUE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ RLE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

+ LLE

0-absent

1-slight or only with activation

2-mild/moderate

3-marked, full range of motion

4-severe

Finger taps

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

Hand Movements (open and close hands in rapid succession)

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

Rapid Alternating Movements (pronate and supinate hands)

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

Leg Agility (tap heel on ground, amp should be 3 inches)

+ Right

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

+ Left

0-normal

1-mild slowing, and/or reduction in amp.

2-moderate impaired. Definite and early fatiguing, may have occasional arrests

3-severely impaired. Frequent hesitations and arrests.

4-can barely perform

Arising From Chair (pt. arises with arms folded across chest)

0-normal

1-slow, may need more than one attempt

2-pushes self up from arms or seat

3-tends to fall back, may need multiple triesbut can arise without assistance

4-unable to arise without help

Posture

0-normal erect

1-slightly stooped, could be normal for older person

2-definitely abnormal, mod. stooped, may lean to one side

3-severely stooped with kyphosis

4-marked flexion with extreme abnormality of Posture

Gait

0-normal

1-walks slowly, may shuffle with short steps,no festination or propulsion

2-walks with difficulty, little or no assistance, some festination, short steps or propulsion

3-severe disturbance, frequent assistance

4-cannot walk

Postural Stability (retropulsion test)

0-normal

1-recovers unaided

2-would fall if not caught

3-falls spontaneously

4-unable to stand

Body Bradykinesia/ Hypokinesia

0-none

1-minimal slowness, could be normal, deliberate character

2-mild slowness and poverty of movement, definitely abnormal, or dec. amp. Of movement

3-moderate slowness, poverty, or small amplitude

4-marked slowness, poverty, or amplitude

18.9. Hamilton Rating Scale for Depression (HAM-D)

HAMILTON DEPRESSION RATING SCALE (HAM-D)

(To be administered by a health care professional)

Patient Name Today's Date

The HAM-D is designed to rate the severity of depression in patients. Although it contains 21 areas, calculate the patient's score on the first 17 answers.

1. DEPRESSED MOOD
(Gloomy attitude, pessimism about the future, feeling of sadness, tendency to weep)
0 = Absent
1 = Sadness, etc.
2 = Occasional weeping
3 = Frequent weeping
4 = Extreme symptoms

2. FEELINGS OF GUILT
0 = Absent
1 = Self-reproach, feels he/she has let people down
2 = Ideas of guilt
3 = Present illness is a punishment; delusions of guilt
4 = Hallucinations of guilt

3. SUICIDE
0 = Absent
1 = Feels life is not worth living
2 = Wishes he/she were dead
3 = Suicidal ideas or gestures
4 = Attempts at suicide

4. INSOMNIA - Initial
(Difficulty in falling asleep)
0 = Absent
1 = Occasional
2 = Frequent

5. INSOMNIA - Middle
(Complains of being restless and disturbed during the night. Waking during the night.) 0 = Absent
1 = Occasional
2 = Frequent

6. INSOMNIA - Delayed
(Waking in early hours of the morning and unable to fall asleep again)
0 = Absent
1 = Occasional
2 = Frequent

7. WORK AND INTERESTS
0 = No difficulty
1 = Feelings of incapacity, listlessness, indeci- sion and vacillation
2 = Loss of interest in hobbies, decreased social activities
3 = Productivity decreased
4 = Unable to work. Stopped working because of present illness only. (Absence from work after treatment or recovery may rate a lower score).

8. RETARDATION
(Slowness of thought, speech, and activity; apathy; stupor.)
0 = Absent
1 = Slight retardation at interview
2 = Obvious retardation at interview 3 = Interview difficult
4 = Complete stupor

9. AGITATION
(Restlessness associated with anxiety.)
0 = Absent
1 = Occasional
2 = Frequent

10. ANXIETY - PSYCHIC
0 = No difficulty
1 = Tension and irritability
2 = Worrying about minor matters
3 = Apprehensive attitude
4 = Fears

11. ANXIETY - SOMATIC
Gastrointestinal, indigestion Cardiovascular, palpitation, Headaches Respiratory, Genito-urinary, etc.
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

12. SOMATIC SYMPTOMS - GASTROINTESTINAL
(Loss of appetite , heavy feeling in abdomen; constipation)
0 = Absent
1 = Mild
2 = Severe

13. SOMATIC SYMPTOMS - GENERAL
(Heaviness in limbs, back or head; diffuse backache; loss of energy and fatiguability)
0 = Absent
1 = Mild
2 = Severe

14. GENITAL SYMPTOMS
(Loss of libido, menstrual disturbances)
0 = Absent
1 = Mild
2 = Severe

15. HYPOCHONDRIASIS
0 = Not present
1 = Self-absorption (bodily)
2 = Preoccupation with health
3 = Querulous attitude
4 = Hypochondriacal delusions

16. WEIGHT LOSS
0 = No weight loss
1 = Slight
2 = Obvious or severe

17. INSIGHT
(Insight must be interpreted in terms of patient's understanding and background.)
0 = No loss
1 = Partial or doubtfull loss
2 = Loss of insight

TOTAL ITEMS 1 TO 17: _____

0 - 7 = Normal
8 - 13 = Mild Depression
14-18 = Moderate Depression
19 - 22 = Severe Depression
≥ 23 = Very Severe Depression

18. DIURNAL VARIATION
(Symptoms worse in morning or evening. Note which it is.)
0 = No variation
1 = Mild variation; AM ( ) PM ( )
2 = Severe variation; AM ( ) PM ( )

19. DEPERSONALISATION AND DEREALISATION
(feelings of unreality, nihilistic ideas)
0 = Absent
1 = Mild
2 = Moderate
3 = Severe
4 = Incapacitating

20. PARANOID SYMPTOMS
(Not with a depressive quality)
0 = None
1 = Suspicious
2 = Ideas of reference
3 = Delusions of reference and persecution
4 = Hallucinations, persecutory

21. OBSESSIONAL SYMPTOMS
(Obsessive thoughts and compulsions against which the patient struggles)
0 = Absent
1 = Mild
2 = Severe

18.10. Brief Psychiatric Rating Scale Positive Subscale (BPRS+)

Overall JE, Gorham DR (1962). The brief psychiatric rating scale. Psychological Reports 1962 vol. 10, pp799-812

BRIEF PSYCHIATRIC RATING SCALE POSITIVE SUBSCALE (BPRS+)

BPRS+ includes just the 4 questions shaded in gray color (#4, #11, #12, and #15)

Please enter the score for the term which best describes the patient's condition.
0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1. SOMATIC CONCERN Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	SCORE ☐	10. HOSTILITY Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (Rate attitude toward interviewer under "uncooperativeness").	SCORE ☐
2. ANXIETY Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety	SCORE ☐	11. SUSPICIOUSNESS Brief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.	SCORE ☐
3. EMOTIONAL WITHDRAWAL Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation	SCORE ☐	12. HALLUCINATORY BEHAVIOR Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different fro	SCORE ☐
4. CONCEPTUAL DISORGANIZATION Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	SCORE ☐	13. MOTOR RETARDATION Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the ba	SCORE ☐
5. GUILT FEELINGS Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	SCORE ☐	14. UNCOOPERATIVENESS Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.	SCORE ☐

6. TENSION Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	SCORE ☐	15. UNUSUAL THOUGHT CONTENT Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.	SCORE ☐
7. MANNERISMS AND POSTURING Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	SCORE ☐	16. BLUNTED AFFECT Reduced emotional tone, apparent lack of normal feeling or involvement.	SCORE ☐
8. GRANDIOSITY Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	SCORE ☐	17. EXCITEMENT Heightened emotional tone, agitation, increased reactivity.	SCORE ☐
9. DEPRESSIVE MOOD Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.	SCORE ☐	18. DISORIENTATION Confusion or lack of proper association for person, place or time.	SCORE ☐

Instructions for the Clinician:

The Brief Psychiatric Rating Scale (BPRS) is a widely used instrument for assessing the positive, negative, and affective symptoms of individuals who have psychotic disorders, especially schizophrenia. It has proven particularly valuable for documenting the efficacy of treatment in patients who have moderate to severe disease.
It should be administered by a clinician who is knowledgeable concerning psychotic disorders and able to interpret the constructs used in the assessment. Also considered is the individual's behavior over the previous 2-3 days and this can be reported by the patient's family.
The BPRS consists of 18 symptom constructs and takes 20-30 minutes for the interview and scoring. The rater should enter a number ranging from 1 (not present) to 7 (extremely severe). 0 is entered if the item is not assessed.
First published in 1962 as a 16-construct tool by Drs. John Overall and Donald Gorham, the developers added two additional items, resulting in the 18-item scale used widely today to assess the effectiveness of treatment.

BPRS Scoring Instructions:
Sum the scores from the 18 items. Record the total score and compare the total score from one evaluation to the next as the measure of response to treatment.

18.11. Montreal Cognitive Assessment (MoCA)

Montreal Cognitive Assessment
(MoCA)
Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: “Copy this drawing as accurately as you can, in the space below”.

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: “Draw a **clock**. Put in all the numbers and set the time to 10 after 11”.

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: "Tell me the name of this animal".

Scoring: One point each is given for the following responses: (1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them". Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time." Put a check in the allocated space for each word the subject recalls after the second trial.

At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "I will ask you to recall those words again at the end of the test."

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span: Administration: Give the following instruction: "I am going to say some numbers and when I am through, repeat them to me exactly as I said them". Read the five number sequence at a rate of one digit per second.

Backward Digit Span: Administration: Give the following instruction: "Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order." Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: "Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop." Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: "I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: **I only know that John is the one to help today."** Following the response, say: "Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: **The cat always hid under the couch when dogs were in the room.**"

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: "Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop."

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: "Tell me how an orange and a banana are alike". If the subject answers in a concrete manner, then say only one additional time: "Tell me another way in which those items are alike". If the subject does not give the appropriate response (fruit), say, "Yes, and they are also both fruit." Do not give any additional instructions or clarification.

After the practice trial, say: "Now, tell me how a train and a bicycle are alike". Following the response, administer the second trial, saying: "Now tell me how a ruler and a watch are alike". Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: "I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember. Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: **Allocate 1 point for each word recalled freely without any cues**.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "Which of the following words do you think it was, NOSE, FACE, or HAND?"

Use the following category and/or multiple-choice cues for each word, when appropriate:
FACE: category cue: part of the body multiple choice: nose, face, hand
VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet
CHURCH: category cue: type of building multiple choice: church, school, hospital
DAISY: category cue: type of flower multiple choice: rose, daisy, tulip
RED: category cue: a colour multiple choice: red, blue, green
Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

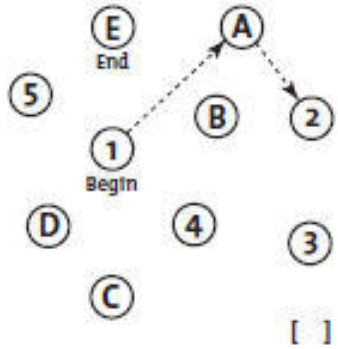
Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: "Tell me the [year, month, exact date, and day of the week]." Then say: "Now, tell me the name of this place, and which city it is in."
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

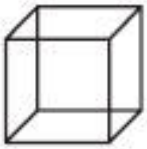
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube [ ]



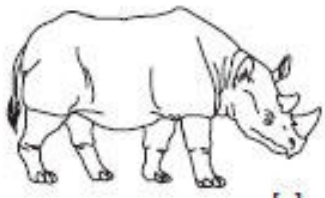
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

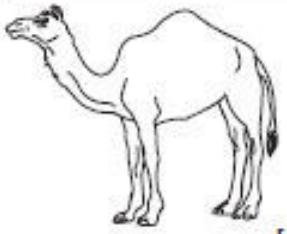
__/5

NAMING

[ ]



[ ]



[ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD Version November 7, 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

18.12. Columbia-Suicide Severity Rating Scale (C-SSRS)

Columbia–Suicide Severity Rating Scale

Scoring and Data Analysis Guide

****

Contributors: Mary E. Nilsson, Shailaja Suryawanshi, Cristiana Gassmann-Mayer, Sarah Dubrava, Paul McSorley, and Kaihong Jiang.

Introduction

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. This guide outlines the proposed safety outcomes and statistical analysis strategy for the C-SSRS for an individual clinical trial.

The actual tables or combination of tables may vary to be consistent with a sponsor's standards, or to be consistent with the needs of a particular regulatory agency/division.

As such this document serves as a general guideline and is not a proposal for mandatory analyses involving the C-SSRS. When analyzing the C-SSRS across studies, the same safety outcomes can be used. However, different statistical methodology would apply to combining data across studies, and is not discussed in this document. The briefing document for the 13 December 2006 Food and Drug Administration (FDA) Advisory Committee Meeting contains a discussion of meta-analytical methods to consider when analyzing suicide-related outcomes across studies (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-index.htm). The CSSRS may also be used to assess efficacy, but specific guidance related to efficacy assessment will be a topic for a separate document.

As noted in the August 2012 draft guidance titled "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials", the FDA has adopted the 11 categories defined in the C-SSRS (five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent) as their standard.

Some data collected on the C-SSRS are not included in these proposed displays for safety analysis (e.g., suicidal behavior lethality and suicidal ideation intensity), but are used for individual clinical management, safety monitoring, or other research purposes.

Analysis Set:

The analysis set should be defined consistently with the sponsor's standards for the safety analysis set. Frequently, this means including patients who have been exposed to at least one dose of study drug. When analyzing the C-SSRS, it is recommended to include patients having at least 1 post-baseline C-SSRS measurement, regardless of whether they had a baseline C-SSRS measurement. For some

analyses of the C-SSRS (e.g., treatmentemergent assessments and shift tables), a pre-treatment C-SSRS measurement is also required.

Outcomes:

There is current debate on whether suicidal ideation and suicidal behavior should be combined and analyzed as a single outcome. Researchers agree on the need for having analyses that keep suicidal ideation and suicidal behavior separate, but disagree on whether there is value to having any outcome that combines them. This document currently includes the combined outcomes measure.

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (athough not suicide-related) and has a binary response (yes/no).

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each patient and is used for determining treatment emergence.

- Suicidal **Ideation** Score: The maximum suicidal ideation category (1-5 on the CSSRS) present at the assessment. Assign a score of 0 if no ideation is present.

Endpoints:

Composite endpoints based on the above categories are defined below.

- Suicidal **ideation**: A “yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal **behavior**: A “yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

- Suicidal **ideation or behavior**: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

Comparative endpoints of interest are defined below. "Treatment emergence" is used for outcomes that include events that first emerge or worsen. "Emergence" is used for outcomes that include events that first emerge.

- Treatment-emergent **suicidal ideation** compared to recent history: An increase in the maximum suicidal ideation score during treatment from the maximum suicidal ideation category during a specified pre-treatment period (C-SSRS scales taken during the specified pre-treatment period; excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).
- Treatment-emergent **serious suicidal ideation** compared to recent history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0-3) during a specified pre-treatment period (C-SSRS scales taken during the specified pretreatment period; excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).
- Emergence of **serious suicidal ideation** compared to recent history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from no suicidal ideation (scores of 0) during a specified pre-treatment period (CSSRS scales taken during the specified pre-treatment period; excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).
- Improvement in **suicidal ideation** at a time point of interest compared to baseline: An improvement in this endpoint can be considered as a decrease in suicidal ideation score at the time point of interest (e.g., the last measurement during treatment) from the baseline measurement (e.g., the measurement taken just prior to treatment. This analysis should only be performed for studies in which a baseline C-SSRS can be defined (i.e., having improvement from the worse event over a lifetime is not clinically meaningful).
- Emergence of **suicidal behavior** compared to all prior history: The occurrence of suicidal behavior (Categories 6-10) during treatment from not having suicidal behavior (Categories 6-10) prior to treatment (includes "lifetime" and/or "screening" scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last Visit C-SSRS scales taken prior to treatment).

Additional comparative endpoints for consideration are defined below. These are not necessarily recommended for all treatment programs, but if used, should follow the nomenclature.

- Treatment-emergent suicidal **ideation** compared to all prior history: An increase in the maximum suicidal ideation score during treatment from the maximum suicidal ideation score prior to treatment (includes "lifetime" and/or "screening" scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last Visit C-SSRS scales taken prior to treatment).
- Emergence of **serious suicidal ideation** compared to all prior history: An increase in the maximum suicidal ideation score to 4 or 5 during treatment from no suicidal ideation (scores of 0) prior to treatment (includes "lifetime" and/or "screening" scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last
- Visit C-SSRS scales taken prior to treatment).
- Treatment-emergent serious suicidal ideation compared to all prior history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0-3) prior to treatment (includes "lifetime" and/or "screening" scores from the Baseline CSSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any "Since Last Visit" from the Since Last Visit C-SSRS scales taken prior to treatment).

Outcomes that can be used for clinical management and safety monitoring or potentially for research purposes are described below.

- Suicidal behavior lethality rating taken directly from the C-SSRS
- Suicidal ideation score

  Any score greater than 0 is important and may indicate the need for mental health intervention. The protocol procedures related to clinical care of patients with treatment emergent suicidal ideation and behaviors will then be implemented to ensure proper management of the event and protection of the patient's safety. For example, a score of 4 (active suicidal ideation with some intent to act) or 5 (active suicidal ideation with specific plan and intent) on suicidal ideation can be used to indicate serious suicidal ideation and can be used to trigger further evaluation and immediate contact with patient's mental health practitioner (for non-psychiatry trials this may be used to trigger a prompt referral to a mental health professional) and/or possibly the emergency room.
- Suicidal ideation intensity rating

  Add the five intensity item scores to create a total score (range 0 to 25) to represent the intensity rating. If the patient did not endorse any suicidal ideation set the intensity rating to 0.

Analytical and Statistical Methods:

The sponsor's standard approaches to present safety data should be used consistently.

Suicidal ideation and suicidal behavior are relatively rare events in individual, doubleblind, controlled clinical trials, except possibly for a population particularly susceptible to this safety risk. In general, no formal statistical hypothesis testing is recommended for individual studies as only few events are typically observed and descriptive summaries will then suffice.

See the mock tables, the mock listing, and mock figure for suggested summaries and presentation of the data. Note that these mock tables can be easily extended to include multiple treatment groups/comparisons as needed. Tables should be modified to fit the needs of the specific analyses performed.

For very small studies (e.g., Phase 1 studies), or indications where suicide-related events are expected to be rare, it may be sufficient to plan on providing a listing only (see Listing 1). Otherwise, Tables 1 and 2 as shown may be provided.

The specific statistical method (or lack of an inferential method) should be consistent with the sponsor's standards. When inferential analyses are not performed the p-value column should be eliminated. Tables 3-4 (options for a shift table) will likely be used when there are findings to understand in more detail and/or when the expected number of suicide-related events is large either due to having a large study or having a population at high risk. A graphical presentation, for example a stacked bar chart, may also be used when appropriate (see Figure 1).

A summary of pre-treatment data is generally desirable and can be added to existing planned tables for patient characteristics (e.g., percent of subjects with lifetime suicidal ideation, baseline suicidal ideation, lifetime suicidal behavior, baseline suicidal behavior, lifetime self-injurious behavior without suicidal intent, and baseline self-injurious behavior without suicidal intent). Alternatively, if all categories of suicidal ideation and suicidal behavior are of interest for pre-treatment summaries, Table 1 can be repeated for providing a summary of lifetime outcomes and again for baseline outcoments. The specific timeframe used for defining baseline will need to be defined.

When inferential statistics are used, methods for consideration include: the Miettinen and Nurminen method, an unconditional, asymptotic method; the Fisher's exact test; 95% confidence intervals (CIs) based on Wilson's score method; and forest plots to present effect across treatment arms or subgroups of interest.

A further consideration for inferential analysis may be the requirement that at least 4 patients in any treatment group exhibit the event. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse

experiences. Appropriate cautionary statements on the interpretation of inferential statistics for purposes of summarizing information or signaling trends should be made.
Methods for assessing dose-response relationships should be consistent with the sponsor's standards.
Calculating and presenting incidence rates (e.g., n/patient-years) should be considered, especially for studies with long patient exposures and expected differential drop-out rates between treatment groups.
In long-term trials where the suicidality scale is administered frequently, a time-to-event analysis where the event is any suicidal event (either ideation or behavior whichever occurs first) can be performed using methods such as Kaplan-Meier method, log-rank test, generalized Wilcoxon test and Cox proportional hazards model adjusting for a limited number of covariates. It is noted that event type-specific analysis (i.e., timeto-first-ideation and time-to-first-behavior analyses) may not be interpretable due to the presence of-competing risks and informative censoring. In situations that warrant an assessment by age, gender and/or other risk factors summary statistics of scores on suicidality endpoints of interest can be presented by visit. For studies with longer duration, scores can be summarized by visit or time period (treatment phase, posttreatment phase etc.).
Based on the individual program strategy, active treatment groups may be pooled for comparisons to placebo/active comparator, or for performing all pair-wise dose comparisons. Analysis methods for assessing effects over several trials, subgroups or indications are presented in.
Note that missing data should not be imputed.

Table 1: Number of Patients with Suicidal Ideation, Suicidal Behavior, and Self-Injurious Behavior without Suicidal Intent Based on the C-SSRS During Treatment; [Define Analysis Set]

Events during treatment	Drug Name N=xx n (%)	Comparator Name N=xx n (%)	p-values[a] (to compare percentages)
Suicidal Ideation (1-5)	x (%)	x (%)	0.xxx
1) Wish to be dead	x (%)	x (%)	
2) Non-specific active suicidal thoughts	x (%)	x (%)	
3) Active suicidal ideation with any methods (not plan) without intent to act	x (%)	x (%)	
4) Active suicidal ideation with some intent to act, without specific plan	x (%)	x (%)	
5) Active suicidal ideation with specific plan and intent	x (%)	x (%)	
Suicidal Behavior (6-10)	x (%)	x (%)	0.xxx
6) Preparatory acts or behavior	x (%)	x (%)	
7) Aborted attempt	x (%)	x (%)	
8) Interrupted attempt	x (%)	x (%)	
9) Non-fatal suicide attempt	x (%)	x (%)	
10) Completed suicide	x (%)	x (%)	
Suicidal Ideation or Behavior (1-10)	x (%)	x (%)	0.xxx
Self-injurious behavior without suicidal intent	x (%)	x (%)	

NOTE: the p-value column should be eliminated when inferential analyses are not performed depending on the Sponsor's standard approach for safety data presentations.

[a] p-values are from [specify test].

Notes: N = number of enrolled patients with at least one post-baseline C-SSRS assessment. In this table, n and (%) refer to the number and percent of patients who experience the event at least once during treatment. For the composite endpoint of suicidal ideation (1-5), n and (%) refer to the number and percent of patients who experience any one of the five suicidal ideation events at least once during treatment. For the composite endpoint of suicidal behavior (6-10), n and (%) refer to the number and percent of patients who experience any one of the five suicidal behavior events at least once during treatment. For the composite endpoint of suicidal ideation or behavior (1-10), n and (%) refer to the number and percent of patients who experience any one of the ten suicidal ideation or behavior events at least once during treatment.

Table 2: Number of Patients with Suicide-Related Treatment-Emergent Events Based on the C-SSRS During Treatment; [Define Analysis Set]

	Drug Name		Comparator Name		
Treatment-emergent (TE) Events	**N**	**n (%)**	**N**	**n (%)**	**p-values[a]**
TE suicidal ideation (1-5) compared to recent history[b]	xx	x (%)	xx	x (%)	0.xxx
TE serious suicidal ideation (0-3 to 4-5) compared to recent history[c]	xx	x (%)	xx	x (%)	0.xxx
Emergence of serious suicidal ideation (0 to 4-5) compared to recent history[d]	xx	x (%)	xx	x (%)	0.xxx
Improvement in suicidal ideation at endpoint compared with baseline[e]	xx	x (%)	xx	x (%)	0.xxx
Emergence of suicidal behavior (6-10) compared to all prior history[f]	xx	x (%)	xx	x (%)	0.xxx

Notes: For the composite endpoint of suicidal ideation (1-5), n and (%) refer to the number and percent of patients who experience treatment-emergent suicidal ideation during treatment. For the composite endpoint of suicidal behavior (6-10), n and (%) refer to the number and percent of patients who experience treatment-emergent suicidal behavior during treatment.

[a] p-values are from [specify test].
[b] N=Number of enrolled patients with at least one post-baseline suicidal ideation score and whose maximum C-SSRS suicidal ideation score during the comparison period is non-missing and <5.
[c] N=Number of enrolled patients with at least one post-baseline suicidal ideation score and whose maximum C-SSRS suicidal ideation score during the comparison period is 0-3.
[d] N=Number of enrolled patients with at least one post-baseline suicidal ideation score and whose maximum C-SSRS suicidal ideation score during the comparison period is 0.
[e] N=Number of enrolled patients whose suicidal ideation score is non-missing and >0 just prior to treatment.
[f] N=number of enrolled patients with at least one post-baseline C-SSRS assessment and who did not have suicidal behavior (6-10) prior to treatment.

NOTE: the p-value column should be eliminated when inferential analyses are not performed depending on the Sponsor's standard approach for safety data presentations.

Table 3. Shift-table to Demonstrate Changes in C-SSRS Categories from Baseline During Treatment; [Define Analysis Set]

Treatment	Baseline Category	Treatment Category		
		No suicidal ideation or behavior n (%)	Suicidal ideation n (%)	Suicidal behavior n (%)
Drug Name (N=xxx)	No suicidal ideation or behavior	x (%)	x (%)	x (%)
	Suicidal Ideation	x (%)	x (%)	x (%)
	Suicidal Behavior	x (%)	x (%)	x (%)
Comparator Name (N=xxx)	No suicidal ideation or behavior	x (%)	x (%)	x (%)
	Suicidal Ideation	x (%)	x (%)	x (%)
	Suicidal Behavior	x (%)	x (%)	x (%)

Notes: N = number of patients with a baseline and post-baseline C-SSRS assessment, n = number of patients in category. % = 100*n/N.
Baseline refers to [specify definition]
Suicidal Ideation includes any one of the five suicidal ideation events (Categories 1-5). Suicidal behavior includes any one of the five suicidal behavior events (Categories 6-10).
Each patient is counted in one cell only. Patients with both Suicidal Ideation and Suicidal Behavior are included in the Suicidal Behavior category.

Table 4. Shift-table to Demonstrate Changes in C-SSRS Suicidal Ideation Scores from Baseline During Treatment; [Define Analysis Set]

Treatment	Maximum Baseline Score	Maximum Suicidal Ideation Score During Treatment					
		0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)
Drug Name (N=xxx)	0	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	1	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	2	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	3	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	4	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	5	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
Comparator Name (N=xxx)	0	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	1	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	2	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	3	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	4	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)
	5	x (%)	x (%)	x (%)	x (%)	x (%)	x (%)

Notes: N = number of patients with a baseline and post-baseline C-SSRS suicidal ideation score, n = number of patients in category,
% = 100*n/N.
Baseline refers to [specify definition]; Maximum refers to the maximum C-SSRS suicidal ideation score during treatment (0 = least severe, 5 = most severe) where 0=No Suicidal Ideation, 1=Wish to be Dead, 2=Non-specific Active Suicidal Thoughts, 3=Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, 4=Active Suicidal Ideation with Some Intent to Act, without Specific Plan, and 5=Active Suicidal Ideation with Specific Plan and Intent.

Listing 1: Listing of Subjects with Suicidal Ideation, Suicidal Behavior, or Self-Injurious Behavior without Suicidal Intent Based on the C-SSRS During Treatment[a]; [Define Analysis Set]

			Suicidal Ideation					Suicidal Behavior					
Patient	**Trt**	**Visit**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Self-Inj Beh wo SI**
xxxx			Y	Y	Y	N	Y	N	N	N	N	N	N

Note: Only patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent are displayed. For patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent at any time, data from all visits are displayed. Self-Inj Beh wo SI = Self-injurious Behavior without Suicidal Intent.

[a] Key: 1=Wish to be Dead, 2=Non-specific Active Suicidal Thoughts, 3=Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, 4=Active Suicidal Ideation with Some Intent to Act, without Specific Plan, 5=Active Suicidal Ideation with Specific Plan and Intent, 6=Preparatory Acts or Behavior, 7=Aborted Attempt, 8= Interrupted Attempt, 9=Actual Attempt (non-fatal), 10=Completed Suicide.

18.13. Fatigue Severity Scale (FSS)

Fatigue Severity Scale (FSS) of Sleep Disorders

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you. The FSS is a short questionnaire that requires you to rate your level of fatigue.

The FSS questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

- A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.

- It is important that you circle a number (1 to 7) for every question.

FSS Questionnaire							
During the past week, I have found that:	**Disagree <--------> Agree**						
My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
Exercise brings on my fatigue.	1	2	3	4	5	6	7
I am easily fatigued.	1	2	3	4	5	6	7
Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7
	Total Score:						

18.14. Berlin Questionnaire (BQ)

CATEGORY 1

1 Complete the following:
height_____ age_____
weight_____ sex_____

2 Do you snore?
- ☐ yes
- ☐ no
- ☐ don't know

If you snore:

3 Your snoring is?
- ☐ slightly louder than breathing
- ☐ as loud as talking
- ☐ louder than talking
- ☐ very loud, can be heard in adjacent rooms

4 How often do you snore?
- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

5 Has your snoring ever bothered other people?
- ☐ yes
- ☐ no

6 Has anyone noticed that you quit breathing during your sleep?
- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ nearly or nearly never

CATEGORY 2

7 How often do you feel tired or fatigued after your sleep?
- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

8 During your wake time, do you feel tired, fatigued or not up to par?
- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

9 Have you ever nodded off or fallen asleep while driving a vehicle?
- ☐ yes
- ☐ no

If yes, how often does it occur?
- ☐ nearly every day
- ☐ 3-4 times a week
- ☐ 1-2 times a week
- ☐ 1-2 times a month
- ☐ never or nearly never

CATEGORY 3

10 Do you have high blood pressure?
- ☐ yes
- ☐ no
- ☐ don't know

BMI =

Berlin Questionnaire Scoring:

Scoring Questions:	Any answer within box outline is a positive response
Scoring Categories:	Category 1 is positive with 2 or more positive responses to questions 2-6
	Category 2 is positive with 2 or more positive responses to questions 7-9
	Category 3 is positive with 1 or more positive response and/or a BMI >30
Final Results:	2 or more positive categories indicates a high risk of obstructive sleep apnea

Netzer, N. C., R. A. Stoohs, et al. (1999). "Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome." Ann Intern Med 131(7): 485-491 [(41)].

18.15. Schedule of Assessments

VISITS Week	Screening period (W-4)	Baseline period (W-1)	Randomisation Visit 1	Treatment Visit 2 (W2)		Treatment Visit 3 or Early Term (W6)	FUP (1)
Study days (referred to D1 [Day of first administration] (allowed deviation days in brackets)	**D-28 to D-8**	**D-7 to D-2**	**D-1**	**D14 (± 2)**	**D35 (2)**	**D42 (± 3)**	**+D28 (± 2)**
Informed consent	X						
Inclusion and exclusion criteria	X	X(3)	X(3)				
Demographics	X						
Medical history and previous medication	X(4)	X					
Concurrent Medical Condition	X						
Physical examination	X					X	
Vital signs (including heart rate and blood pressure)	X			X		X	X
Pregnancy test	X		X(5)			X	
Laboratory tests	X	X(6)				X	
Pharmacogenomic blood sample	X(7)						
Electrocardiogram	X					X	
Eye examination	X					X(8)	
Epworth Sleepiness Scale (ESS)	X		X	X		X	
Scales for Outcome in Parkinson's Disease Sleep (SCOPA-Sleep)			X	X		X	
Parkinson's Disease Sleep Scale (PDSS-2)			X	X		X	
Fatigue Severity Scale (FSS)	X					X	
Berlin Questionnaire (BQ)	X						
Unified Parkinson's Disease Rating Scale (UPDRS Part III)(9)			X	X		X	
Cognitive Impairment (Montreal Cognitive Assessment – MoCA	X					X	
Hamilton Rating Scale for Depression (HAM-D)(10)	X			X		X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) (10)	X			X		X	X
Brief Psychiatric Rating Scale positive subscale (BPRS+)(10)	X			X		X	X
Maintenance of Wakefulness Test (MWT)(11)		X				X	
Polysomnography(11)		X				X	
Free living activity (GENEActiv ®)(2)		X	X		X	X	
Randomisation			X				
Treatment intake(12)				X	X	X	
Adverse Events		X	X	X	X	X	X
Concomitant medication		X	X	X	X	X	

(1)All subjects will perform a safety follow-up visit 28 days after last study visit performed.
Additional unscheduled visits may be arranged in case of eye examination, ECG, or adverse event findings.
(2) GENEActiv® to be worn for 7 days continuously on the non-dominant hand day -7 to day -1 at baseline and before the last dose, day 35 to day 42.
(3) Inclusion / Exclusion criteria to be reconfirmed before randomisation
(4) Prohibited medical history will be assessed 4 weeks before Screening D-28
(5) Dipstick pregnancy test to be completed before randomisation
(6) If there are more than 14 days between screening and baseline
(7) Pharmacogenomic blood sample to be obtained in subjects who specifically consented for this exploratory analysis.
(8) The eye examination should be performed after the last treatment on Day 42 and before the follow up safety call.
(9) Subjects will be instructed to have already taken their normally scheduled dose of anti-parkinsonian medication and their IMP prior to arriving at the study site in order to have their UPDRS Part III evaluated in ON (within approximately 1 to 3 hours after taking their levodopa dose). UPDRS in OFF will not be evaluated.
It is recommended that all assessment (s) establishing eligibility for the study to be performed first.
(10) Any positive finding on the HAM-D, C-SSRS, or BPRS+ scales during the study will be referred to a trained mental health professional to be followed.
(11) MWT and Polysomnography will be performed on a minimum of 50% of subjects (all recruited in sites with sleep units available)
(12) Treatment will be taken from Day 1 to Day 42, both inclusive.