CLINICAL STUDY PROTOCOL

"A double blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)"

Study code:	CL07-ORY-2001	Study development phase:	Phase IIb
EudraCT number:	2020-003469-20	Investigational medicinal product:	VAFIDEMSTAT
		Indication:	Borderline Personality Disorder (BPD)
Version:	7.0	Date:	31 March 2023

Sponsor Signatory: [redacted]

Chief Medical Officer of CNS Clinical & Product Development
Oryzon Genomics, S.A.

SIGNATURES

This Clinical Study Protocol is approved by:

SPONSOR'S REPRESENTATIVE:

DATE:

[redacted]

Chief Medical Officer, CNS Clinical & Product Development

Oryzon Genomics, S.A.

PROTOCOL VERSION TRACKING

Version	Date	Changes	Reason for change
1.0	**31 Jul 2020**	**N/A**	N/A
2.0	**08 Oct 2020**	**NON-RELEVANT MODIFICATION**	AEMPS REQUEST
		Correction of exclusion criteria nº7	
3.0	**27 Nov 2020**	**RELEVANT MODIFICATION**	
		Typos corrected throughout the document	Grammar
		Modification to study endpoints' evaluation times	Changes on statistical methods
		A separate genotyping consent will not be used	Unified consent process
		A window of ±5 days has been added at screening	To detect protocol deviations
		Urine drug screening will be performed at each visit	To allow for short delays or small disruptions in the processing of lab samples
		Sample size corrected to 156 participants, 78 participants per arm and 124 participants expected to complete the trial.	New statistical analysis aims for an effect size of 0.45 instead of 0.5.
		Screening visit can be split between 2 days	To allow extra time for all the screening procedures
		Sentence "Only participants that fulfil eligibility criteria (...) will be randomized to the study" moved to section 7.7.2	Clarification of the conditions for a participant to be randomized
		Addition of section 7.7.10 Unscheduled visits	To allow extra visits for safety reasons or kit replacement needs
		7.2.8 text clarifications on AAPI-CR scale	N/A
		Sections 7.6.1 and 7.6.2 have been modified.	Clarify storage and sample analysis
		9. Statistical Methods section has been amended with the following changes: • PPS analysis definition modified • Clarification of section 9.3.2 regarding the handling of missing values • Efficacy Analysis will use MMRM instead of ANCOVA plus new fixed factors • Sensitivity analysis section clarified • Interim analysis will be performed after the first 90 evaluable patients instead of 70 and study can be stopped for futility if the power is too low	Changes in study statistical considerations
		Section "10.7 COVID-19 Contingency Plan" added.	To prevent missing data in a covid-19 surge scenario
		Addition of 3 examples that define a major protocol deviation in section 10.9	Clarify what situations could lead to a major protocol deviation
4.0	**07 April 2021**	**RELEVANT MODIFICATION**	
		Typos corrected throughout the document	Grammar
		Inclusion criteria # 4: Added "**Outpatient**..."	Clarification of the conditions for a participant to be included in the study
		Inclusion criteria # 5: Deleted	

Inclusion criteria # 6 (former # 7): Change in BMI gap from 18.5 kg/m^2 - 30 kg/m^2 to 18.5 kg/m^2 **- 35 kg/m^2**	
Inclusion criteria # 11 (former # 12): Addition of "…**permitted** regimen of background therapy …" and two clarifications added in brackets	
Addition of "**Regulatory Authorities**/Competent Authorities…" and its clarification (-**i.e.: European Competent Authorities and FDA**-) in Synopsis (Blinded Protocol), Section 4.3 (Premature Termination)	To be clearer and more inclusive of both, EU and US, Regulatory Authorities
Table 1: Change (**decrease**) in the schedule of administrations at study visits of the Brief Assessment of Cognition (**BAC**) & the Agitation-Aggression Psychiatric Inventory-Clinician Report (**AAPI-CR**) scales, from being administered at every visit from V2 (Baseline) to V9 (i.e., 8 administrations in total) to being **administered 5 times (BAC) and 6 times (AAPI-CR)**	To reduce patient burden (as per PI feed-back) and facilitate compliance with study visits and study completion
Foot Note (1) in Table 1: Change *Screening (V1)* for **Baseline (V2)**, as the reference for visits' schedule	To provide the correct reference for the schedule of visits
Addition of a paragraph on **Reproductive and developmental toxicology** in Section 1.3. (Non-clinical Pharmacology & Toxicology Studies)	To provide a more accurate dose justification from a reproductive toxicology perspective
REIMAGINE study (Phase IIa) Conclusion in Section 1.4.2. has been edited	To be aligned with conclusions reported in the CSR
Deletion of *in a younger and healthier BPD population* from: "Therefore, it is considered appropriate to evaluate the 1.2 mg/day dose of vafidemstat ~~in a younger and 'healthier' BPD population~~ for this Phase IIb trial." in Section 1.6. (Potential Risks & Benefits)	To provide a more accurate general dose justification
Modification of sentence, addition of the word *blinded*: "Finally, **blinded** medical monitors will review safety and efficacy data throughout the trial in order to assure the study safety and a continuous risk/benefit assessment." (last paragraph, Section 1.6. Potential Risks & Benefits)	To prevent unblinding of study results throughout the trial
Addition of "**Institutional Review Boards (IRBs)**" to Independent Ethics Committee(s) (IECs)…"and "**Regulatory Authorities (RAs)**" to "Competent Authorities (CAs)" in Section 4.3. (Premature Termination of the Study), as well as in Section 10.6. Deletion of last paragraph sentence in relation to European Directive 2001/20/EC in Section 4.3. Deletion of "... *authorized by a Qualified Person (QP) in the European Union (EU) will be issued*." from first paragraph in Section 5.1.2. (Identity of IMP) Addition of "…**and US CFR Title 21 – Part 210**" in section 5.1.3. (Packaging and Labelling of IMP) and change of "Royal decree (RD)" by "… **pertinent EU and US regulations**" in Section 5.1.4.	To be more inclusive of both, EU and US, context regulations
Addition of an explanatory paragraph about the general **Clinical Global Impression (CGI) Scale** in Section 7.2.7 (Efficacy Assessments)	Clarification of the characteristics of this scale
Addition of the **Columbia-Suicide Severity Rating Scale (C-SSRS)** to the list of safety assessments in Section 7.3 (Safety Assessments)	Clarification of the safety purpose of this scale
	To provide accurate information on Pharmacovigilance

		Addition of "**as well as all AEs judged as unassessable /unclassifiable**" for AEs to be considered as related to IMP in section 8.2.2 (Causality) Correction of who is responsible for submission of SUSAR: [redacted] instead of "Drug Safety at [redacted], is to handle the submission of SUSARs in Section 8.2.3 (Follow-up of participants after AEs)	To avoid overreporting as AEs any non-clinically significant decrease in platelet & neutrophils count
		Addition of a **cut-off** to the definition of **platelet & neutrophils' count decrease** in relation to AEs reporting, in Section 8.4 (AEs of special interest)	Safety reporting clarification
		Addition of "**Overdose should be reported as an adverse event**" in Section 8.5 (Precautions/Overdose)	To improve & implement a more precise and appropriate statistical methodology
		Statistical Methods, Section 9., has been amended with the following changes and clarifications: • Full Analysis Set (**FAS**) will be used for the **primary efficacy analysis** instead of the per protocol set (PPS) population. • Clarification of the **handling of missing values** in section 9.3.2 • Details added for the Primary Efficacy Analysis. **Use of the FAS population**, instead of the PPS, in section 9.3.4. • **No imputation of missing values** will be performed for the Secondary Efficacy analysis, section 9.3.5. • Secondary Safety Analyses: time point has been replaced by **visit** for Vital signs, ECG, and Laboratory assessments in section 9.3.5. • Prior and Concomitant Treatment: FAS corrected and replaced by SAF in section 9.3.10. • **Sensitivity analysis strategy** has been fully developed in section 9.3.11. • Addition of **justification** of the **estimand of the effect size** in Determination of Sample Size, section 9.4. • **Interim analysis**, section 9.6.: - IA strategy is further detailed and **'stopping rules'** have been defined - *Evaluable* has been deleted from the timing of Interim analysis: "Interim analysis will be performed after the last of the first 90 ~~evaluable~~ participants has completed the specific week assessments"	
		Addition of **two new references** in relation to the addition of the CGI Scale text and the US Regulation CFR Title 21 – Part 210	To update references' list
5.0	**23 July 2021**	Typos corrected throughout the document.	Grammar
		Inclusion criteria # 11: Deletion of "… Prohibited/Permitted concomitant medication) as per the Summary Of Product Characteristics (SmPC) (i.e., drug labelling)".	To provide clarity in the criteria
		Inclusion criteria #13: Addition of "**Abstinence**" to birth control methods.	To complete information in the criteria
		Exclusion criteria #6: Addition between brackets of "(**including medically indicated illicit drugs**)" and addition of "**prior**" 24 hours prior to a study visit.	To provide clarity in the criteria To provide clarity in the criteria

	Exclusion criteria #12.b: Addition of "**Long half-life benzodiazepines are not allowed**"	To adhere with regulator´s requirements and provide clarity in the criteria
	Exclusion criteria #12.f: Rewriting of the criteria. "**The concomitant use of MAO inhibitors is forbidden 14 days before Screening visit and throughout the study**. The concomitant use of other antidepressants in stable dose for at least 2 months before the Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) ~~when these medications are prescribed as per their labelled indications~~ (**)." (**) The MAO inhibitory activity of vafidemstat has only been observed in vitro; data in humans does not support a MAO inhibitory effect at the doses selected in this protocol. Specifically, the MAO inhibitory activity has not been observed in humans at the vafidemstat therapeutic dose range in clinical trials-to-date, but a potential impact at higher doses (e.g., overdose) cannot be ruled out. Therefore, the concomitant use of other drugs for which cases of serotonin syndrome or hypertensive crisis have been reported when in combination with MAO inhibitors should be carefully monitored. **The concomitant use with these drugs should be done with caution. Participants will be provided with educational material at the Baseline Visit to create awareness around serotonin syndrome**.	
	Exclusion criteria #12.j and Table 3: "guanidine" is replaced by "guanethidine". Guanethidine is not a centrally active antihypertensive drug.	To correct typo and clarify drug category
	Table 2 "Prohibited Concomitant medication": Updated to include **MAO inhibitors**	To adhere with regulator´s requirements
	Table 3 "Allowed Concomitant Medication to be used with caution": Updated.	To align with exclusion criteria 12
	Section 7.7 and Table 1 "Schedule of assessments and procedures". The statement "prior to any blood sample collection" beside vital signs and ECG has been removed throughout the section.	To provide clarity in the criteria
	Section 7.7. "Schedule of assessments and procedures". Addition of new text: "**Participants should be informed at screening and throughout the study that the ingestion of foods with a high tyramine content should be used with caution throughout the study. Study staff will provide the patients with the necessary dietary recommendations as it relates to this study requirement**".	To adhere with regulator´s requirements
	Section 7.7. "Schedule of assessments and procedures": Addition of new text: **"Although no serotoninergic syndrome has been reported thus far in the clinical development of vafidemstat, the study staff should educate the participant at Baseline visit and throughout the study around the symptoms which may be compatible with serotonin syndrome. Additionally, a follow-up call will be required approximately 6-8 hours after the first intake of vafidemstat, as well as at 24 hours and 48 hours to check in on the participant and ensure they are not experiencing any signs or symptoms of serotonin syndrome. The follow-up phone calls are only applicable if the participant is receiving**	To adhere with regulator´s requirements

concomitant treatment with antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SRNIs), tricyclics, tetracyclics, and triazolopyridines). **Participants should be informed at screening and throughout the study that the ingestion of foods with a high tyramine content should be used with caution throughout the study. Study staff will provide the patients with the necessary dietary recommendations as it relates to this study requirement."**	
Table 1 "Schedule of Assessments and Procedures" has been adapted accordingly to previous change described in Section 7.7 to add the **follow-up phone calls after first IMP intake**.	To adhere with regulator´s requirements
Table 1 "Schedule of Assessments and Procedures". Screening and Baseline Days at the top of the table has been changed to match the info on IWRS. The total number of days to complete these two visits (2 weeks) does not change.	To be consistent with information in IWRS system
Section 5.1.6 and section 7.7.2. Visit 2 (Week 0, Day 1) - Baseline Visit. Specification added about "**IMP intake at Visit 2 should occur after** the completion of all study procedures **and the administration of the AAPI-CR and C-SSRS but before the administration of the rest of COAs in order to allow more time for observation of potential serotoninergic syndrome symptoms after first drug intake**"	To adhere with regulator´s requirements
Section 7.3.5. "Laboratory Safety Assessments". Addition of new text: "**Study medication must be halted in all patients who fail to have platelet counts checked at the scheduled timepoints. The study medication should not be resumed until testing has been completed and confirmed to be within an acceptable range**".	To provide clarity on this Safety requirement
Section 1.1. "Disease Background". Conceptual Framework language for BPD and references have been added.	To adhere with regulator´s requirements
Section 1.5. "Study Rationale". Extended justification on agitation and aggression as a core feature of BPD, as well as on previous vafidemstat studies, has been added.	To update the rationale of the study with additional relevant information
Section 7.2.4. "Borderline Personality Disorder Checklist". Further information on the excellent internal consistency, as well as validity of the BPDCL scale added. Validation reference *Calvo et. al., 2018* has been added.	To complete BPDCL background information
Section 7.2.8. "Agitation and Aggression Psychiatric Inventory – Clinician Report". Extended information on the AAPI-CR properties added.	To update AAPI-CR background information
Sections 7.3.5, 7.3.6 and 7.6.1. Volume of blood samples to be collected have been accurately adjusted.	To match the actual volumes required by Central Laboratory
Section 9.3. "Statistical Analysis". Definition of **study estimand** has been added. Also, a **two-sided** test, instead of one-sided will be used at a type I error level of 5%. The estimated effect size changes from 0.45 to 0.51 for the same study sample size (Section 9.4.)	To adhere with regulator´s requirements

		Reference *'Antonijoan, 2021'* has been added in Section 1.4. (Introduction: Clinical Studies).	To update text with a new publication from March 2021
		Table 1 "Schedule of Assessments and Procedures". **For US sites ONLY**, at Visit 9, a subset of participants and the PI at each site will complete **qualitative research data**.	To adhere with regulator´s requirements
		Section 7.4. "Pharmacokinetic Assessment". **For US sites ONLY**, additional PK assessment for **C_{max} calculation**, in a subset of patients, has been added.	To adhere with regulator´s requirements
6.0	**13 May 2022**	Inclusion criteria # 4: Deleted.	Flexibilization of the conditions for a participant to be included in the study
		Exclusion criteria # 6: Addition of "Regarding cannabis, patient self-report of abstinence within 24 hours will be used for inclusion decision-making versus the urine drug test results."	To complete information in the criteria
		Exclusion criteria # 12b: Separate "benzodiazepines" from "Z-drugs" in two sub-criteria ("b" & "c"). Same for Table 3.	To provide clarity in the criteria
		Exclusion criteria # 12g (now "h"): Addition of "In addition, the concomitant use of an atypical antipsychotic medication (e.g., quetiapine) is allowed for the treatment of insomnia AND only at sub-therapeutic dose (e.g., below that typically used to treat schizophrenia)."	Flexibilization of the conditions for a participant to be included in the study
		Table 1, Window period (number of days) between V1 (Screening) and V2 (Baseline) has been increased: "*Screening period can last up to two-weeks with a window of ± 7 days*".	To allow more time between these visits
		Section 5.1.6 "Administration of IMP" clarifications and additional wording included regarding afternoon/evening study visits: "*no fasting conditions are required before IMP intake at the clinic*".	To address study visits scheduled in the afternoon/evening
		Section 6.1.2 "Prohibited/Permitted concomitant meds"- Table 2: washout period prior to V1 (Screening) for short and medium half-life oral benzodiazepines extended from "2" to "8 weeks".	To account for the potential study participants' addiction to benzodiaze-pines
		Section 7.3.5 "Lab Safety Assessments" additional wording included in case the study visit is scheduled in the afternoon/evening, *"fasting conditions will only be required at Visit 2 (Baseline – Day 1), Visit 4 (Day 29), Visit 6 (Day 57) and Visit 8 (Day 85). Fasting conditions should last 6-8 hours before blood sampling"*.	To address study visits scheduled in the afternoon/evening
		Section 7.7 "Schedule of Assessments & Procedures" additional wording included to reflect IMP administration and blood sampling when visits are scheduled in the afternoon/evening	To address study visits scheduled in the afternoon/evening
		"Statistical Methods & Study design" (Section 9 & Section 3.1) has been updated/amended including edits and clarifications. • Interim analysis strategy is further detailed, with "the last of the first" deleted and "the specific week assessments" changed	To reflect suggestions from FDA meeting and written response.
7.0	**31 March 2023**	"Synopsis" and "Statistical Analysis & Determination of Sample Size" (Section 9.3 & Section 9.4) have been updated. The alpha has been adjusted to control for a type 1 error rate of 5%, split evenly between the two endpoints. Assuming an	To reflect suggestions from FDA meeting and written response.

	effect size of 0.51 (mean 510, standard deviation 1000) a sample size of 150 completers (75 per arm) is required for 80% power at a two-sided alpha of 0.025 for each endpoint. Assuming 20% dropout would require 188 patients enrolled.	
	"Table 2. Prohibited Concomitant Medication" Long half-life benzodiazepine treatment minimum wash out period has been modified from "10.5" to "8"5 weeks.	To provide clarity on the use of these concomitant meds.
	"Section 8.2.3. Follow-up of Subject Participants after Adverse Events" has been updated.	To provide clarity on how Adverse Events should be followed.
	The term "subject" has been changed to "participant" when applicable and minor grammatical errors have been corrected.	Grammar
	"Synopsis": Update of study timelines.	

TABLE OF CONTENTS

Section ***Page***

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

A/A	Agitation/Aggression
AAPI-CR	Agitation-Aggression Psychiatric Inventory-Clinician Report
ADHD	Attention Deficit Hyperactivity Disorder
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
AIC	Akaike information criterion
ALP	Alkaline Phosphatase
ALT (SGPT)	Alanine Aminotransferase
AML	Acute Monocytic Leukemia
API	Active Pharmaceutical Ingredient
AR	Adverse Reaction
AST (SGOT)	Aspartate Aminotransferase
BAC	Brief Assessment of Cognition
BDI-II	Beck Depression Inventory – II
BEST	Borderline Evaluation of Severity over Time
BMI	Body Mass Index
BPD	Borderline Personality Disorder
BPDCL	Borderline Personality Disorder Checklist
CA	Competent Authority
CGI-I	Clinical Global Impression of Improvement
CGI-S	Clinical Global Impression of Severity
CI	Confidence Interval
C_{max}	Maximum concentration reached
CK	Creatine Kinase
CNS	Central Nervous System
CREC	Clinical Research Ethics Committee
ClinRO	Clinician Reported Outcome
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia – Suicide Severity Rating Scale
DET	Detection Test
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSUR	Development Safety Update Report
EAE	Experimental Autoimmune Encephalomyelitis
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECT	Electroconvulsive Therapy
EMR	Electronic Medical Records
EoS	End of Study
EU	European Union
FAD	Flavin Adenine Dinucleotide
FAS	Full Analysis Set
fiw	Five times in week
FPI	First Patient In

FUP	Follow-Up
GAD	Generalized Anxiety Disorder
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HBV	Hepatitis B Virus
HCT	Hematocrit
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPMC	Hydroxypropyl Methylcellulose
HR	Heart Rate
ICH	International Conference on Harmonization
IWRS	Interactive Web Response System
IA	Interim Analysis
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IWG	International Working Group's
KDM	Lysine demethylases
LDH	Lactate Dehydrogenase
LLT	Low Level Term
LPLV	Last Patient Last Visit
LPO	Last Patient Out
LSD1/KDM1A	Lysine Specific Demethylase 1
MAO	Monoamine Oxidase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MDD	Major Depressive Disorder
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
MID	Minimum Intolerated Dose
MINI	Mini-International Neuropsychiatric Interview
MTD	Maximum Tolerated Dose
NOAEL	Non-Observed Adverse Effect Dose Level
PerfO	Performance-based Outcome (measure)
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetics
PPS	Per Protocol Set
PROs	Patient-Reported Outcome (measures)
PT	Preferred Term
PTSD	Post-Traumatic Stress Disorder
Q1	25^{th} percentile
Q3	75^{th} percentile
QP	Qualified Person

RBC	Red Blood Cell
RA	Regulatory Authority
RAs/CAs	Regulatory Authorities/Competent Authorities
RNA	Ribonucleic Acid
SAD	Social Anxiety Disorder
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
S-hCG	Serum human Chorionic Gonadotropin
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SSRI	Selective serotonin reuptake inhibitor
SSNRI	Selective serotonin–norepinephrine reuptake inhibitor
SST	Serum Separator Tube
STAI	State-Trait Anxiety Inventory
STAXI-2	State-Trait Anger Expression Inventory 2
STEAE	Serious TEAE
SUSAR	Suspected Unexpected Serious Adverse Reaction
T_{max}	Time necessary to reach the maximum concentration observed
TB	Tuberculosis
TE	Target Engagement
TEAE	Treatment Emergent Adverse Events
TH	Tyrosine Hydroxylase
TMEV	Theiler's Murine Encephalomyelitis Virus
TMS	Transcranial Magnetic Stimulation
TSE	Transmissible Spongiform Encephalopathy
WBC	White blood cell
WHO	World Health Organization

DEFINITION OF TERMS

Competent Authority	A government body or government appointed body that has legal authority to approve or disapprove clinical studies
Eligible Participant	Any potential participant who upon entrance into the treatment phases of the study meets all the inclusion criteria and none of the exclusion criteria set forth in the protocol and had signed a valid institutional review board (IRB)/ independent ethics committee (IEC) approved informed consent form.
Informed Consent Form	The form prepared in conformance with the regulations (as hereinafter defined), in consultation with the Sponsor, and the IRB/IEC (as hereinafter defined), approved by the IRB/IEC and signed by all participants and their parents/legal representatives before they begin to participate in the study.
Regulations	Any relevant legislation, codes or guidelines directly or indirectly related to the conduct of the study including but not limited to (as applicable) the Royal Decree 1090/2015 of 4 December and its transforming legislation in the relevant countries of the European Union, the ICH E6 (R2) of November 2. 016, and/or any other relevant applicable legislation, codes or guidelines issued by any competent authority. For the avoidance of doubt such legislation, codes or guidance shall include those related to the protection and privacy of the personal data of individuals.
Serious Adverse Event	Any untoward medical occurrence that at any dose: • Results in death • Is life-threatening • Requires in- hospitalization or results in prolongation of existing hospitalization • Results in persistent or significant disability/incapacity • Is a congenital anomaly/birth defect • Is another medically important event or reaction Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed in the definition 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 hospitalization, or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.
Study	The clinical study known as protocol CL07-ORY-2001 to be conducted according to the protocol.
Study Center	The location where study-related activities are conducted.

SYNOPSIS

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

TITLE OF THE STUDY

"A double blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)"

OBJECTIVES

Primary Objectives

- To investigate the efficacy of vafidemstat in the treatment of agitation and aggression in adult BPD patients
- To investigate the efficacy of vafidemstat in the treatment of adult BPD patients

Secondary Objectives

- To investigate the effect of vafidemstat in reducing the severity of BPD symptoms in adult patients
- To evaluate the safety of vafidemstat in adult BPD patients

Exploratory Objectives

- To explore the impact of vafidemstat on functional impairment in adult BPD patients
- To explore the impact of vafidemstat on cognition in adult BPD patients
- To evaluate vafidemstat plasma concentrations (pharmacokinetics) as well as vafidemstat's LSD1-target engagement in peripheral blood mononuclear cells (PBMCs) (pharmacodynamics) after treatment

OVERALL STUDY DESIGN

PORTICO is a double blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population. The trial is designed to help inform potential future trials and registration efforts.

Up to188 participants will be enrolled and randomized in a 1:1 ratio (94 participants per arm) to active treatment with vafidemstat (1.2 mg) or placebo to yield an expected 150 completed study participants, since it is anticipated that 20% of participants will drop out of the trial. The sample size may be adjusted upwards based on the outcome of the interim analysis.

PORTICO will involve 9 study visits as reflected in the Schedule of Assessments and Procedures (Table 1). There will be a two-week screening period to ensure study eligibility criteria, followed by 12-week double-blind period of active treatment (vafidemstat 1.2 mg/day) or placebo with study visits every two weeks, then a 2-week safety follow-up participant-blind placebo run-out period (Figure 1).

The study treatment, vafidemstat or placebo, will be administered orally as single capsule in the early morning before the first daily food intake. Participants will be asked to maintain a stable regimen of

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

background therapy, not to initiate any prohibited medications during the trial and to advise their study physician of any medication changes throughout the study.

Considering that psychotherapy is the standard of care for BPD, all enrolled participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration. Participants entering the study cannot start any type of psychotherapy within 3 months prior to enrollment or throughout the trial duration. Specifically, participants receiving psychotherapy before initiating the study need to remain in psychotherapy throughout the trial. However, those participants not receiving psychotherapy before the study should not initiate psychotherapy during the trial. Participants deemed needing immediate or emergent psychotherapy and those initiating psychotherapy during the study will be discontinued from the trial.

INVESTIGATIONAL MEDICINAL PRODUCT

The Sponsor will supply the IMP (vafidemstat). Swedish orange colored size 3 capsules [redacted] are used. [redacted].

Placebo capsules will be supplied as Swedish orange colored size 3 capsules that look identical to the vafidemstat capsules but contain no drug substance.

NUMBER OF PARTICIPANTS

Up to 188 participants will be enrolled and randomized in a 1:1 ratio (94 participants per arm) to vafidemstat (1.2 mg) or placebo. It is expected that 150 study participants will complete the trial.

NUMBER OF STUDY CENTERS

The study will be a global, multicenter clinical trial conducted in approximately 20 study sites in Europe and the US.

INCLUSION AND EXCLUSION CRITERIA

The inclusion and exclusion criteria for participant qualification and enrollment are described below.

Inclusion Criteria

The participant must meet all inclusion criteria:

1. Men and women 18-65 years of age.
2. DSM-5 diagnostic criteria for BPD at least 3 months before the Screening visit. The Mini-International Neuropsychiatric Interview (MINI) will be administered at screening in order to confirm BPD diagnosis, as well as to confirm participant does not meet other relevant exclusion criteria.
3. Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR) Agitation & Aggression (A/A) subscale score of $\geq$ 16 (severity x frequency) summed across the four (4) items comprising the A/A subscale, and the sum of the A/A subscale severity scores $\geq$ 6.
4. Stable living environment for > 6 months before the Screening visit.
5. Body mass index (BMI) of at least 18.5 kg/m^2, but no more than 35 kg/m^2.

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

6. Willing and able to adhere to the prohibitions, restrictions and requirements specified in this protocol.
7. Otherwise, healthy, and medically stable based on medical history.
8. Clinical and neurological examinations and laboratory tests, as well as 12-lead ECG performed during screening that confirms participant is healthy and medically stable.
9. Able to read and write fluently and must have adequate hearing and visual acuity to complete the required testing outlined in this protocol.
10. Stable in their permitted regimen of background therapy (see section 6.1.2) for concomitant medications at the Screening visit. Participants should maintain treatment throughout the study and not initiate any prohibited medications during the trial, as well as agree to inform their study physician of any medication changes throughout the trial.
11. Enrolled participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration. That is, participants receiving psychotherapy will need to have it started at least 3 months before the Screening visit and remain in psychotherapy throughout the trial. Participants not receiving psychotherapy should not initiate psychotherapy during the trial.
12. Fertile male and female participants must use highly efficient contraception, from the Screening visit until 30 days after last dose of the IMP, defined as:

    A method with less than 1% failure rate (e.g., permanent sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner)

    OR

    The use of two methods of contraception (e.g., one barrier method [condom, diaphragm or cervical/vault caps] with spermicide and one hormonal contraceptive [e.g., combined oral contraceptives, patch, vaginal ring, injectable and implants])

    OR

    Abstinence
13. Female participants of childbearing potential must have a negative urine pregnancy test at screening and baseline.
14. Signed informed consent by participant prior to the initiation of any study specific procedure.

Exclusion Criteria

The participant must not meet any of the exclusion criteria:

1. Failure to perform screening or baseline procedures.
2. DSM-5 diagnosis of intellectual disability, autism spectrum disorder, schizophrenia, schizoaffective disorder, bipolar disorder (or related disorders) or major depressive disorder (MDD) with psychosis.
3. Current DSM-5 diagnosis of conduct disorder, anorexia nervosa, bulimia nervosa, binge-eating disorder,

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

oppositional defiant disorder, paranoid personality disorder or obsessive-compulsive disorder.

4. Current DSM-5 diagnosis of panic disorder or post-traumatic stress disorder (PTSD). However, participants with PTSD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), MDD without psychosis, attention deficit hyperactivity disorder (ADHD) are eligible if symptoms have been stable for at least 90 days prior to the Screening visit, these disorders are not the primary focus of treatment, changes in any treatment for these disorders would not likely be required for the duration of the study, and in the investigator´s opinion these disorders will not interfere with the assessment and/or accuracy of the study endpoints.
5. History of moderate or severe substance or alcohol use disorder according to DSM-5, with the exception of nicotine and caffeine, within 6-months before screening.
6. Use of illicit drugs (including medically indicated illicit drugs) for at least one week before Screening and participants unwilling to abstain from use of these substances during the study. Use of alcohol or cannabinoids is not allowed within 24 hours prior to a study visit. Regarding cannabis, patient self-report of abstinence within 24 hours will be used for inclusion decision-making versus the urine drug test results.
7. Hospitalization or medication change for any reason, two months prior to the Screening visit or during the Screening period, that makes the participant medically or mentally unsuitable for trial participation.
8. Clinically significant, advanced or unstable disease that is likely to result in rapid deterioration of the participant's condition or affect their safety during the study, including but not limited to:
    a. Seizure disorders, excluding febrile seizures of childhood
    b. Respiratory insufficiency, the status must be determined as usual clinical practice
    c. Hepatic impairment (serum values of total bilirubin value, alanine aminotransferase [ALT], aspartate aminotransferase [AST] and gamma-glutamyltransferase [ma] 1.5 x upper limit of normal [ULN])
    d. Renal insufficiency (serum creatinine >2mg/dl)
    e. Heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within 6 months before Screening visit)
    f. Hypertension treatment with more than 2 drugs
    g. Atrioventricular block (type II/Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or prolonged QTcF-interval (males >450 msec and females >470 msec)
    h. Uncontrolled diabetes (Hb1Ac >7.5)
    i. Hematological disorders
    j. Platelets <130,000/mm^3 and/or neutrophils <1,800/mm^3
    k. Malignant tumors within the last 5 years other than basal cell or Stage 1 squamous cell carcinoma of the skin
9. Positive results for tuberculosis (the status must be determined as usual clinical practice, i.e., by medical history, signs, and symptoms), Human Immunodeficiency Virus (HIV), Hepatitis C or Hepatitis B (Hepatitis

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

B surface Antigen [HbsAg]) serology obtained at the Screening Visit.

10. Uncontrolled hypo- or hyperthyroidism at Screening Visit, based on laboratory parameters.
11. Clinically significant infection within the previous 30-days (e.g., persistent or acute infection such as a urinary tract infection or upper respiratory infection).
12. Chronic drug intake of:

a) Anticoagulants (only 81 mg/day acetylsalicylic acid is permitted).

b) Short and medium half-life oral benzodiazepines are allowed in occasional short-term prescription use. Participants should not take these medications within 24 hours before any study visit. Long half-life benzodiazepines are not allowed.

c) Z-drugs – i.e.: zaleplon, zolpidem, zopiclone – are allowed in occasional short-term prescription use. Participants should not take these medications within 24 hours before any study visit.

d) Corticosteroids or immunosuppressant (only inhaled or topical suspension are allowed).

e) Myelosuppressive treatments such as chemotherapy and radiation.

f) Medications known to be UGT inhibitors or inducers should be used with caution (*)

- (*) UGT Inhibitors (e.g.: adenine, propofol, flunitrazepam, ertugliflozin, ketoconazole, valproic acid, flurbiprofen, silibinin, sodium aurothiomalate, gemfibrozil, deferasirox, probenecid, amitriptyline, indomethacin, ubrogepant)
- UGT inducers (e.g.: carbamazepine, phenytoin, phenobarbital, rifampicin, testosterone propionate, lamotrigine, primidone, ethinylestradiol, desogestrol, orthosiphon stamineus)

These lists are not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label.

g) The concomitant use of MAO inhibitors is forbidden 14 days before Screening visit and throughout the study. The concomitant use of other antidepressants in stable dose for at least 2 months before the Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) (**).

(**) The MAO inhibitory activity of vafidemstat has only been observed in vitro; data in humans does not support a MAO inhibitory effect at the doses selected in this protocol. Specifically, the MAO inhibitory activity has not been observed in humans at the vafidemstat therapeutic dose range in clinical trials-to-date, but a potential impact at higher doses (e.g., overdose) cannot be ruled out. Therefore, the concomitant use of any other drugs for which cases of serotonin syndrome or hypertensive crisis have been reported when in combination with MAO inhibitors should be carefully monitored. The concomitant use with these drugs should be done with caution. At Baseline Visit, participants will be provided with educational material to create awareness around serotonin syndrome.

h) The concomitant use of typical antipsychotics is forbidden. The concomitant use of atypical antipsychotics in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria). In addition, the concomitant use of an

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

atypical antipsychotic medication (e.g., quetiapine) is allowed for the treatment of insomnia AND only at sub-therapeutic dose (e.g., below that typically used to treat schizophrenia).

i) The concomitant use of mood stabilizers in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) when these medications are prescribed as per their labelled indications.

j) The concomitant use of nootropics; for instance, racetams, amphetamines, methylphenidate, levodopa, atomoxetine, preparations containing Gingko biloba in stable dose for at least 2 months before Screening are allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) when these medications are prescribed as per their labelled indications.

k) The concomitant use of centrally active anti-hypertensive drugs, such as clonidine, a-methyldopa, and guanfacine, as well as guanethidine, in stable dose for at least 2 months before Screening are allowed but should be used with caution.

l) The concomitant use of medications which may have an impact on blood count changes should be used with caution (e.g.: heparin, quinine, quinidine, penicillin, sulfonamides, NSAIDs, anticonvulsants, antirheumatics, oral antidiabetics, gold salts, diuretics rifampicin, ranitidine). This list is not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

m) The concomitant use of platelet aggregation inhibitors should be used with caution (e.g.: COX-2 inhibitors, ADP receptor inhibitors, thromboxane inhibitors). This list is not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

13. Esketamine in the past 90 days before the Screening visit.
14. Electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) in the past 90 days before the screening visit.
15. Any regular intake of medications acting directly on central nervous system that investigator considers relevant to the study.
16. Member or immediate family of the study personnel or subordinate to any of the study personnel.
17. Enrollment in another investigational study or intake of investigational drug within the previous 3 months.
18. Suicide attempt within the 6-month prior to the Screening visit or significant risk of suicide (in the opinion of the investigator, defined as a “yes” to suicidal ideation questions 4 or 5, or answering “yes” to suicidal behavior on the Columbia-Suicide Severity Rating Scale within the past 6-months).
19. Any condition that in the opinion of the investigator makes the participant unsuitable for inclusion in the study.

ENDPOINTS

Primary – Efficacy

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

- To evaluate the difference on the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) from baseline to specific weeks, between the active treatment arm and the placebo arm
- To evaluate the difference on the Borderline Personality Disorder Checklist (BPDCL), from baseline to specific weeks, between the active treatment arm and the placebo arm

Secondary – Efficacy

- To evaluate the change over time on the CGI-S A/A
- To evaluate the change over time on the BPDCL
- To evaluate the difference on the following measures, from baseline to specific weeks, as well as change over time, between the active treatment arm and the placebo arm:
    a) Borderline Evaluation of Severity over Time (BEST)
    b) Beck Depression Inventory – II (BDI-II)
    c) State-Trait Anger Expression Inventory 2 (STAXI-2)
    d) State-Trait Anxiety Inventory (STAI)

Secondary – Safety

- To evaluate the following safety endpoints throughout the study, from baseline to week 14, including:
    a) Number, frequency and severity of Treatment Emergent Adverse Events (TEAEs)
    b) Number, frequency and severity of Serious TEAEs
    c) Number and percentage of withdrawn participants due to TEAEs
    d) Frequency of physical examination parameters, vital signs and ECG parameters of potential clinical concern throughout the study period
    e) Frequency of clinical laboratory parameters (hematology, including platelets, and clinical chemistry) of potential clinical concern throughout the study period
    f) Columbia – Suicide Severity Rating Scale (C-SSRS)
    g) Use of concomitant medication throughout the study period
- To evaluate the change from baseline to specific weeks of the following safety endpoints:
    a) Physical examination, vital signs, and ECG parameters
    b) Clinical laboratory parameters (hematology, including platelets, and clinical chemistry)

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

Exploratory

- To evaluate the difference on the following measures, from baseline to specific weeks, as well as change over time, between the active treatment arm and the placebo arm:
  a) Columbia – Suicide Severity Rating Scale (C-SSRS)
  b) Number of visits to healthcare services outside of the trial (primary care, mental health services and ER visits)
  c) Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR)
  d) Brief Assessment of Cognition (BAC) Scale
- To evaluate vafidemstat plasma concentrations (pharmacokinetics) as well as vafidemstat's LSD1-target engagement in peripheral blood mononuclear cells (PBMCs) (pharmacodynamics) after treatment, at baseline and at weeks 4, 8, and 12

EXPLORATORY ASSESSMENTS

Possible future exploratory analyses helping to increase the understanding of BPD etiology and the molecular basis for drug response.

- To investigate exploratory biomarkers
- To investigate genetic polymorphisms by DNA genotyping

STATISTICAL METHODS

The Phase IIb trial randomizes 1:1 to vafidemstat (1.2 mg) or placebo. A planned sample size of up 188 total study participants (N =188) will be enrolled. The Full Analysis Set (FAS) will be used for the primary efficacy analysis. It consists of all patients and includes all randomized participants who received at least one dose of the IMP or placebo and have completed at least one assessment evaluating efficacy of the treatment with an available score, for at least one visit after baseline. Individuals will be analyzed as randomized.

The primary efficacy analysis compares active treatment to placebo. Both primary endpoints (CGI S A/A and BPDCL) will be analyzed for significance as the difference between active treatment and placebo from baseline to specific week.

The estimand for the primary efficacy analysis is defined with the FAS population as determined by the inclusion/exclusion criteria, the endpoints targeted are the primary efficacy endpoints for the study and mean changes from baseline to specific week. Intercurrent events that are expected to occur include early treatment discontinuation due to patient choice or due to adverse events both unrelated to the medication or study indication (e.g., Covid-19) and related to the study medication or indication, as well as the initiation and/or discontinuation of psychotherapy during the trial.

The post-baseline results for both primary endpoints will be analyzed using a mixed model repeated measures (MMRM), including as fixed factors: visit, treatment arm, psychotherapy at baseline, the interaction between treatment and visit as well as the baseline value (last measurement prior to treatment initiation) for the endpoint. Participant ID will be included as a random factor.

Name of the Sponsor/Company: Oryzon Genomics S. A.	**Study Code:** CL07-ORY-2001
Name of Investigational Medicinal Product: VAFIDEMSTAT	**EudraCT No.:** 2020-003469-20
Development Phase of the Study: Phase IIb	

Overall alpha will control for type 1 error at a rate of 5% using the Hochberg correction. If one endpoint is below the 2.5% level or if both endpoints are below the 5% level of significance the study is declared a success.

The sample size for the study was calculated assuming an estimate of the effect size between active treatment and placebo of 0.51 on both endpoints..

For the secondary efficacy analysis, the same MMRM as for the primary analysis will be calculated without a formal confirmatory significance test. At each visit, estimates for the adjusted changes from baseline in both the treatment and the placebo arm (adjusted for individual differences and differences in baseline and therapy status) as well as for the difference in changes between the two arms will be presented, including 95% confidence intervals (CI).

An interim analysis will be performed after 90 participants have completed the specific week assessments (expected 108 patients enrolled after accounting for 20% dropout). Individuals that had the opportunity to complete their specific week visit, but were lost to follow-up, will also be included in the analysis, however, will not be included in the 90-patient count required for initiation of the interim analysis. The objective of this interim analysis will be to reassess the sample size based on the observed variability and effect sizes. If the conditional power is too low for both endpoints or the required sample size adjustment is considered to be too large, the study sample size will not be adjusted.

Details of the planned analyses will be provided in the SAP which will be finalized prior to conduct of the interim analysis.

STUDY PERIOD

- First patient in (FPI) is planned on Q1-2021
- Last patient in (LPI) is planned on Q3-2023
- Last patient out (LPO) is planned on Q4-2023

BLINDED PROTOCOL

This is a blinded protocol where some information related to the study design has been blinded in order to reduce the risk of bias in the assessment of the study endpoints.

Investigators and study-related staff in direct contact with the investigators (e.g. study monitors/CRAs) will only have access to the blinded study protocol.

Regulatory Authorities/Competent Authorities (RAs/CAs) -i.e., European Competent Authorities and FDA- and Independent Ethics Committes (IECs)/Institutional Review Boards (IRBs) will have access to the blinded study protocol, as well as to a Clinical Study Protocol Addendum-Unmasked Information that contains the blinded details.

Table 1. Schedule of Assessments and Procedures

Study Procedures	Visit	V1 (Screening)	V2 (Baseline)	V3	V4	V5	V6	V7	V8 / EoS [2]	V9 Run-out (Safety F-up) [13]
	Week	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**
	Day [1]	(-14 to -1) *	(-7 to 1) ±7	15±2	29±2	43±2	57±2	71±2	85±2	99±2
Informed Consent Form [3]		X								
Inclusion/Exclusion Criteria		X	X							
Mini-International Neuropsychiatric Interview (MINI)		X								
Demographics		X								
Medical history		X								
Prior and concomitant medication		X	X	X	X	X	X	X	X	X
Physical examination (height –only at V1- and weight)		X	X	X	X	X	X	X	X	X
Tuberculosis status by medical history, signs, and symptoms		X								
Urine pregnancy test (females of reproductive age)		X	X						X	
Urine drug screening		X	X	X	X	X	X	X	X	X
Participant Eligibility Form		X [4]								
Randomization			X							
Follow-up phone calls (only applicable if participant is receiving concomitant antidepressants) [12]		At V2 (Baseline): after 6-8h; 24h; and 48 h, after first drug administration								
Rating Scales/Clinical Outcomes Assessments (COAs)										
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	X	X	X	X	X	X	X	X [5]
Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR)		X	X		X		X		X	X [5]
Brief Assessment of Cognition (BAC) Scale		X	X			X			X	X [5]
Beck Depression Inventory – II (BDI-II)		X	X	X	X	X	X	X	X	X [5]
Borderline Evaluation of Severity over Time (BEST)		X	X	X	X	X	X	X	X	X [5]
Borderline Personality Disorder Checklist (BPDCL)		X	X	X	X	X	X	X	X	X [5]
State-Trait Anxiety Inventory (STAI) [6]		X	X	X	X	X	X	X	X	X [5]

Study Procedures	Visit	V1 (Screening)	V2 (Baseline)	V3	V4	V5	V6	V7	V8 / EoS [2]	V9 Run-out (Safety F-up) [13]
	Week	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**
	Day [1]	(-14 to -1) *	(-7 to 1) ±7	15±2	29±2	43±2	57±2	71±2	85±2	99±2
State-Trait Anger Expression Inventory 2 (STAXI-2)		X	X	X	X	X	X	X	X	X [5]
Clinical Global Impression-Severity for Agitation/Aggression (CGI-S A/A)		X	X	X	X	X	X	X	X	X [5]
Number of visits to healthcare services outside of the trial (primary care, mental health services & ER visits)			X [7]		X [7]		X [7]		X [7]	X [5]
Safety Assessments										
Adverse events			X	X	X	X	X	X	X	X
Vital signs [8]		X	X	X	X	X	X	X	X	X
Electrocardiogram [8]		X							X	
Blood sample for laboratory safety assessments [8]										
Hematology		X	X	X	X	X	X	X	X	X [5]
Biochemistry		X	X	X	X	X	X	X	X	X [5]
Hep C, Hep B, HIV testing		X								
Blood sample for pharmacokinetic and target engagement [9]										
PK [9i]			X		X [9i]		X [9i]		X	
LSD1-TE			X		X		X		X	
Blood sample for exploratory assessments [10]										
Biomarkers' analysis			X						X	
Genotyping			X							
Investigational Medicinal product (IMP)										
Assess IMP compliance (manual accountability of returned IMP at site)				X	X	X	X	X	X	X [5]
Dispense IMP [11]			X	X	X	X	X	X	X [5]	

** Screening period can last up to two-weeks with a window of ± 7 days.*

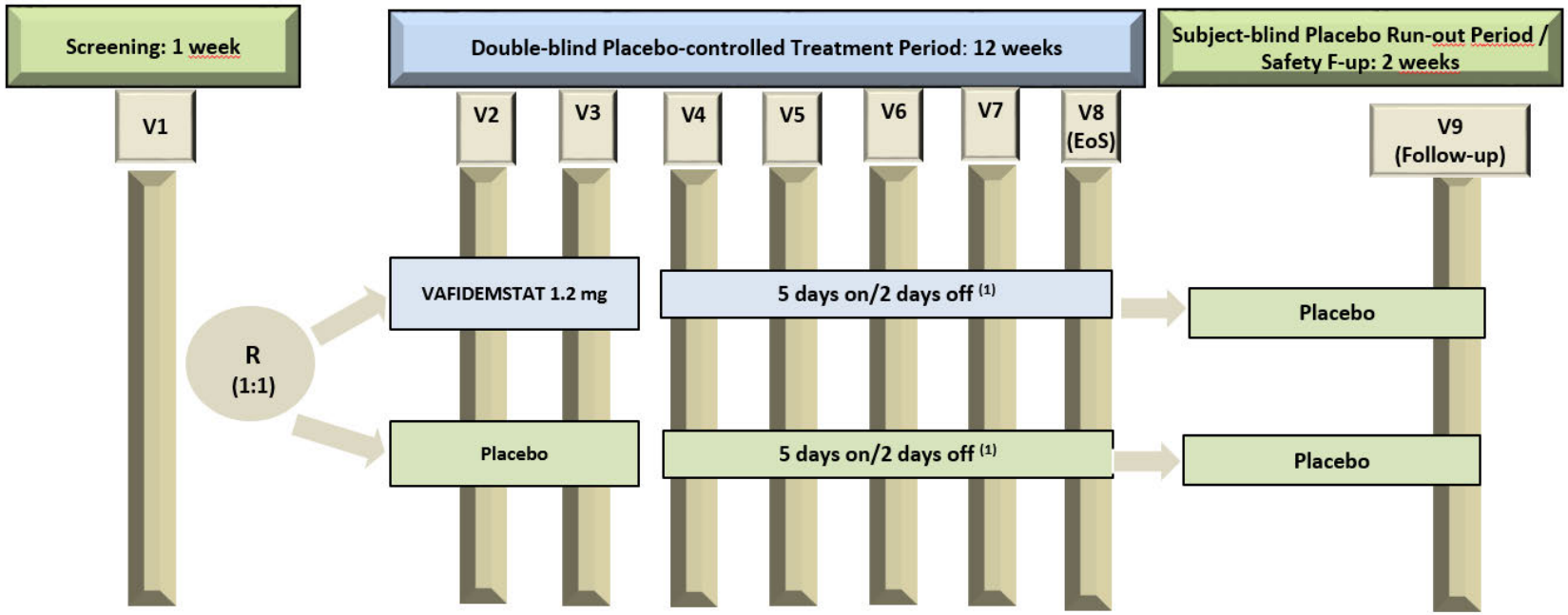
(1) All assessments from a specific visit may be completed over a maximum of two consecutive days. In this case, the first day should be considered as the visit day. The forecasting for visit schedule should take V2 (Baseline) date as the reference. If the date of a visit changes within the allowed window, the following visits will still be scheduled based on V2 (Baseline) date.

(2) After Visit 2, seven visits, every two weeks, are planned until Visit 9. If participants do not complete all study visits (early termination), then they should complete all the Visit 8/EoS assessments. All participants are classified as follows:

a. *Completers:* Participants completing Visit 9.
b. *Non-completers:* Participants that received at least one dose of study treatment, but prematurely discontinued the study before completion of Visit 9 for any reason other than withdrawal of the informed consent. These participants will be asked to complete an End of Study (EoS) Visit as soon as possible after withdrawal. Non-completers will not enter the 2-week participant-blind placebo run-out period.
    i. If there has been, at least, one week between the last intake of study drug and this EoS visit, no further Safety follow-up visit will be required.
    ii. If there has been less than one week between the last intake of study drug and EoS visit, participant will be asked to attend to a Safety-follow up visit, two weeks after the last intake of study drug, to perform safety assessments only.
c. *Non-completers who discontinue the study because they withdraw their consent:* Participants that received at least one dose of study treatment, but prematurely discontinued from the study before completion of Visit 9 due to withdrawal of informed consent. These participants, if possible, will be asked to attend to an EoS Visit.
    i. The visit must be scheduled as soon as possible after withdrawal.
    ii. If the participant withdraws consent during a visit but agrees to complete the visit, then, the investigator will complete an EoS Visit. All the data collected up to and including this visit will be used in the analysis.
    iii. If the participant withdraws consent and refuses to complete the EoS Visit, no new information will be collected. However, it is recommended, outside the scope of this study, to perform a safety assessment within 2 weeks after treatment discontinuation.

(3) Informed consent at the Screening visit must be obtained before any study specific procedure.
(4) Participant eligibility should be documented in a Participant Eligibility Form and submitted to the study medical monitor immediately after Visit 1 for approval before Visit 2.
(5) Not applicable for non-completers (i.e.: participants who received at least one dose of study treatment but prematurely discontinue the study before its completion).
(6) The full State-Trait Anxiety Inventory (STAI) (Forms Y-1 & Y-2) will only be administered at Screening (Visit 1), Baseline (Visit 2) and Visit 8/EoS, whereas Form Y-1 ("state" anxiety) will be administered at all other visits.
(7) The number of visits to healthcare services outside of the trial (primary care, mental health services & ER visits) will be evaluated 'in the last month' at Baseline and at V4, V6 and V8/EoS.
(8) Vital signs and electrocardiogram (ECG) should be obtained for a participant in the same manner throughout the study (e.g., obtained from the same arm).
(9) Blood extractions should ideally take place at the same time of the day and in fasting conditions (e.g., preferably, first thing in the morning) in order to allow participants to ingest food before going on with the rest of study assessments. In case the study visit is scheduled in the afternoon/evening, fasting conditions will only be required at Visit 2 (Baseline), Visit 4, Visit 6 and Visit 8. Fasting conditions should last 6-8 hours. All blood samples will be collected prior to study drug intake at all study visits.
(9i) For US Sites ONLY: C_{max} will be assessed in a subset of participants. In these participants, one extra blood sample for PK assessments will be obtained 1 to 2 hours after IMP intake on Visits 4 and 6 (in addition to the pre-dose sample already scheduled on these visits). Participants will have to sign a separate specific informed consent form.
(10) As blood sampling for the exploratory assessments is an integral part of the study, the main Patient Information Sheet covers these analyses
(11) Study treatment will be dispensed at each study visit from Visit 2 to Visit 8. Each dispensation will consist in a box containing the treatment for 14±2 days. At each visit, the first study drug intake, corresponding to the new treatment box dispensed on that visit, should occur at the clinic in fasting conditions, however If the study visit is scheduled in the afternoon/evening, no fasting conditions are required before IMP intake at the clinic .
(12) ONLY APPLICABLE IN CASE THE PARTICIPANT IS RECEIVING CONCOMITANT TREATMENT WITH ANTIDEPRESSANTS (i.e., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclics, tetracyclics, and triazolopyridines): A follow-up call will be required approximately 6-8 hours post first IMP administration, as well as at 24 hours and 48 hours to ensure participants are not experiencing any signs or symptoms of serotonin syndrome. If a participant is experiencing moderate symptoms of serotonin toxicity such as agitation, tachycardia, diaphoresis, and/or hyperthermia, then they will immediately be referred to local emergency services.
(13) For US Sites ONLY: A subset (i.e., 3-4) of participants and the PI at each US Site will complete qualitative research regarding their experience with some of the measures used in PORTICO (i.e., BPDCL for participants & CGI-S A/A and AAPI-CR for clinicians) at Visit 9. Participants will have to sign a separate specific informed consent form.

Figure 1. Overall Study Design



(1) During the 2 days off, patients will be taking placebo capsules

Note: An interim analysis will be performed after 90 participants have completed the specific week assessments. The objective of this interim analysis will be to reassess the sample size based on the observed variability and effect sizes.

1. INTRODUCTION

1.1. Disease Background

Borderline personality disorder is a common mental health disorder with an estimated prevalence in the general adult population between 0.5% and 5.9% % (Grant et al 2008 & Lenzenweger *et al*., 2007) and higher in clinical settings. For instance, prevalence in primary care clinics is 6% versus 10% of psychiatric outpatients and 20% in psychiatric inpatient units (Torgersen, 2005 & Gunderson *et al*., 2009).

Diagnosis

According to the categorical diagnostic model of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), published by the American Psychiatric Association (American Psychiatric Association, 2013), BPD is a "pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity, beginning by early adulthood and present in a variety of contexts" and its clinical expression can be broken down in nine criteria or clinical features. According to DSM-5, to be diagnosed with BPD, patients must exhibit five or more of the clinical criteria:

- Emotional instability (i.e.: unstable emotional experiences and frequent mood changes; emotions that are easily aroused, intense, and/or out of proportion to events and circumstances). Regarding mood symptoms, BPD patients typically exhibit changes from irritability to depression (usually lasting a few hours and only rarely more than a few days) in a general frame of negative emotionality (a sort of chronic dysphoria) (Gunderson, 2010)
- Anxiousness (i.e.: intense feelings of nervousness, tenseness, or panic, often in reaction to preoccupation with real or imagined abandonment and rejection)
- Chronic feeling of emptiness
- Inappropriate, intense anger or difficulty controlling anger (with fears of losing control) and episodes of violent outbursts
- Impulsivity in at last two areas that are potentially self-damaging, e.g., sex, substance abuse, reckless driving, binge eating
- Recurrent suicidal behavior, gestures, or threats, or deliberate self-harming behavior
- Pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation, where patients often express perceptions of bad intentions from others to themselves
- Markedly and persistently unstable self-image or sense of self (identity disturbance), with irrational beliefs as perception of self as bad
- Dissociative episodes with depersonalization and derealization (perceive self or the world as disconnected, unreal) with episodic stress-related paranoid ideation (Gunderson, 2010)

BPD patient's relationships are commonly described as intense, worsened by conflict (i.e., verbal and/or physical aggression) and their frantic efforts to avoid real or imagined abandonment. Frequently BPD individuals vacillate between idealization to devaluation (e.g., love or hate) in their relationships with others (e.g., partners, co-workers, teachers, supervisors), which also contributes to instability of these relationships.

Individuals with BPD also commonly have an identity disturbance characterized by markedly and continually unstable self-image and sense of self. They also are frequently impulsive across situations that are potentially self-damaging such as spending money excessively on shopping sprees or making reckless unwise investments, using illicit substances, drinking excessively, or abusing over the counter

medications. Impulsive sexual behaviors with the potential for damaging consequences such as one-night stands or brief affairs are common. Individuals with BPD may also impulsively eat to excess to the point of pain, and then force themselves to throw up; bulimia nervosa is a common co-occurring comorbidity in this population. Impulsive illegal behaviors such as buying/selling drugs, stealing, speeding or reckless driving are common. Finally, BPD patients frequently exhibit impulsive and aggressive behaviors including yelling/screaming, threatening to physically harm others, verbal or physical assaults and/or deliberate property damage (e.g., breaking dishes, punching walls, kicking/slamming doors or damaging someone's car).

Borderline personality disorder patients frequently exhibit internalized aggressive behaviors such as self-harm (e.g., mutilation, head banging, punching themselves) as well as suicidal thoughts, gestures and/or attempts, which may occur several years after the first presentation of symptoms. Suicide is common in people with borderline personality disorder and may occur several years after the first presentation of symptoms (Paris & Zweig-Frank, 2001). The rate of completed suicide in people with borderline personality disorder has been estimated to be approximately 10%, 50-times higher than in the general population (Oldham, 2006). A well-documented association exists between borderline personality disorder and depression (Skodol *et al*., 1999; Zanarini *et al*., 1998), and the combination of the two conditions has been shown to increase the number and seriousness of suicide attempts (Soloff *et al*., 2000). BPD patients also exhibit externalized aggressive behaviors including inappropriate anger, difficulties controlling anger and intense anger that can manifest itself in verbal and/or physical fights or property damage as noted previously.

Many researchers have attempted to determine whether BPD is best conceptualized as a one-factor higher-order BPD concept or DSM-multidimensional model. Bloo *et al.*, 2017 empirically examined various BPD conceptual models (as summarized below) in a population of BPD patients ($n_1 = 140$), Cluster C personality disorder patients ($n_2 = 55$), Axis I psychopathology patients ($n_3 = 57$) and nonclinical controls ($n_4 = 87$) while psychometrically validating the Borderline Personality Disorder Checklist (BPDCL). These authors performed a first-order confirmatory factor analyses using structural equation modelling. In addition, they performed test statistics and AICs of seven different conceptual models. These researchers found that all-factor models (i.e., those leveraging DSM-IV criteria as factors) explained the BPDCL data, based on the Akaike information criterion (AIC), significantly better than other multifactor or one-factor structures (all $p < .001$). In other words, the AICs reflected that more information was gained using an all-factor model compared to simpler three- or four-factor models.

Examined BPD conceptual models included: Zanarini *et al.*, 1989 (four factor model including affect, cognition, impulsivity and interpersonal relationships); Hurt *et al.,* 1990 (three factor model of BPD criteria based upon correlations between the DSM-III, including identity, affect and impulsivity); Morey, 1991; Adams *et al.*, 2001; (four dimensional model, including affective instability, identity problems, negative relationships and self-damaging behavior); Livesley and Schröder, 1991 (three factor model, including instability/disorganization, interpersonal exploitation and self-damaging behavior); Clarkin *et al.*, 1993 (a three factor-structure, including uncertainty about self & interpersonal difficulties, affect & affect regulation, and impulsivity, as well as a four-factor model, including those three plus anger/hostility); Sanislow *et al.*, 2002 (unitary construct, as well as a three-factor model, including disturbed relatedness, behavioral dysregulation, and affective dysregulation.

Overall, Bloo and colleagues concluded that first-order confirmatory factor analyses with the BPDCL items across these various BPD conceptual models supported a one-dimension BPD model, as well as a nine-dimensional one based on the DSM BPD diagnostic criteria.

Age of onset

According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), symptoms of BPD begin in early adulthood. Although features of personality disorders usually become recognizable during adolescence, by definition, a personality disorder represents a persistent pattern of thoughts, behaviors and feelings that remain stable over a period of time. During adolescence, many symptoms or features may relapse or remit and not persist until adulthood. Thus, personality disorders are usually not diagnosed in an individual younger than 18 years old. However, there are reports in the literature that borderline characteristics are often identifiable at a much earlier age, including early adolescence (Bradley *et al*., 2005).

Etiology

Evidence supports BPD as the result of the interaction between biological factors and psychosocial factors (e.g., adverse childhood events) in early stages of human development. In this sense, the biopsychosocial model is the one that better fits to borderline personality disorder etiology, with an early expression of essentially three components of psychopathology (affective dysregulation, behavioral dysregulation and disturbed relatedness) (Leichsenring et al., 2011). The genetic bases for BPD development have been suggested from results of familial and twin studies and the heritability has been estimated to be of approximately 40%. However, the mechanisms that better explains the expression of a BPD phenotype are gene-environment interactions and epigenetic changes, instead of the presence of a concrete polymorphism (Bulbena-Cabre A., 2018).

Course & Prognosis

The course of borderline personality disorder is highly variable. According to Zanarini et al, approximately half of those that receive psychotherapy for BPD improve sufficiently to not meet the criteria for borderline personality disorder 5 to 10 years after first diagnosis (Zanarini et al., 2003). However, there are several caveats to these findings. First, it is unknown whether symptom remission is a consequence of psychotherapy as evidence suggests that a significant proportion of improvement is spontaneous and resultant from increased age, greater maturity and self-reflection. Second, different types of psychotherapy yield different outcomes with dialectical behavior therapy reportedly the most efficacious. Third, although psychotherapy may result in symptom remission, less is known regarding how longstanding the effect. In fact, recurrent self-harm has been reported to be a problem in elderly BPD patients. Finally, throughout the world, the majority of the BPD population does not have exposure to the resources (i.e., providers and/or financially) to receive psychotherapy. Taken together, this means there remains a high-unmet medical need for a safe and effective treatment for this population.

Treatment

There is no currently approved drug therapy for BPD, and symptomatic and comorbid pharmacologic treatments have limited efficacy and/or have significant side effects (e.g., weight gain, somnolence, tardive dyskinesia). Psychotherapy is, therefore, the first-line treatment for this population though efficacy is limited, and duration of response is variable with more research needed in this area.

1.2. The Investigational Medicinal Product (IMP): Vafidemstat

Vafidemstat is a novel chemical entity, which is being developed as a drug for the treatment of psychiatric and neurodegenerative conditions.

Vafidemstat is a brain penetrant, orally bioavailable, small molecule irreversible inhibitor of the histone lysine demethylase (LSD1), also known as KDM1A. In vitro, vafidemstat also inhibits the catalytic activity of MAOB through irreversible binding to the FAD cofactor. In vivo, however it inhibits primarily KDM1A, and MAOB inhibition is not significant in the therapeutic dose range after oral administration. Moreover, preliminary evaluation of MAO-B inhibitor activity in the ongoing Phase II studies showed that vafidemstat did not inhibit PBMC MAO-B. In summary, all data collected to-date support that in vivo and in humans vafidemstat is a LSD1 inhibitor.

Transcription disequilibria are characteristic of many neurodegenerative diseases. The activity-evoked transcription of immediate early genes (IEGs), important for neuronal plasticity, memory and behavior, is altered in CNS diseases and governed by epigenetic modulation. KDM1A forms part of transcription regulation complexes and has been implicated in the control of IEG transcription.

LSD1 is a nuclear enzyme that demethylates methylated lysines in a series of target proteins, most relevantly histone H3. Histones are nuclear proteins that form scaffolds around which the DNA of the cell is packaged. Tightly packaged chromatin is transcriptionally inactive, it has to be loosened up and partially unwound to permit binding of protein complexes that mediate transcription. LSD1 does not bind to the DNA itself but is recruited to specific target sites in the genome by various transcription regulation complexes (Maes *et al.*, 2015). Inhibition of LSD1 by vafidemstat leads to changes in the methylation marks on histone H3 and changes in transcription.

LSD1 has a well-known function in hematopoiesis (Sprüssel *et al.*, 2012) but is also expressed in other tissues. In the brain, LSD1 has both early developmental functions in stem cell proliferation and late functions in cell type specification. A neuro specific LSD1 isoform has been described. There is currently no consensus on the exact mechanism of action of the neuro-specific LSD1 isoform, but there is a general agreement that it counteracts the ubiquitous form and favors differentiation of neurons and synapse formation (Chao Wang, 2014; Lin *et al.*, 2011).

Vafidemstat produces significant benefits in vitro and in animal models and has the potential for the non-sedative treatment of behavior disturbances associated with a variety of neuropsychiatric disorders in addition to neurodegenerative diseases (Maes *et al.*, 2020).

In particular, vafidemstat has been shown to improve cognition in SAMP8 mice, a non-transgenic model for accelerated aging, which presents several characteristics reminiscent of Alzheimer's disease, and in the R6/1 mice model of Huntington disease (Maes *et al.*, 2020). In the SAMP8 model, vafidemstat treatment up-regulated the expression or response capacity of genes related to synaptic plasticity, neurogenesis and memory while down-regulated an inflammatory signature, which included the alarmin and amplifier of inflammation S100a9. In addition, vafidemstat promoted the responsiveness of Immediate Early Genes (IEG)s. The anti-inflammatory properties of vafidemstat were further confirmed in the myelin oligodendrocyte glycoprotein (MOG) induced experimental autoimmune encephalomyelitis (EAE) and the Theiler's Murine Encephalomyelitis Virus (TMEV) models for multiple sclerosis (Cavalcanti F *et al.*, ACTRIMS 2018; Maes T *et al.*, ACTRIMS 2017; Maes T *et al.*, ECTRIMS 2017; Maes T *et al.*, ECTRIMS 2017 – Scientific Poster presentations).

Importantly, LSD1 inhibition has been also described to rescue complex phenotypes in genetic models of Autistic Spectrum Disorder and Schizophrenia as detailed below.

Shank3 mutations are relatively frequent in ASD. In the Shank3 +/Δc mouse model of autism (Qin *et al.*, 2018), neuronal impairments, social deficits, and aggressive behavior are restored by LSD1 inhibition (Zhang *et al.*, 2021). Shank3 deficiency has been described to induce NMDA receptor hypofunction.

Inhibition of LSD1 has also been reported to partially restore learning function in mice with NMDA receptor hypofunction (Matsuda *et al.*, 2019).

LSD1 inhibition reverses the schizophrenia related phenotype in the Setd1a+/-mouse model, producing a rebranching of the prefrontal cortex, rescuing the contralateral axon branching deficits in vivo and rescuing working memory performance (Mukai *et al*., 2019).

Additionally, non-clinical and early clinical studies confirmed that vafidemstat has a satisfactory ADME profile (including high bioavailability and efficient passage through the blood brain barrier) with well-established pharmacokinetic (PK) and pharmacodynamic (PD) efficacy relationships. No relevant off-target activity or toxicity warnings, and no in vitro cardiotoxicity (hERG) nor effects on ECG parameters and heart rate were identified. The compound has been characterized in toxicology studies to evaluate the effects of long-term administration in rats and dogs. Therefore, results from non-clinical pharmacology and toxicology studies support further development of vafidemstat as a potential novel pharmacological therapy for the oral treatment of psychiatric disorders, including borderline personality disorder.

LSD1-TE and MAO-B activity data obtained in Phase II clinical trials show that vafidemstat binds to LSD1 in a dose-dependent manner and that differences between the placebo and active arms and between the two active arms are statistically significant. An average LSD1-TE of 63% and 73% was reached at the doses of 0.6 mg and 1.2 mg, respectively, and maximum levels were already observed on day 5. On the other hand, vafidemstat did not inhibit PBMC MAO-B, i.e., activity showed no differences between placebo and vafidemstat active arms and no changes over time were observed for any arms.

Finally, all data collected in clinical trials to-date support that is safe and well tolerated across a number of CNS diseases, including BPD. See Investigator Brochure for a complete review on the clinical safety data on vafidemstat.

1.3. Non-clinical Pharmacology and Toxicology Studies

The non-clinical Good Laboratory Practice (GLP) safety evaluation of vafidemstat has included the following studies of single dose and repeat dose, general toxicology, and safety pharmacology by the oral route of administration in rats and dogs (data available in internal Pre-clinical Regulatory Reports).

Pharmacokinetics and metabolism

- PK data obtained in rat: studies by oral and intravenous administration showed dose linearity of exposure, a good bioavailability of ~90%, low plasma clearance, and elimination half-life of 2 hours.

- PK data obtained in dog: studies by oral and intravenous administration showed very low plasma clearance, good bioavailability of ~76%, and middle terminal half-life of 7 hours.

Vafidemstat is stable in rat, dog, and human liver microsomes and hepatocytes for 120 min at 37°C. The plasma protein binding is high for humans (97% bound fraction). In human hepatocytes, non-CYP pathways (predominantly glucuronidation) were shown to play a major role in the metabolism of vafidemstat. CYP pathways, in particular CYP2C8 and CYP2C9 were of subordinate importance.

Additionally, vafidemstat did not inhibit any of the tested major CYP isozymes (1A2, 2C9, 2C19, 2D6, 3A4, 2A6, 2B6, 2C8 and 2E1) up to 100 µM. Likewise, CYP1A2, CYP2B6 or CYP3A4 were not induced at clinically relevant concentrations.

Plasma levels of vafidemstat were determined and toxicokinetic parameters calculated in the preliminary and 28-day toxicity studies in rats and dogs. In both species, exposure increased with increasing doses and time necessary to reach the maximum concentration observed (t_{max}) was within 1.0 hour across the tested dose levels.

Toxicology

To establish the Non-Observed Adverse Effect Level (NOAEL) special attention was paid to the hematological parameters since the target LSD1 is involved in hematopoiesis and excessive pharmacology was expected to affect hematology. The NOAEL was established as the dose that would not provoke a reduction of hematological parameters over 50% from the baseline levels.

In the repeated dose 28-day oral toxicity study in Wistar rats, vafidemstat was well tolerated and caused no adverse clinical signs or mortality at doses ranging from 0.07 to 0.6 mg/kg/day.

All the clinical chemistry/urinalysis/organ weights values were within the normal range. Only at 0.6 mg/kg, a platelet depletion of 78% and 85%, for male and female, respectively, was observed.

In the repeated dose 28-day oral toxicity study in dogs, vafidemstat was well tolerated and caused no adverse clinical signs or mortality at doses ranging from 0.025 to 0.225 mg/kg, with the exception of pale ears and mucosa (1/5) in males and mucoid feces (2/5) and bruising (1/5) in females at the highest dose.

All the clinical chemistry/urinalysis/organ weights values were within the normal range. At 0.225 mg/kg/day, platelet depletion was 76% and 82%, for male and female animals, respectively.

After the safety evaluation, the NOAEL in rats and dogs in the above studies was established at 0.200 (HED 1.9 mg/day) and 0.075 mg/kg (HED 2.4 mg/day), respectively, under the test conditions and doses employed.

The toxicity of vafidemstat in Wistar rats after daily oral administration for 26-week cycles (5 consecutive days/week including 2 days of wash-out) using doses between 0.07 and 0.4 mg/kg/day showed a good tolerability. No adverse clinical signs and no treatment-related mortality were reported, the impact on platelets was less profound than in the 28-day study and attributed to compensatory mechanisms. It can be concluded that the high dose level, 0.4 mg/kg/day (HED 3.8 mg/day) administered during 26 consecutive cycles (once daily, for 5 consecutive days/week followed by two treatment-free days) could be considered as the NOAEL.

Moreover, the toxicity of vafidemstat in dogs after daily oral administration for 39 weeks cycles (once daily, for 5 consecutive days/week followed by two treatment-free days) at dose levels of 0.025 to 0.150 mg/kg/day showed that vafidemstat was satisfactorily tolerated, having induced only mild or moderate and almost completely reversible changes, mainly at 0.150 mg/kg/day. The NOAEL in dogs was established at 0.075 mg/kg/day (HED 2.4 mg/day) under the test conditions and doses employed.

Reproductive and developmental toxicology

Specific reproductive toxicology studies on vafidemstat have not been completed. However, no vafidemstat related changes in organ weights and macroscopic/microscopic observation in both ovary and testicles as compared to vehicle control group were observed in the toxicological studies (28-day and long-term studies in rat and dog). Additionally, preliminary embryo-fetal development study to select the doses for the main study has been completed. Results from this study show that low (0.2 mg/kg (HED=3.8 mg)) and mid (0.6 mg/kg (HED=11.5 mg)) doses were well tolerated, without significant changes in the fetal viability or malformation incidence compared to the control group. The high dose (1.8 mg (HED=34.6

mg)) showed high incidence of spontaneous abortion. The tested mid-dose allows for a 10-fold safety margin, considering the highest clinical dose (1.2 mg/day). Available data, along with the double barrier protection in the inclusion criteria of vafidemstat clinical trials, is considered to adequately support the inclusion of women of child-bearing potential.

In vivo Pharmacology

As for its pharmacology properties, vafidemstat has been shown to modulate aggressiveness and other social behavior alterations in different animal models of neuropsychiatric pathologies.

For instance, the SAMP8 male mice are an interesting model to study the aggression associated with AD as well as other dementias. In the resident-intruder test (a standardized experiment to evaluate social interaction, including offensive aggression and defensive behavior) the SAMP8 males show a very aggressive behavior against the intruder mice compared with their control strain SAMR1. Treatment for 6 weeks with vafidemstat diminishes this aggressive behavior at similar levels to those observed in the SAMR1.

Vafidemstat modulates the gene expression response in the prefrontal cortex (PFC). The PFC is known to play an important role in the control of aggressive behavior. We performed a genome-wide microarray-based survey on pooled PFC samples from vehicle and treated SAMP8 mice. The survey revealed that the immediate-early genes Fos, Npas4 were down-regulated by treatment in the PFC; GABAergic genes relevant to synaptic plasticity such as Calb2 and Gad1; genes involved in signal transduction such as Gng4 and Doc2g, or neuropeptides like Penk1, involved in pain signaling and anhedonia. Many of the genes down regulated by vafidemstat were over-expressed in vehicle treated SAMP8 vs SAMR1 mice, therefore treatment, at least partially, rebalanced the expression profile.

In addition to aggressiveness, another behavior alteration that is associated with AD and a multitude of neuropsychiatric pathologies such as autism, schizophrenia and other dementias is the lack of interest in social interaction. To evaluate the interest of a mouse by the interaction with a conspecific one, the three chambers test (TCT) can be used, where the animal can freely choose between a chamber with an inert object or another chamber where an unknown mouse is placed. In this social behavior test, the time spent by the mouse in each chamber is measured as an index of their interest in social interaction. Unlike female SAMR1 control mice, females of the SAMP8 strain do not show preference for the social chamber. However, the SAMP8 females treated during 4 months with vafidemstat did show a restored preference for social interaction.

In diseases where the normal neurodevelopment of the brain is affected (e.g., autism, schizophrenia), periods ranging from the gestational phase to adolescence are critical. In this sense, different animal models have been investigated that try to imitate some of the aspects of these neuro-pathologies. One of these models is that of social isolation after weaning in highly social animals such as rats; this intervention induces an alteration in the habitual patterns of social behavior that is interpreted as a lack of interest in social contact (social withdrawal) in adult rats. In animals kept in isolation since weaning, an increase in active avoidance of social interaction is observed in the resident-intruder test. However, treatment with vafidemstat for one month restores the interest in social contact.

Finally, treatment with vafidemstat has no sedative effects in any of the models analyzed and in a wide range of doses. Both the SAMP8 mice and the rats of the social isolation model treated with vafidemstat show normal motor activity, similar to their vehicle-treated controls.

1.4. Clinical Studies

1.4.1. Phase I results of single-dose and multiple-dose studies in healthy adult and elderly volunteers

The first clinical study with vafidemstat finished in June 2017 (CL01- vafidemstat, EudraCT No.: 2015-003721-33): "A Study to Assess the Safety, Tolerability and Pharmacokinetics of Single and Multiple Oral Doses of vafidemstat in Healthy Male, Female Patients and Elderly Population." The primary objective of the study was to characterize the safety, tolerability, PK and pharmacodynamics (PD) of vafidemstat for oral intake in healthy volunteers. CL01-ORY-2001 involved two stages, the first one a single dose study in healthy male volunteers and the second one a multiple dose in healthy male and female population and healthy male and female elderly population.

The first stage was a single center, randomized, double-blind, dose escalation study in which vafidemstat was administered as single oral dose to healthy young male volunteers following a dose escalation scheme. Up to five different dose levels were tested in a block of 8 participants. For each dose level, the participants were randomized to active drug or placebo, 2 participants being randomly assigned to placebo and 6 to the active drug. First, one volunteer received active drug (block 1); after 72h of safety and tolerability assessment a second block of 3 volunteers received active drug (2 volunteers) and placebo (1 volunteer); after 72h of safety and tolerability parameters assessment a third block of 4 volunteers received active drug (3 volunteers) and placebo (1 volunteer). After evaluation of safety/tolerability of the corresponding dose level, the process was replicated in the following dose. Given there were no safety issues regarding safety during the first stage, the second stage was initiated.

The second stage was a single-center, randomized, double-blind, placebo-controlled and parallel groups study, in which vafidemstat was administered as single oral daily dose during 5 days to young male and female healthy volunteers. Five dose levels were tested. For each dose level, 8 participants were included divided in two blocks (1:3 proportion of placebo: active treatment, each). The second block started 72h after the first one. The participants were randomly assigned to active drug or placebo: 2 participants randomized to placebo and 6 participants to the active drug. The five dose levels were administered in sequential fashion. After evaluation of safety/tolerability of the corresponding dose level, the process was replicated in the following dose. Additionally, for this multiple dose study, an elderly population group was included in the maximum tolerated dose (MTD) dose level. The second stage was stopped when the minimum intolerated dose (MID) was reached, at 4.0 mg daily.

Data from the Phase I study demonstrated good safety and tolerability profile after single dose or multiple doses administration during in a 5-day time period (Antonijoan *et al.*, 2021). The most common adverse event (AE) reported during vafidemstat administration was headache, which was rarely considered related with the study treatment. No serious AEs (SAEs) or AEs leading to treatment discontinuation were reported in study participants who received either single or multiple doses. On the other hand, vafidemstat 4.0 mg/day (the highest dose administered) resulted in a significant decrease (≥50% from baseline) in the platelet count. Consequently, the MTD for a multiple doses' regimen was 2.5 mg/day. In addition, all hematology (except for platelet account), biochemistry, urinalysis, vital signal and electrocardiogram (ECG) parameters seemed to remain constant during the treatment with vafidemstat. Moreover, vafidemstat did not cause any somnolence effects, did not have potential for abuse and did not disrupt the sleeping patterns during a 5-day treatment period.

1.4.2. Phase IIa: REIMAGINE study

REIMAGINE is a single center, one-arm, open-label 8-week trial to evaluate the safety and tolerability of vafidemstat (1.2 mg dose) across three adult psychiatric patient cohorts: Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD) and Borderline Personality Disorder (BPD). Another goal of REIMAGINE was to investigate the efficacy of vafidemstat in treating aggression in adults with ADHD, ASD and BPD.

REIMAGINE enrolled thirty participants (N = 30) distributed as follows: 11 ADHD, 12 BPD and 7 ASD participants. Participant inclusion was based on significant or persistent agitation or aggression that was disruptive to participant's daily living or put the participant in harm´s way for at least 3 days per week for at least 4-weeks prior to screening visit. Participants were treated with 1.2 mg/day (five days a week on - two days off (fiw)) of vafidemstat for 8-weeks, then, completed a 4-week safety follow-up period. Treatment compliance was monitored through pharmacokinetic and pharmacodynamics parameters.

Information below includes the study results presented at the European Psychiatry Association (EPA) Congress in July 2020.

All participants were included in the safety evaluation (n=30). A total of 23 participants were evaluated for efficacy (n=23): 8 ADHD, 9 BPD and 6 ASD.

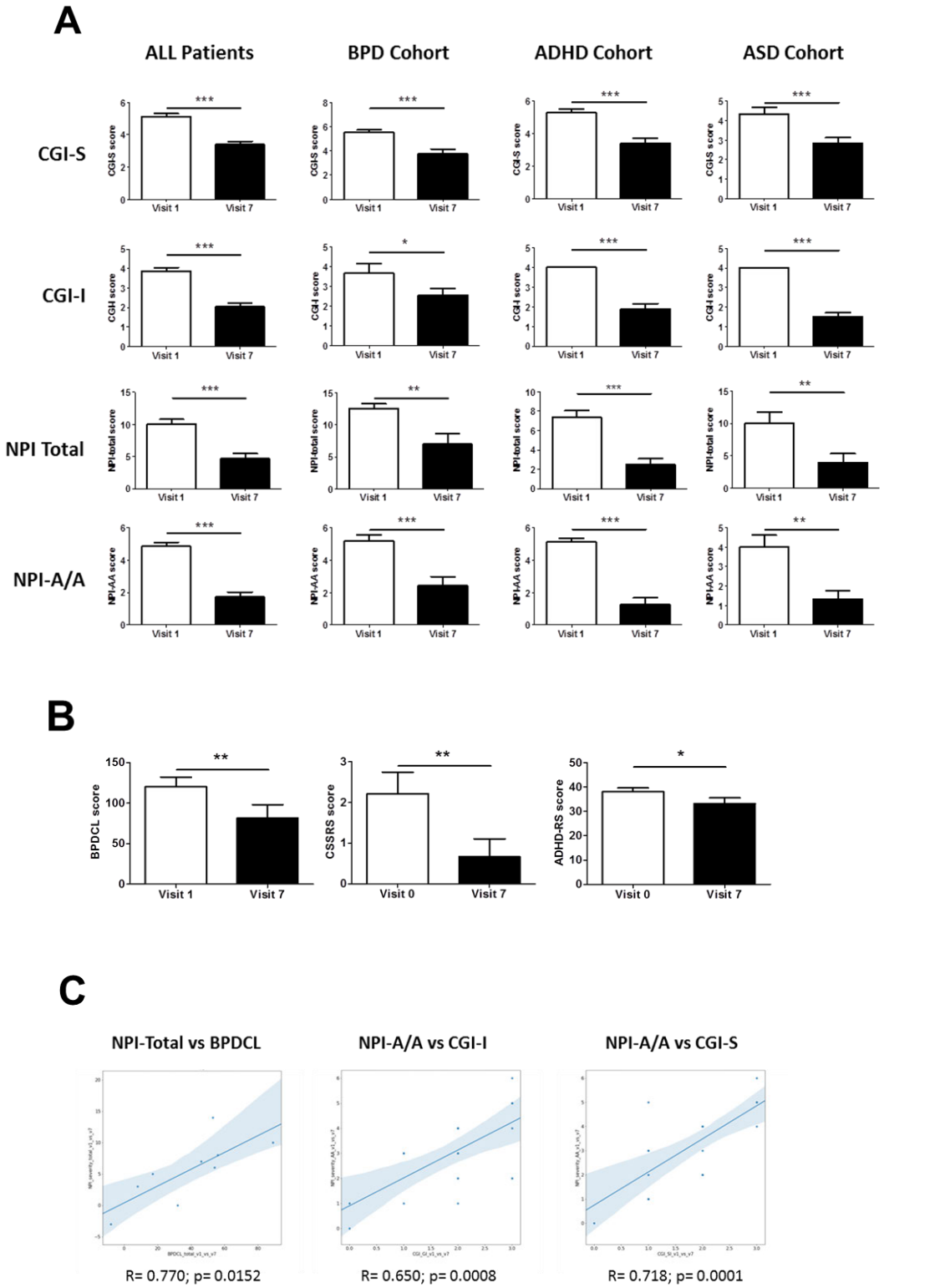
Collected safety data included treatment emergent adverse events (TEAEs), changes in concomitant medications, physical exam, vital signs, ECG, and laboratory results. Overall, treatment with vafidemstat was safe and well tolerated, only non-clinically relevant mild events that spontaneously recovered without any intervention or treatment modification were observed. There were no Serious Adverse Events (SAEs) and none of the participants withdrew due to safety related events.

Aggression was assessed using the Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I) scale focused on agitation and aggression, and the Neuropsychiatric Inventory (NPI) Agitation-Aggression 4-item subscale (NPI-A/A). Overall participants' functioning was assessed using the Total NPI (12-items) scale, as well as the disease-specific scales, ADHD-Rating Scale (ADHD-RS) and Borderline Personality Disorder Checklist (BPDCL), for ADHD and BPD participants, respectively. No validated treatment-sensitive scale for ASD patients is currently available.

After treatment with vafidemstat, a statistically significant reduction in the CGI-S, CGI-I and NPI A/A scales evaluating aggression and a significant improvement in Total NPI assessing overall function were observed both, in the aggregated data for all participants, as well as in the three disease's groups (Figure 2, Panel A). Furthermore, participant scores for the disease-specific scales, BPDCL for BPD and ADHD-RS for ADHD participants, were also significantly improved (Figure 2, Panel B). Additionally, a statistically significant reduction of suicidal ideation, measured by the C-SSRS scale, was observed in BPD participants, the only cohort where this trait is relevant.

Finally, a clear correlation was observed between most of the clinical outcomes (Figure 2, Panel C) and with vafidemstat exposure (data not shown). REIMAGINE provided a preliminary support for vafidemstat as an emerging therapeutic option to treat aggression-agitation, as well as non-aggression features of psychiatric diseases.

Figure 2: REIMAGINE Efficacy Results



A) and B) Comparison between the values of clinical scores CGI-S, CGI-I, NPI-AA, NPI-total (A) and BPDCL-total and C-SSRS scores in BPD Cohort and ADHD-RS score in ADHD Cohort (B) at the beginning of the study (Visit 1) and after 8 weeks of treatment with vafidemstat (Visit 7). Each bar represents mean ± SEM. All graphs include p-values for the 1-tail, paired Student t-test comparing scores at Visit 1 and Visit 7 (*p-value<0.05; **p-value<0.01; ***p-value<0.001). Similar data is obtained when 1 tail paired Wilcoxon Signed-rank is used as non-parametric test on the specific subsets (not shown). NPI scores correspond to the sum of severity values for each NPI item. **C)** Linear correlation graphs of pairs of clinical scores at Visit 1 and Visit 7. Pearson R value is reported in the figure together with the related p-value. The 95% confidence interval for the linear regression is shaded in blue.

1.5. Study Rationale

Borderline personality disorder is a common mental health disorder with an estimated prevalence in the general adult population between 0.5% and 5.9% (Grant *et al*., 2008 & Lenzenweger *et al*., 2007) and higher in clinical settings, up to 10% in psychiatric outpatients and 20% in psychiatric inpatients (Torgersen, 2005 & Gunderson *et al.*, 2009). This disorder is associated with a higher risk of suicide and self-harm with up to 10% of patients committing suicide (Oldham, 2006), as well as a high comorbidity for other mental disorders, such as anxiety disorders (60.5%), mood disorders (34.3%), eating disorders (53.8%) and substance abuse (38.2%) (Skodol *et al*., 2005 & Grant *et al*., 2008). The association between borderline personality disorder and depression has been studied and contributes to an increased number and the seriousness of suicide attempts (Soloff *et al*., 2000).

Agitation and aggression is not unique to BPD, as there are many other neurological (e.g., Alzheimer's disease) and psychiatric disorders where it is a core feature of the disease. In BPD, however, agitation and aggression underlie and/or contribute to these patients' unstable and intense interpersonal relationships (DSM-V criteria in parentheses #2), affective instability (#3), self-damaging impulsivity (#4) recurrent suicidal behaviors, threats and self-injurious behavior (#5), as well as inappropriate, intense anger or difficulty controlling anger (#8). Altogether, internal, and external agitation and aggression, impulsivity, emotional instability results in severe and significant functional impairment and disability, as well as a lower quality of life for BPD patients in general. Therefore, agitation and aggression is a core feature of BPD that not only negatively impacts five (5) of the DSM-V BPD diagnostic criteria, but more importantly BPD patient functioning and quality of life.

The earlier the disease expression, the greater the functional impairment secondary to deficits in psychosocial functioning. Across the lifespan these deficits become progressively evident reducing BPD patient's autonomy. Although BPD patients may experience a symptomatic remission as they age, frequently they experience more difficulties in finding and maintaining employment and healthy and stable interpersonal relationships thereby reducing their quality of life. In comparison, patients with BPD have more functional impairment and higher use of medical, mental health and social services than patients with major depressive disorder (Skodol *et al*., 1999).

According to the NICE Borderline Personality Disorder Clinical Guideline (NICE BPD CG, 2009/2018), BPD patients use mental health services at higher rates than most other mental health patients, except for schizophrenia. They also have higher use of medical resources such as primary care and emergency care because self-harm injuries, accidents, and suicide attempts. Likewise, BPD patients are heavy users of other type of services, for instance, they are overrepresented in the criminal justice system (NICE BPD CG). Studies demonstrate that most of the associated BPD treatment related-cost are indirect costs, as a consequence of BPD course over the lifetime (e.g., development of a substance use disorder) and/or functional impairment related-costs (e.g., lack of productivity) (Salvador-Carulla *et al*., 2014).

Currently, psychotherapy is the first line treatment for borderline personality disorder. Several methods of psychotherapy are available including cognitive behavioral, interpersonal, or psychodynamic treatments. Dialectical behavioral therapy seems to be the most efficacious. If psychotherapy results in remission, less is known regarding whether the effect is maintained. Finally, it should be noted that the majority of the BPD population does not have exposure to the resources (i.e., providers and/or financially) to receive psychotherapy.

Despite the burden of this disease, which represents a high cost to patients, their families and society, no pharmacological treatment has been approved for BPD (NICE BPD CG, 2009/2018). Many treatments are

prescribed to manage the symptoms and/or comorbidities (Stoffers *et al*., 2010), but these have limited efficacy and/or have significant side-effects (e.g., weight gain, somnolence, tardive dyskinesia). If there is a formal diagnosis of comorbid depression, psychosis, or bipolar disorder, then the use of antidepressants, antipsychotics, and mood stabilizers, respectively would be within their licensed indications. In situations where depressive or psychotic symptoms or affective instability fall short of diagnostic criteria for mental illness, the use of psychotropic drugs is largely unlicensed or "off-label".

Psychotherapy is, therefore, the first-line treatment for this population though efficacy is limited, and duration of response is variable with more research needed in this area. Altogether, the BPD prevalence, severity, functional impairment, resource utilization and lack of an adequate treatment all reinforce the high unmet need in this population.

Vafidemstat has demonstrated an ability to increase sociability, as well as decrease agitation and aggression across seven different animal species, and in several clinical trials including the REIMAGINE trial in BPD. The REIMAGINE trial not only saw significant improvements in BPD patient's agitation and aggression, but also improvements in the other non-agitation and aggression aspects of the disease (DSM-V BPD Diagnostic Criteria #1, 3, 6, 7, and 9). The REIMAGINE Phase IIa CNS basket trial on agitation and aggression also provided important information that influenced PORTICO's design, as there were statistically significant results in the treatment of agitation and aggression as well as positive global effects across three psychiatric disorders (BPD, ADHD and ASD). Therefore, the primary aim of PORTICO is to investigate vafidemstat's efficacy in treating agitation and aggression associated with BPD and to examine its potential to treat the overall disease, as well as evaluate the safety profile in adult BPD patients

In REIMAGINE, vafidemstat's impact on adult BPD participants was assessed using the Borderline Personality Disorder Checklist (BPDCL), the Neuropsychiatric Inventory (NPI) and the Clinical Global Impression of Severity and Improvement (CGI-S, CGI-I) scale focused on agitation and aggression. In addition to improvements in the scales measuring agitation/aggression (CGI-S, CGI-I, NPI 4-item Agitation/aggression subscale), results showed benefit of vafidemstat treatment on the scales assessing overall status of the patients, the global BPDCL and the Total NPI scales, with several BPD participants falling below the threshold for BPD diagnosis after 8 weeks of treatment. There were also significant differences for the BPDCL on the combined agitation/aggression-related domains, as well as the combined non-aggression related domains. These results suggest that vafidemstat has a broader psychiatric impact beyond the effect on agitation and aggression and may provide an overall BPD treatment benefit. Therefore, PORTICO will primarily focus on both, the treatment of agitation and aggression in BPD and the broader effect on the overall disease.

According to the Gunderson & Hoffman (2005), research on BPD is 20 to 30 years behind that on other major psychiatric disorders such as bipolar disorder and schizophrenia. Moreover, Zimmerman & Gazarian (2014) conducted a search of the National Institute of Health (NIH) Research Portfolio Online research grants for the last 25 years and concluded that the level of funding for bipolar disorder was more than 10 times greater than the level of funding for BPD, suggesting that NIH research funding for BPD is not proportionate to the morbidity, mortality, and the psychosocial and health cost associated with this disorder. Therefore, more evidence is needed to identify an appropriate medical treatment for the management of this psychiatric disorder. The PORTICO study is designed to address this important knowledge gap and high unmet need in BPD patients. PORTICO will be one of the few current studies to investigate the efficacy of a treatment in the pharmacological management of BPD. The study results may also guide and inform the design of future clinical trials.

1.6. Potential Risks and Benefits

The guiding principle for dose adjustment in Phase II trials is to avoid unnecessary over- or under-exposure to a given active ingredient. Vafidemstat safety and tolerability dose selection was first based on toxicology, pharmacokinetic (PK) and pharmacology non-clinical studies to estimate the clinically safe and effective dose.

LSD1/KDM1A has been shown to play a role in hematopoiesis and, thus, NOAEL for vafidemstat was established as the dose that would not provoke a reduction of hematological parameters over 50% from the baseline levels.

Since the initiation of clinical trials with vafidemstat, no significant safety related actions were taken by ORYZON GENOMICS S.A. or the Regulatory Authorities. After analysis of information collated in the last available Development Safety Update Report (DSUR), no relevant safety findings were identified with vafidemstat use.

Appropriate vafidemstat safety and tolerability was demonstrated in the Phase I clinical study. Based on this Phase I trial, vafidemstat 1.2 mg/day was established as the maximal dose where hematological impact was minor (i.e., <30% decrease in platelets). Therefore, the 1.2 mg/day dose was selected for the REIMAGINE Phase II study. Other Phase II trials where two different vafidemstat doses (0.6 and 1.2 mg/day) were assessed also supported vafidemstat's safety and tolerability, including those enrolling an elderly AD population. Therefore, it is considered appropriate to evaluate the 1.2 mg/day dose of vafidemstat for this Phase IIb trial.

All collected data support the potential benefit of vafidemstat in the treatment of CNS diseases, reducing agitation and aggression, as well as its safety data demonstrating that it is safe and well-tolerated. Therefore, the benefit-risk ratio for vafidemstat appears positive when the drug is used according to the guidelines outlined in the PORTICO protocol.

Appropriate participant selection is one factor in considering the balance of risks of AEs against potential clinical benefit. Therefore, the PORTICO study protocol includes inclusion and exclusion criteria, as well as details of routine follow-up safety monitoring and participant management. For instance, there are no available data on vafidemstat's impact on the reproductive system (see Section 1.3 for Reproductive and developmental toxicity). Thus, the protocol includes the requirement for the use of effective contraception methods in all enrolled participants and their partners.

In addition, a DMC will be appointed (see Section 10.4.1), which will review unblinded safety data to monitor the study safety throughout the trial. Finally, blinded medical monitors will review safety and efficacy data throughout the trial in order to assure the study safety and a continuous risk/benefit assessment.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

Primary Objectives

- To investigate the efficacy of vafidemstat in the treatment of agitation and aggression in adult BPD patients
- To investigate the efficacy of vafidemstat in the treatment of adult BPD patients

Secondary Objectives

- To investigate the effect of vafidemstat in reducing the severity of BPD symptoms in adult patients
- To evaluate the safety of vafidemstat in adult BPD patients

Exploratory Objectives

- To explore the impact of vafidemstat on functional impairment in adult BPD patients
- To explore the impact of vafidemstat on cognition in adult BPD patients
- To evaluate vafidemstat plasma concentrations (pharmacokinetics) as well as vafidemstat's LSD1-target engagement in peripheral blood mononuclear cells (PBMCs) (pharmacodynamics) after treatment

2.2. Study Endpoints

Primary endpoints – Efficacy

- To evaluate the difference on the Clinical Global Impression-Severity focused on Agitation/Aggression (CGI-S A/A) from baseline to specific weeks, between the active treatment arm and the placebo arm.
- To evaluate the difference on the Borderline Personality Disorder Checklist (BPDCL), from baseline to specific weeks, between the active treatment arm and the placebo arm

Secondary endpoints – Efficacy

- To evaluate the change overtime on the CGI-S A/A
- To evaluate the change over time on the BPDCL
- To evaluate the difference on the following measures, from baseline to specific weeks, as well as change over time, between the active treatment arm and the placebo arm:
    a) Borderline Evaluation of Severity over Time (BEST)
    b) Beck Depression Inventory – II (BDI-II)
    c) State-Trait Anger Expression Inventory 2 (STAXI-2)
    d) State-Trait Anxiety Inventory (STAI)

Secondary endpoints – Safety

- To evaluate the following safety endpoints throughout the study, from baseline to week 14, including:

a) Number, frequency and severity of Treatment Emergent Adverse Events (TEAEs)

b) Number, frequency and severity of Serious TEAEs

c) Number and percentage of withdrawn participants due to TEAEs

d) Frequency of physical examination parameters, vital signs and ECG parameters of potential clinical concern throughout the study period

e) Frequency of clinical laboratory parameters (hematology, including platelets, and clinical chemistry) of potential clinical concern throughout the study period

f) Columbia – Suicide Severity Rating Scale (C-SSRS)

g) Use of concomitant medication throughout the study period

- To evaluate the change from baseline to specific weeks of the following safety endpoints:

a) Physical examination, vital signs, and ECG parameters

b) Clinical laboratory parameters (hematology, including platelets, and clinical chemistry)

Exploratory endpoints

- To evaluate the difference on the following measures, from baseline to specific week, as well as change over time, between the active treatment arm and the placebo arm:

a) Columbia – Suicide Severity Rating Scale (C-SSRS)

b) Number of visits to healthcare services outside of the trial (primary care, mental health services and ER visits)

c) Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR)

d) Brief Assessment of Cognition (BAC) Scale

- To evaluate vafidemstat plasma concentrations (pharmacokinetics) as well as vafidemstat's LSD1-target engagement in peripheral blood mononuclear cells (PBMCs) (pharmacodynamics) after treatment, at baseline, and at weeks 4, 8, and 12

3. STUDY DESIGN

3.1. Overall Study Design

PORTICO is a double blind, randomized, placebo-controlled, adaptive 14-weeks Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population.

The study will be a global, multicenter clinical trial conducted in approximately 20 study sites in Europe and the US.

Up to 188 participants will be enrolled and randomized in a 1:1 ratio (94 participants per arm) to active treatment with vafidemstat (1.2 mg) or placebo to yield an expected 150 completed study participants, since it is anticipated that 20% of participants will drop out of the trial.

An interim analysis will be performed after 90 participants have completed the specific week assessments (expected 108 patients enrolled after accounting for 20% dropout). Individuals that had the opportunity to complete their specific week visit, but were lost to follow-up, will also be included in the analysis, however, will not be included in the 90-patient count required for initiation of the interim analysis. The objective of this interim analysis will be to reassess the sample size based on the observed variability and effect sizes. If the conditional power is too low for both endpoints or the required sample size adjustment is considered to be too large, the study sample size will not be increased.

All recruited participants will have to complete a 2-week screening period to ensure study eligibility criteria, followed by 12-week double-blind period of active treatment (vafidemstat 1.2 mg/day) or placebo in a 1:1 randomization scheme; then, a 2-week follow-up participant-blind placebo run-out period (Figure 1). The purpose of the participant-blind placebo run-out period is to obtain safety and efficacy data after two-weeks without active study treatment. Participants will be kept treatment blinded in order to avoid efficacy assessment bias.

PORTICO will involve 9 study visits. Study visits are planned every two weeks after Baseline as reflected in the Schedule of Assessments and Procedures (Table 1).

The study treatment, vafidemstat or placebo, will be administered orally as single capsule in the early morning before the first daily food intake.

Participants will be asked to maintain a stable regimen of background pharmacological therapy, not to initiate any prohibited medications during the trial and to advise their study physician of any medication changes throughout the study.

All enrolled participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration, given that psychotherapy is the standard of care for BPD. Participants entering the study cannot start any type of psychotherapy within 3 months prior to enrollment or throughout the trial duration. Specifically, participants receiving psychotherapy before initiating the study need to remain in psychotherapy throughout the trial. However, those participants not receiving psychotherapy before the study should not initiate psychotherapy during the trial. Participants deemed needing immediate or emergent psychotherapy and those initiating psychotherapy during the study will be discontinued from the trial.

3.2. Study Timelines

The anticipated first patient in (FPI) is planned for Q1 2021. The planned last patient, first visit (LPFV) is on Q1 2023. The end of study is defined as the date of the last patient out (LPO) planned on Q3 2023.

4. STUDY POPULATION

4.1. Selection Criteria

Participant selection will be based on the inclusion and exclusion criteria listed below. Participants who meet each of the inclusion criteria at the Screening Visit and Baseline Visit (unless otherwise specified) and none of the exclusion criteria at the Screening Visit or Baseline Visit (unless otherwise specified) are eligible to participate in this study. A patient could be re-screened only after the sponsor's approval. Sponsor has the final decision in determining clinical trial participation after medical monitor review of each participant's medical history, concomitant medications, laboratory findings and participant eligibility form, as well as review against the inclusion and exclusion criteria below.

4.1.1. Inclusion Criteria

The participant must meet all inclusion criteria:

1. Men and women 18-65 years of age.
2. DSM-5 diagnostic criteria for BPD at least 3 months before the Screening visit. The Mini-International Neuropsychiatric Interview (MINI) will be administered at screening in order to confirm BPD diagnosis, as well as to confirm participant does not meet other relevant exclusion criteria.
3. Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR) Agitation & Aggression (A/A) subscale score of $\geq$ 16 (severity x frequency) summed across the four (4) items comprising the A/A subscale, and the sum of the A/A subscale severity scores $\geq$ 6.
4. Stable living environment for > 6 months before the Screening visit.
5. Body mass index (BMI) of at least 18.5 kg/m^2, but no more than 35 kg/m^2.
6. Willing and able to adhere to the prohibitions, restrictions and requirements specified in this protocol.
7. Otherwise, healthy and medically stable based on medical history.
8. Clinical and neurological examinations and laboratory tests, as well as 12-lead ECG performed during screening that confirms participant is healthy and medically stable.
9. Able to read and write fluently and must have adequate hearing and visual acuity to complete the required testing outlined in this protocol.
10. Stable in their permitted regimen of background therapy (see section 6.1.2) for concomitant medications at the Screening visit. Participants should maintain treatment throughout the study and not initiate any prohibited medications during the trial, as well as agree to inform their study physician of any medication changes throughout the trial.
11. Enrolled participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration. That is, participants receiving psychotherapy will need to have it started at least 3 months before the Screening visit and remain in psychotherapy throughout the trial. Participants not receiving psychotherapy should not initiate psychotherapy during the trial.
12. Fertile male and female participants must use highly efficient contraception, from the Screening visit until 30 days after last dose of the IMP, defined as:

    A method with less than 1% failure rate (e.g., permanent sterilization, hormone implants, hormone injections, some intrauterine devices, or vasectomized partner)

OR

The use of two methods of contraception (e.g., one barrier method [condom, diaphragm or cervical/vault caps] with spermicide and one hormonal contraceptive [e.g., combined oral contraceptives, patch, vaginal ring, injectable and implants])

OR

Abstinence

13. Female participants of childbearing potential must have a negative urine pregnancy test at screening and baseline.
14. Signed informed consent by participant prior to the initiation of any study specific procedure.

4.1.2. Exclusion Criteria

The participant must not meet any of the exclusion criteria:

1. Failure to perform screening or baseline procedures.
2. DSM-5 diagnosis of intellectual disability, autism spectrum disorder, schizophrenia, schizoaffective disorder, bipolar disorder (or related disorders) or major depressive disorder (MDD) with psychosis.
3. Current DSM-5 diagnosis of conduct disorder, anorexia nervosa, bulimia nervosa, binge-eating disorder, oppositional defiant disorder, paranoid personality disorder or obsessive-compulsive disorder.
4. Current DSM-5 diagnosis of panic disorder or post-traumatic stress disorder (PTSD). However, participants with PTSD, generalized anxiety disorder (GAD), social anxiety disorder (SAD), MDD without psychosis, attention deficit hyperactivity disorder (ADHD) are eligible if symptoms have been stable for at least 90 days prior to the Screening visit, these disorders are not the primary focus of treatment, changes in any treatment for these disorders would not likely be required for the duration of the study, and in the investigator´s opinion these disorders will not interfere with the assessment and/or accuracy of the study endpoints.
5. History of moderate or severe substance or alcohol use disorder according to DSM-5, with the exception of nicotine and caffeine, within 6-months before screening.
6. Use of illicit drugs (including medically indicated illicit drugs) for at least one week before Screening and participants unwilling to abstain from use of these substances during the study. Use of alcohol or cannabinoids is not allowed within 24 hours prior to a study visit. Regarding cannabis, patient self-report of abstinence within 24 hours will be used for inclusion decision-making versus the urine drug test results.
7. Hospitalization or medication change for any reason, two months prior to the Screening visit or during the Screening period, that makes the participant medically or mentally unsuitable for trial participation.
8. Clinically significant, advanced or unstable disease that is likely to result in rapid deterioration of the participant's condition or affect their safety during the study, including but not limited to:
    a. Seizure disorders, excluding febrile seizures of childhood
    b. Respiratory insufficiency, the status must be determined as usual clinical practice
    c. Hepatic impairment (serum values of total bilirubin value, alanine aminotransferase

[ALT], aspartate aminotransferase [AST] and gamma-glutamyltransferase [GGT] 1.5 x upper limit of normal [ULN])

d. Renal insufficiency (serum creatinine >2mg/dl)

e. Heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within 6 months before Screening visit)

f. Hypertension treatment with more than 2 drugs

g. Atrioventricular block (type II/Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or prolonged QTcF-interval (males >450 msec and females >470 msec)

h. Uncontrolled diabetes (Hb1Ac >7.5)

i. Hematological disorders

j. Platelets <130,000/mm^3 and/or neutrophils <1,800/mm^3

k. Malignant tumors within the last 5 years other than basal cell or Stage 1 squamous cell carcinoma of the skin

9. Positive results for tuberculosis (the status must be determined as usual clinical practice, i.e., by medical history, signs and symptoms), Human Immunodeficiency Virus (HIV), Hepatitis C or Hepatitis B (Hepatitis B surface Antigen [HbsAg]) serology obtained at the Screening Visit.
10. Uncontrolled hypo- or hyperthyroidism at Screening Visit, based on laboratory parameters.
11. Clinically significant infection within the previous 30-days (e.g., persistent or acute infection such as a urinary tract infection or upper respiratory infection).
12. Chronic drug intake of:

a) Anticoagulants (only 81 mg/day acetylsalicylic acid is permitted).

b) Short and medium half-life oral benzodiazepines are allowed in occasional short-term prescription use. Participants should not take these medications within 24 hours before any study visit. Long half-life benzodiazepines are not allowed.

c) Z-drugs – i.e.: zaleplon, zolpidem, zopiclone – are allowed in occasional short-term prescription use. Participants should not take these medications within 24 hours before any study visit.

d) Corticosteroids or immunosuppressant (only inhaled or topical suspension are allowed).

e) Myelosuppressive treatments such as chemotherapy and radiation.

f) Medications known to be UGT inhibitors or inducers should be used with caution (*)

- (*) UGT Inhibitors (e.g.: adenine, propofol, flunitrazepam, ertugliflozin, ketoconazole, valproic acid, flurbiprofen, silibinin, sodium aurothiomalate, gemfibrozil, deferasirox, probenecid, amitriptyline, indomethacin, ubrogepant)
- UGT inducers (e.g.: carbamazepine, phenytoin, phenobarbital, rifampicin, testosterone propionate, lamotrigine, primidone, ethinylestradiol, desogestrel, orthosiphon stamineus)

These lists are not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label.

g) The concomitant use of MAO inhibitors is forbidden 14 days before Screening visit and throughout the study. The concomitant use of other antidepressants in stable dose for at least 2 months before the Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) (**).

(**) The MAO inhibitory activity of vafidemstat has only been observed in vitro; data in humans does not support a MAO inhibitory effect at the doses selected in this protocol. Specifically, the MAO inhibitory activity has not been observed in humans at the vafidemstat therapeutic dose range in clinical trials-to-date, but a potential impact at higher doses (e.g., overdose) cannot be ruled out. Therefore, the concomitant use of any drugs for which cases of serotonin syndrome or hypertensive crisis have been reported when in combination with MAO inhibitors should be carefully monitored. The concomitant use with these drugs should be done with caution. At Baseline Visit, participants will be provided with educational material to create awareness around serotonin syndrome.

h) The concomitant use of typical antipsychotics is forbidden. The concomitant use of atypical antipsychotics in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria). In addition, the concomitant use of an atypical antipsychotic medication (e.g., quetiapine) is allowed for the treatment of insomnia AND only at sub-therapeutic dose (e.g., below that typically used to treat schizophrenia).

i) The concomitant use of mood stabilizers in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) when these medications are prescribed as per their labelled indications.

j) The concomitant use of nootropics; for instance, racetams, amphetamines, methylphenidate, levodopa, atomoxetine, preparations containing Gingko biloba in stable dose for at least 2 months before Screening are allowed for the treatment of psychiatric comorbidities (as per inclusion/exclusion criteria) when these medications are prescribed as per their labelled indications.

k) The concomitant use of centrally active anti-hypertensive drugs, such as clonidine, a-methyldopa, and guanfacine, as well as guanethidine, in stable dose for at least 2 months before Screening are allowed but should be used with caution.

l) The concomitant use of medications which may have an impact on blood count changes should be used with caution (e.g.: heparin, quinine, quinidine, penicillin, sulfonamides, NSAIDs, anticonvulsants, antirheumatics, oral antidiabetics, gold salts, diuretics rifampicin, ranitidine). This list is not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

m) The concomitant use of platelet aggregation inhibitors should be used with caution (e.g.: COX-2 inhibitors, ADP receptor inhibitors, thromboxane inhibitors). This list is not intended to be exhaustive. Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

13. Esketamine in the past 90 days before the Screening visit.
14. Electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS) in the past 90 days before the screening visit.
15. Any regular intake of medications acting directly on central nervous system that investigator considers relevant to the study.

16. Member or immediate family of the study personnel or subordinate to any of the study personnel.
17. Enrollment in another investigational study or intake of investigational drug within the previous 3 months.
18. Suicide attempt within the 6-month prior to the Screening visit or significant risk of suicide (in the opinion of the investigator, defined as a "yes" to suicidal ideation questions 4 or 5, or answering "yes" to suicidal behavior on the Columbia-Suicide Severity Rating Scale within the past 6-months).
19. Any condition that in the opinion of the investigator makes the participant unsuitable for inclusion in the study.

4.2. Removal of Participants from Therapy or Assessment

Participants are free to discontinue trial participation at any time. Withdrawal from the trial will not affect or prejudice participants further care or treatment. In addition, participants may be withdrawn from study treatment and assessments at any time, if deemed necessary by the PI or Sponsor.

Potential reasons for withdrawal of participants from this study include, but are not limited to:

- The participant withdraws his or her consent (defined as a participant who explicitly takes back his or her consent)
- The PI considers it, for safety and/or study compliance reasons, in the best interests of the participant that he or she be withdrawn
- Initiation of concomitant medication prohibited by the study protocol (see Table 2)
- Initiation of psychotherapy in psychotherapy naïve participants at baseline
- Discontinuation of psychotherapy in participants receiving therapy at baseline
- Pregnancy
- Participant is lost to follow-up (defined as a participant who fails to comply with scheduled study visits or contact, who has not actively decided to withdraw from the study, and for whom no alternative contact information is available [this implies that at least two attempts have been made to contact the participant])
- Any center personnel break the randomization code for that participant
- The participant attempts suicide or is at significant risk of suicide (either in the opinion of the investigator or defined as a "yes" to suicidal ideation questions 4 or 5 or answering "yes" to suicidal behavior on the C-SSRS during the study)

The reason and date the participant is withdrawn from the study and further treatment with the IMP will be documented in the electronic case report form (eCRF) (e.g., lost to follow-up, consent withdrawn, incorrect enrollment, AEs, etc.).

If a participant is withdrawn from the study, the PI should attempt to complete all study assessments in Table 1 for the EoS Visit.

Participants who withdraw due to an AE should be followed until resolution of the AE, or the PI or delegated center personnel decides that the AE is stable, and the participant does not need further follow-up. All AEs should be followed up according to Section 8 ADVERSE EVENTS.

If a participant is withdrawn from the study, all data collected until the time of withdrawal will be included in the analyses.

Participants who drop out after they have been randomized and have received at least one IMP administration will not be replaced.

4.3. Premature Termination of the Study

The PI or the Sponsor may terminate this study prematurely for any reasonable cause. The Independent Ethics Committee(s)/Institutional Review Board(s) (IECs/IRBs), Competent Authority (CA)/Regulatory Authorities (RAs) and DMC should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in the study, or potential study participants
- A decision on the part of the Sponsor to suspend or discontinue development of the IMP

If the CA/RA obtains information that raises doubts about the safety or scientific validity of the clinical study, the CA/RA can suspend or prohibit the study.

If the study is prematurely terminated or suspended for any reason, the PI/institution should promptly inform the study participant and should assure appropriate therapy and follow-up for the participants.

5. STUDY TREATMENT

5.1. Investigational Medicinal Product

5.1.1. Treatment Regimens

During the 12-week, double-blind, randomized, placebo-controlled *Treatment period,* from Visit 2 to Visit 8, participants will be randomized to one of these two treatment arms:

- Vafidemstat 1.2 mg/day fiw: participants will receive 1 capsule with 1.2 mg/day of vafidemstat from Monday to Friday and 1 capsule of placebo from Saturday to Sunday.
- Placebo: participants will receive 1 capsule of placebo per day.

During the 2-week, participant-blind, *Run-out Safety follow-up period*, from Visit 8 to Visit 9, all participants will receive 1 capsule of placebo per day.

Participants will be instructed to take the IMP orally as a single capsule, in the early morning before the first food intake (after overnight fasting conditions), once daily.

When attending planned study visits, participants must return to the investigator all the empty, partially used or unused blisters as well as the box and must take the IMP from the new box dispensed at the clinic, after all the corresponding blood extractions have been performed.

5.1.2. Identity of Investigational Medicinal Product

The Sponsor will supply the IMP (i.e., vafidemstat and placebo). Batch numbers, Transmissible Spongiform Encephalopathy (TSE) statements, and Certificates of Analysis authorized by a Qualified Person (QP) in the European Union (EU) will be issued.

[redacted].

[redacted] manufactures vafidemstat capsules containing 1.2 mg of vafidemstat as well as capsules with placebo, in accordance with Good Manufacturing Practice (GMP). Each medication unit will be labelled following the rules in Addendum 13 of the GMP guidelines (EU Commission GMP Guidelines for IMPs, Annex 13, 2017).

Vafidemstat and placebo capsules will be transported and stored at [redacted]

5.1.3. Packaging and Labelling of Investigational Medicinal Product

Secondary packaging, labelling, including blinding of drug and placebo products will be performed by [redacted]. Medication label will follow the EU rules in Annex 13 of the GMP guidelines and the US CFR Title 21 – Part 210.

It is the responsibility of the Sponsor to guarantee that the samples of the clinical trial will be supplied to the investigative center correctly labelled according to Annex 13 of the GMP of the EU and CFR Title 21 – Part 210 of the US. The Sponsor can delegate this function to the elaborating entity of the samples, the CRO or to the pharmacy service of the centers.

Medication will be packed in 14-day treatment boxes. Each 14-day treatment box will contain 3 blisters with 5 active or placebo capsules and 3 more blisters identified as Saturday and Sunday containing 2 placebo capsules each. Therefore, the whole study treatment for a participant will be composed by seven 14-day treatment boxes to be dispensed individually at each study visit. Each box contains a sufficient number of capsules to cover the period between visits as per study protocol, including the window period (±2 days).

The wording on the labels will be in accordance with Good Manufacturing Practice regarding labelling and national and/or local regulatory requirements.

No manipulation, repackaging, or relabeling of IMP is permitted after QP release by the IMP supplier unless a repackaging/relabeling agreement exists, and the documentation is available to [redacted] and, where necessary, new QP releases are made.

Each of the treatment boxes will be identified using a unique kit number. The study medication must be stored in a safe and secure location, and in accordance with the storage conditions specified on the label.

The details of the secondary packaging and the instructions for the IMP intake are available in a separate Pharmacy Manual.

5.1.4. Reception, Storage and Handling of Investigational Medicinal Product

The sponsor has the responsibility of providing the IMP for free, perfectly identified and prepared in agreement with GMP's procedures as established in pertinent EU and US regulations.

The medication of the clinical trial can only be sent to the investigation center after having obtained all the required approvals.

The IMP supplier will send the samples of medication to the Pharmacy Service of the study center together with the pertinent documentation (mainly, the analytical memory of the samples).

The Pharmacy Service is responsible for receiving the samples of medication, to verifying and/or assuring that they follow the in forced legislation of labelling, preserving them correctly and sending them to the study center after verifying that all the approvals have been obtained and the contracts have been signed.

The PI, or the responsible investigator with delegated function, must assure the correct reception in the study center of the medication for the clinical trial (inventory of samples and review of the labelling) as well as its correct storage according to the specific procedure of conservation. The reception, storage and dispensation of the medication in the study center will be documented properly according to the guidelines established in the corresponding SOP.

The samples of medication will be stored [redacted], according to the normative of conservation, in a room of restricted access [redacted] IMP storing temperature at the site should be constantly monitored and registered.

Participant should be instructed to store the study medication [redacted] reflected in the study medication label.

5.1.5. Method of Assigning Participants to Treatment

An Interactive Web Response System (IWRS) will be used in this study. When a participant is to be randomized, the investigator will contact the IWRS. The IWRS will allocate the participant to a treatment group and assign the participant a randomization number in accordance with the specifications from the Department of Biostatistics, [redacted], and then follow up by fax, e-mail, or the web (depending on availability or preference at the site).

5.1.6. Administration of Investigational Medicinal Product

The dispensation of the medication will be conducted by a member of the investigative team to which the PI has delegated the above-mentioned responsibility and who must inform the participant about the correct ingestion.

At each study visit, only one box for a 14-days treatment period should be dispensed to the participant. One box contains a sufficient number of capsules to cover the 14±2 day's period between the study visits.

At Visit 2 (Baseline Visit), the first IMP intake should occur after the completion of all study procedures but before the administration of the COAs in order to allow more time for observation of potential serotoninergic syndrome symptoms after first drug intake.

For the remaining visits, on the day of the study visit, the participant should not take the capsule at home before attending this visit. The intake of the first capsule of the new box dispensed at the visit should take place at the clinic under overnight fasting conditions after blood sampling.

If the study visit is scheduled in the afternoon/evening, no fasting conditions are required before IMP intake at the clinic.

In between study visits, participants will be instructed to take the IMP orally once daily as a single capsule with a glass of water in the early morning before the first food intake (after overnight fasting conditions).

The details of the secondary packaging and the instructions for the IMP intake are available in a separate Pharmacy Manual.

Any dispensation of the IMP will have to be registered in the participant's file, the eCRF and the record form of dispensation of medication, according to the specific Standard Operating Procedures (SOP) of the study center.

5.1.7. Return or destruction of Investigational Medicinal Product

At each study visit, the participant should return all the empty, partially used, or unused blisters as well as the box.

Once the clinical trial is finished, the entire remaining unused IMP, as well as the boxes of used medication (empty or partially used) will be returned for central destruction.

Any return of the remaining IMP will be documented according to the correspondent SOP of the study center.

5.2. Selection of Doses in the Study

Results from the Phase I single and multiple oral doses of vafidemstat (0.2 mg; 0.6 mg; 1.5 mg; 2.5 mg; 4 mg for the single dose study and 0.2 mg; 0.6 mg; 1 mg; 1.5 mg; 2.5 mg and 4 mg for the multiple dose study) in healthy young and elderly volunteers showed a good safety and tolerability profile. Thus, vafidemstat 4.0 mg/day was the MID for a multiple dose regimen as participants who received the active treatment reported a significant decrease (≥50% from baseline) in the platelet count. Considering that the MID was met at this dose, the MTD was 2.5 mg/day based on the guiding principle for dose adjustment, to avoid unnecessary over- or under-exposure to a given active ingredient.

Vafidemstat dose selection was initially based on toxicology, pharmacokinetic and pharmacology non-clinical studies allowing the estimation of the clinically safe and effective dose. In particular, the NOAEL established from short and long-term rat and dog toxicology studies corresponded to human equivalent doses (HED) in the range of 2-4 mg/day, being platelet and neutrophil depletion the most relevant (on-

target) tolerability effects. Additionally, maximum target engagement and signs of therapeutic activity had been observed in non-clinical efficacy models from doses as low as the HED of 0.5 mg/day. Subsequently, appropriate vafidemstat safety and tolerability had also been shown in healthy volunteers in a 5-day treatment Phase I clinical trial and in patients at several long-term (up to 15 months) Phase IIa trials. Doses of 0.6 mg/day and 1.2 mg/day have been used in these Phase II trials. None of these two doses had any clinically relevant hematological impact. Furthermore, in the REIMAGINE Phase IIa clinical study, efficacy in reducing aggression in BPD patients as well as a significant improvement in the overall function was shown with a 1.2 mg/day dose of vafidemstat (see Section 1.4.2). Therefore, is considered appropriate to evaluate this dose of vafidemstat, 1.2 mg/day, in a BPD population.

- **Placebo**
  Name: Placebo
  Pharmaceutical form: [redacted]
  Administration route: Oral
  Unit Dose: [redacted], packed in blisters (blisters of 2 or 5 capsules, 3 blisters in a box)
  Manufactured by: [redacted]

- **Dose – 1.2 mg**
  Name: vafidemstat
  Pharmaceutical form: [redacted] packed in blisters (blisters of 5 capsules, 3 blisters in a box)
  Administration route: Oral
  Unit Dose: 1.2 mg
  Manufactured by: [redacted]

If a participant's medication is lost by breakage or spillage, the PI will retrieve the replacement medications and communicate to the Sponsor. The reason why the replacement medication has been used should be documented on the eCRF “Comments Form”.

5.3. Blinding

To guarantee double-blind conditions, vafidemstat and placebo will be presented in identical capsules consisting of special opaque material for clinical studies, and participants will take the same number of capsules daily. The sample labels will have no information that would allow identification of the treatment administered.

The IWRS unblinding procedure is described in the IWRS User Guide.

The study randomization should only be broken for valid medical or safety reasons, for example, a SAE where it is necessary for the PI to know which treatment the participant is receiving to ensure the appropriate SAE treatment. In the event of an emergency, the PI will have to decide on the necessity of unblinding the participant’s treatment assignment. The PI will report about this event to the Sponsor as soon as possible. If unblinding occurs, the investigator must record the reason for unblinding, as well as the date and time of the event. Corresponding information will be recorded on the eCRF and will be documented in a note to file which will be filed in the Trial Master File.

5.4. Post-study Access to IMPs

Post-study access to the IMP will not be available.

6. Prior and Concomitant Therapy

Prior medication is defined as medication received prior to first IMP intake. Any medication received at least once after the first IMP intake will be considered as concomitant medication.

All prior medications taken within four weeks prior to screening will be recorded in the eCRF at Visit 1.

Concomitant medication will be recorded in the concomitant medication log/page of the eCRF throughout the study. Prior to initiating a new concomitant medication, participants should check with their study doctor.

Participants will be asked to maintain a stable regimen of background pharmacological therapy, not to initiate any prohibited medications during the trial and to advise their study physician of any medication changes throughout the study.

Psychotherapy treatment should also be registered in the eCRF.

6.1.1. Permitted/Prohibited psychotherapy

Considering that psychotherapy is the standard of care for BPD, all enrolled participants will need to maintain their pre-screening psychotherapy schedule throughout the trial duration. Participants entering the study cannot start any type of psychotherapy within 3 months prior to enrollment or throughout the trial duration.

Specifically, participants receiving psychotherapy before initiating the study need to remain in psychotherapy throughout the trial. However, those participants not receiving psychotherapy before the study should not initiate psychotherapy during the trial. Participants deemed needing immediate or emergent psychotherapy and those initiating psychotherapy during the study will be discontinued from the trial.

6.1.2. Prohibited/Permitted concomitant medications

Prohibited concomitant medications are shown below in Table 2. These concomitant medications are prohibited for the duration of the study. Washout periods prior to Visit 1 (Screening) are described in Table 2. The administration of these medications during the study treatment will lead to withdrawal of the participants from the study (see Section 4.2).

Any concomitant medications for psychiatric comorbidities (as per inclusion/exclusion criteria) are allowed when these medications are used as prescribed (see Table 3).

Table 2. Prohibited Concomitant Medication

	Washout period before Screening Visit (weeks)
Anticoagulants (e.g.: acenocumarol, warfarin, apixaban, dabigatran and rivaroxaban) - Only 81 mg acetylsalicylic acid is permitted	2
Short and medium half-life oral benzodiazepines are allowed in occasional short-term prescription. Participants should not take these medications within 24 hours before any study visit	8
Z-drugs (i.e.: zaleplon, zolpidem, zopiclone) are allowed in occasional short-term prescription. Participants should not take these medications within 24 hours	2

	Washout period before Screening Visit (weeks)
before any study visit	
Corticosteroids or immunosuppressant (only inhaled or topical suspension are allowed)	2
Typical antipsychotics	5
Long half-life benzodiazepines	8 - 21
Esketamine (in the past 90 days)	2.5
MAO inhibitors	2

Table 3. Allowed Concomitant Medication to be used with caution

UGT Inhibitors (e.g.: adenine, propofol, flunitrazepam, ertugliflozin, ketoconazole, valproic acid, flurbiprofen, silibinin, sodium aurothiomalate, gemfibrozil, deferasirox, probenecid, amitriptyline, indomethacin, ubrogepant)

UGT inducers (e.g.: carbamazepine, phenytoin, phenobarbital, rifampicin, testosterone propionate, lamotrigine, primidone, ethinylestradiol, desogestrel, orthosiphon stamineus)

Antidepressants in stable dose for at least 2 months before the Screening visit is allowed for the treatment of psychiatric comorbidities when these medications are used as prescribed per the inclusion and exclusion criteria*

Atypical antipsychotics in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities *

Mood stabilizers in stable dose for at least 2 months before Screening visit is allowed for the treatment of psychiatric comorbidities when these medications are prescribed as per their labelled indications*

Nootropics (e.g.: racetams, amphetamines, methylphenidate, levodopa, atomoxetine, preparations containing Gingko biloba) in stable dose for at least 2 months before Screening are allowed for the treatment of psychiatric comorbidities when these medications are prescribed as per their labelled indications*

Centrally active anti-hypertensive drugs, such as clonidine, a-methyldopa, and guanfacine, as well as guanethidine, in stable dose for at least 2 months before Screening are allowed but should be used with caution.

Medications which may have an impact on blood count changes (e.g.: heparin, quinine, quinidine, penicillin, sulphonamides, NSAIDs, anticonvulsants, antirheumatics, oral antidiabetics, gold salts, diuretics rifampicin, ranitidine). Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

Platelet aggregation inhibitors (e.g.: COX-2 inhibitors, ADP receptor inhibitors, thromboxane inhibitors). Drug-Drug Interactions (DDI) interactions should be reviewed in the label of the concomitant medication.

** Always as per inclusion/exclusion criteria*

7. STUDY ASSESSMENTS

7.1. Diagnostic Assessment

7.1.1. Mini-International Neuropsychiatric Interview (MINI)

The Mini-International Neuropsychiatric Interview (MINI) is a clinician-reported outcome measure administered as a structured diagnostic interview. The MINI was developed to enable the use of a brief structured interview for accurate diagnosis in multicenter trials and epidemiological studies (Sheehan *et al.*, 1998). The MINI has multiple modules and can be administered in its entirety or with a subset of the modules. Within each module there are decision trees which allow for screening questions to be asked to determine whether the entire module needs to be assessed. The MINI is designed to be administered by experienced clinicians with the capability to make the clinical judgments necessary to come to an accurate diagnostic profile.

7.2. Efficacy Assessments

The study efficacy assessments, for each of the main objectives, are summarized below in Table 4.

Table 4. Study Efficacy Assessments

Objective	Assessments
Primary – Efficacy	
	• Clinical Global Impression Severity focused on Agitation/ Aggression (CGI-S A/A) • Borderline Personality Disorder Checklist (BPDCL)
Secondary – Efficacy	
	• Borderline Evaluation of Severity over Time (BEST) • Beck Depression Inventory – II (BDI-II) • State-Trait Anger Expression Inventory 2 (STAXI-2) • State-Trait Anxiety Inventory (STAI)
Exploratory-Efficacy	
	• Agitation-Aggression Psychiatric Inventory-Clinician Report (AAPI-CR) • Brief Assessment of Cognition (BAC) • Columbia-Suicide Severity Rating Scale (C-SSRS) • Number of visits to healthcare services outside of the trial (primary care, mental health services and ER visits)

All efficacy assessments will be measured at each of the indicated visits shown in the Schedule of Assessments and Procedures (Table 1) and Section 7.7.

All scales and questionnaires will be administered in the local language. Only scales and questionnaires provided by the Sponsor that have been validated in the local language, to which they have been translated, will be used as primary and secondary endpoints in this study.

Raters will be trained and certified in all scales before rating patients. Training and certification process will be outlined in the training material. For each individual patient, the same certified rater should rate

the patient throughout the study. In case of unforeseen circumstances, certified back-up raters should be available throughout the study.

Performance-based Outcome (PerfO) measure

7.2.1. Brief Assessment of Cognition (BAC) Scale

The Brief Assessment of Cognition (BAC) is a performance-based outcome measure that directly assesses cognitive performance via verbal memory/learning, working memory, motor function, verbal fluency, speed of processing, and executive function tasks (Atkins *et al*., 2017). An electronic tablet-based version of the BAC will be used in this study. The tablet BAC was developed to allow standardized presentation of task instructions and stimuli, audio-recording of responses, and automatized scoring and data management. The BAC provides a composite measure of cognition, as well as individual scores for each of the six tasks. It has demonstrated equivalence with the original pen-and-paper measure (Atkins *et al*., 2017).

Patient-Reported Outcome (PROs) measures

7.2.2. Beck Depression Inventory – II (BDI-II)

The Beck Depression Inventory, Version 2 (BDI-II) is a widely used 21-item patient-reported outcome (PRO) assessing the severity of depressive symptoms (Beck *et al*., 1996). The BDI-II was developed to correspond to the DSM-IV and includes items measuring cognitive, affective, somatic, and vegetative symptoms of depression. Each item is rated on a 4-point scale with scores ranging from 0 (not at all) to 3 (extreme) for the severity of each symptom over the past two weeks. The BDI-II has excellent psychometric properties and has been found to be sensitive to change in depression.

7.2.3. Borderline Personality Disorder Evaluation of Severity over Time (BEST)

The Borderline Personality Disorder Evaluation of Severity over Time (BEST) is a 15-item PRO developed to assess BPD symptom severity and adaptive coping responses (Pfohl *et al.*, 2009). The first 12 items are focused on thoughts, emotions and behaviors related to BPD and participants are asked to rate each one on a 1 - 5 scale. The last 3 items ask about how frequently each of the three adaptive coping skills are used on a scale from “Almost Always” (5) to “Almost Never” (1). This instrument has good test-retest reliability and excellent internal consistency. The scale also demonstrated excellent discriminant validity and sensitivity to clinical change occurring as early as week 4 of the study (Pfohl *et al.*, 2009).

7.2.4. Borderline Personality Disorder Checklist (BPDCL)

The Borderline Personality Disorder Checklist (BPDCL) is a DSM-IV-based PRO designed to assess the extent to which respondents have been bothered by a range of BPD symptoms, over the course of the past month. Responses to the 47-items range from “Not at All” (1) to “Extremely” (5). Validation studies have demonstrated that the BPDCL discriminates between individuals with and without a diagnosis of BPD, and that it is sensitive to change of BPD symptoms (Bloo *et al.*, 2017; Calvo et. al., 2018). Overall, the BPDCL has good-to-excellent internal consistency, as well as very good discriminant, convergent and construct validity. Finally, as the confirmatory factor analysis on the BPDCL supported a nine-factor model aligned with the DSM-IV (as well as now DSM-V) BPD Diagnostic criteria, construct validity has been firmly established.

7.2.5.State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI, forms Y-1 and Y-2) is a 40-item PRO designed to measure two types of anxiety: *state-anxiety*, or current state anxiety about an event, and *trait-anxiety*, or general anxiety level as a personal characteristic (Spielberger *et al.*, 1983). Form Y, the most commonly used version of the scale, has 20-items for assessing state anxiety (STAI Form Y-1) and 20-items for assessing trait anxiety (STAI Form Y-2). State anxiety items (item 1 to item 20) include statements such as, "I am tense; I am worried" and "I feel calm; I feel secure" that measure the respondent's feeling in that moment. Trait anxiety items (item 21 to item 40) include statements such as, "I worry too much over something that really doesn't matter" and "I am content; I am a steady person" that measure how the respondent "generally" feels. All items, in both Form Y-1 and Form Y-2, are rated on a 4-point scale, where state anxiety items assess intensity of current feeling from "not at all" to "very much so", and trait anxiety items assess frequency of feeling in general from "almost never" to "almost always", with higher scores indicating greater anxiety. High scores on the STAI instrument have been found to indicate the presence of an anxiety or a depressive disorder among older adults. Considerable evidence attests to the construct and concurrent validity of the scale (Spielberger, 1999).

7.2.6.State-Trait Anger Expression Inventory 2 (STAXI-2)

The State-Trait Anger Expression Inventory-2 (STAXI-2) is a 57-item PRO designed to measure the intensity and expression of anger as an emotional state (State Anger) and as a personality trait (Trait Anger). Items are scored on a 4-point scale ranging from "Not at All" to "Almost Always." Responses are based on the intensity and frequency of anger as well as how it is expressed and controlled. Concurrent validity of this instrument is strong in both clinical and nonclinical samples (Spielberger, 1999). Importantly, psychiatric patients showed higher experience and expression of anger than the general population sample (Lievaart *et al.*, 2016).

Clinician Reported Outcome (ClinRO) measures

7.2.7.Clinical Global Impression

The Clinical Global Impression (CGI) is one of the most widely used assessment measures used in psychiatry (Guy, 1976). It was originally designed for use in NIMH-sponsored clinical trials as a brief, stand-alone assessment of the clinician's view of patient global functioning before and after study treatment (Busner & Targum, 2007). The illness severity and improvement items are most often used (versus therapeutic response) in clinical and research settings, and the measure has proved to be a robust efficacy measure in clinical drug trials (Guy, 1976). The CGI was designed to be completed with the totality of the information on the patient (i.e., collateral information), and has been adapted for use across various psychiatric (e.g., Depression, Schizophrenia, Anxiety, Bi-Polar Disorder, Impulse) and non-psychiatric (e.g., Restless Leg Syndrome, Ulcerative Colitis, Migraine) disorders. According to Busner and Targum (2007), the CGI has extraordinary utility as it is applicable across all CNS disorders and can be used regardless of the condition, population, or drug. Altogether, CGI construct validity is firmly established given the measure is designed for a specific condition or symptom under examination (i.e., the construct), and utilized by trained clinicians considering the totality of the collateral patient information for the specific condition or symptom under investigation.

For PORTICO, the Clinical Global Impression of Severity will be used focusing specifically on Agitation/Aggression (CGI-S-A/A). For the CGI-S A/A, the clinician is asked, "Considering your total clinical experience with this particular population, how agitated/aggressive (i.e., ill) is the patient at this time?" Responses are on a 1-7 scale with higher scores indicating more severe illness. The CGI-S A/A should be

assessed considering the totality of collected data during the visit, including PRO performance, responses to the other ClinROs and information gleaned while talking with the patient during the visit.

7.2.8.Agitation and Aggression Psychiatric Inventory-Clinician Report (AAPI-CR)

The Agitation and Aggression Psychiatric Inventory – Clinician Report (AAPI-CR) is an 11-item semi-structured interview format ClinRO measure that was developed in consultation with experts in the field of scale development and psychometric validation and BPD experts.

As a semi-structured interview, the AAPI-CR allows clinicians to interact with patients and clarify responses to determine the most accurate clinical rating for each of the Frequency and Severity topic area items. The eleven topic area items (in parentheses) and their respective interview questions were developed in alignment with DSM-5 diagnostic criteria for Anxiety Disorders (Anxiety), Attention-Deficit Hyperactivity Disorder (Attention/Distractedness), Depression (Depression), Bi-Polar Disorder (Mania), Posttraumatic Stress Disorder (Traumatic Experiences), Schizophrenia (Delusions and Hallucinations), as well as behavioral characteristics of Borderline Personality Disorder (Agitation, Aggression, Disinhibition/Impulsivity, and Irritable Mood or Behaviors) (American Psychiatric Association, 2013). Considering the semi-structured interview asks questions regarding DMS-V diagnostic criteria for various disorders, construct validity is inherent in the measure's design.

Although the AAPI-CR was designed to align with the DSM-V criteria for various disorders and the behavioral symptoms of BPD, it was not intended to be used as a diagnostic measure, but rather will be employed to objectively quantify patients' frequency of symptoms, as well as determine the severity of these symptoms.

The score for each of the eleven topic area items is calculated by multiplying the average Frequency x average Severity score. The 11-items of the AAPI-CR contribute to two primary subscales of the AAPI-CR, namely the Agitation & Aggression Subscale (AAPI-A/A Subscale) and the Psychiatric Subscale (AAPI-P Subscale). The AAPI-A/A Subscale contains 4-items: Agitation, Aggression, Disinhibition/Impulsivity and Irritable Moods and Behaviors, and the Psychiatric Subscale is comprised of 7-items: Anxiety, Attention/Distractedness, Delusions, Depression, Hallucinations, Mania, and Traumatic Experiences.

As designed, the AAPI-CR is employed in PORTICO as an objective and quantifiable baseline measurement of participants' agitation and aggression, as well as the severity of their other symptoms. The AAPI-CR was developed because there is not currently commonly accepted measure of agitation and aggression; though the most commonly used measures of agitation and aggression are the NPI and CMAI, which are not appropriate for BPD because they are designed for use in an elderly population with dementia (De Mauleon *et al.*, Poster presentation at CTAD, 2019; Sano *et al.*, 2018). The NPI Agitation/Aggression (NPI-A/A) Subscale is comprised of the four items (i.e., Agitation, Aggression, Disinhibition and Aberrant Motor Behaviors). The NPI A/A minimum possible score is 0 and maximum 48. A total score (i.e., Frequency x Severity) cutoff of 8 in one of these items has been leveraged in Alzheimer's Disease Agitation and Aggression clinical trials (Porsteinsson *et al.*, 2014; Soto *et al.*, 2014), which corresponds to approximately 17% (i.e., 8/48 = 16.67) of the possible range of the total NPI A/A. The AAPI-A/A has a minimum score of 4 and a maximum of 100. Therefore, an AAPI-AA total score (i.e., Frequency x Severity) cutoff of >16 (i.e., 16/96 = 16.67) and a severity of > 6 was selected for this trial to ensure enrollment of a sufficiently agitated and aggressive BPD population experiencing at least moderately distressing agitation/aggression.

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

The Columbia Suicide Severity Rating Scale (C-SSRS) is a ClinRO administered in a semi-structured interview format, designed to evaluate suicide risk by assessing and tracking suicidal ideation and

behavior (Posner *et al.*, 2011). The C-SSRS identifies specific behaviors which may be indicative of an individual's intent to complete suicide. The C-SSRS has five-questions addressing suicidal ideation, five-sub-questions assessing the intensity of ideation, and four-questions addressing suicidal behavior. The scale should be administered by a certified rater and all positive scores should receive a careful clinical review to determine if intervention is needed. This instrument demonstrated good convergent and divergent validity with other suicidal ideation and behavior scales and has high sensitivity and specificity for suicidal behavior classifications. Both the ideation and behavior subscales are sensitive to change over time. The intensity of ideation subscale demonstrated moderate to strong internal consistency (Posner *et al.*, 2011).

7.2.10. Number of visits to healthcare services outside of the trial

The use of health care resources, including all the participant visits to primary care, mental health and emergency care services, will be recorded at each study visit, starting at baselined as described in Table 1 and Section 7.7. The number of visits to healthcare services outside of the trial (primary care, mental health services & ER visits) will be evaluated '*in the last month'* at Baseline Visit as well as at Visit 4, Visit 6 and Visit 8/EoS.

7.3. Safety Assessments

The following safety variables will be measured at all visits as shown in the Schedule of Assessments and Procedures (Table 1) and Section 7.7.

- Treatment emergent adverse events (TEAEs) and Serious TEAEs
- Use of concomitant medication
- Physical examination (including height (screening only) and body weight; body mass index will be calculated from these)
- Vital signs (systolic and diastolic blood pressure, pulse and body temperature, all supine after 5 min rest)
- ECG
- Clinical laboratory results: hematology - including platelets and biochemistry
- Columbia Suicide Severity Rating Scale (C SSRS)

7.3.1. Treatment emergent Adverse Events (TEAEs)

Adverse events (AEs) will be recorded during the study period from the signing of informed consent to the completion of the Follow-Up Visit.

Treatment emergent adverse events are defined as AEs that started after first intake of study drug. If no unambiguous assignment to treatment emergent is possible due to incomplete or missing dates, the AE will be considered as treatment emergent.

All information obtained on TEAEs will be displayed and tabulated by participant, treatment and dose (i.e. arm). Classification based in the Medical Dictionary for Regulatory Activities (MedDRA latest version available) by System Organ Class (SOC), Preferred Term (PT) and Low-Level Term (LLT) will also be provided.

For further information of definitions and reporting of AEs and SAEs, see Section 8.2.

7.3.2. Physical Examination

All participants will undergo a standard physical examination including the evaluation of general appearance, eyes, throat-nose-ears, teeth, skin, lung, and heart. A general examination of abdomen, liver, spleen, kidneys, spine, lymph nodes, extremities and a short neurological status will also be performed.

The observed values will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”. All occurring abnormalities will be displayed by participant number.

An asymptomatic abnormal physical examination finding should only be reported as an AE if it is clinically significant, if it fulfils the criteria for an SAE, or if it causes the participant to discontinue the study.

If an abnormal physical examination finding is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated physical examination finding should be considered additional information.

In addition to the physical examination described above, height (at screening only) and body weight will be measured at each visit.

The timing of the assessments is described in Table 1 and Section 7.7.

7.3.3. Vital Signs

The following vital signs will be monitored as safety variables:

- Supine diastolic and systolic blood pressure (mmHg), after 5 minutes sitting down
- Supine heart rate (beats per minute), after 5 minutes sitting down
- Digital axillary or oral temperature (°C)

The observed values will be recorded and assessed as “normal” or “abnormal”. Abnormal findings will be assessed as “clinically significant” or “not clinically significant”. All occurring abnormalities will be displayed by participant number.

An asymptomatic abnormal vital sign finding must only be reported as an AE if it is clinically significant, if it fulfills the criteria for an SAE, or if it causes the participant to discontinue the study.

If an abnormal vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign result should be considered additional information.

Vital signs will be measured in all the study visits as described in Table 1 and Section 7.7.

7.3.4. Electrocardiogram

A standard 12-lead ECG recording will be performed locally, at the clinical sites, including the parameters Heart Rate (HR), PR, QRS, QT and QTc. However, ECGs will be interpreted at a central reading center. Description of ECG intervals will be obtained and tabulated. All occurring abnormalities will be identified.

ECG parameters will be measured at Visit 1 and Visit 8 (EoS) as described in Table 1 and Section 7.7.

7.3.5. Laboratory Safety Assessments

A maximum of 20 mL blood sample will be collected under fasting conditions at each visit. However, if the study visit is scheduled in the afternoon/evening, fasting conditions will only be required at Visit 2 (Baseline – Day 1), Visit 4 (Day 29), Visit 6 (Day 57) and Visit 8 (Day 85). Fasting conditions should last 6-8 hours before blood sampling.

Blood samples will be collected prior to study drug intake at all study visits as shown in the Schedule of Assessments and Procedures (Table 1) and Section 7.7.

At all study visits, the participant will be provided a snack/meal before completing the COAs.

The blood sampling and handling procedures are described in the study-specific Laboratory Specification Manual.

All blood samples for the laboratory safety assessments will be analyzed by a central laboratory. Urine drug screening and pregnancy test will also be analyzed at a central laboratory.

Laboratory kits for biological sampling (blood and urine) will be supplied by a central laboratory.

The different laboratory safety parameters to be measured are listed below in Table 5.

Table 5. Laboratory – Safety

Hematology Parameters (2 mL blood sample, potassium EDTA tube)	
White blood cell (WBC) count	Neutrophils absolute and %
Red blood cell (RBC) count	Lymphocytes absolute and %
Hemoglobin (Hb)	Monocytes absolute and %
Hematocrit (HCT)	Eosinophils absolute and %
Mean corpuscular volume (MCV)	Basophils absolute and %
Mean corpuscular hemoglobin (MCH)	Platelet count
Mean corpuscular hemoglobin concentration (MCHC)	
Serum Biochemistry Parameters (8.5 mL blood sample, Serum Separator Tube [SST])	
Sodium	Alkaline phosphatase (ALP)
Potassium	ALT
Calcium	AST
Urea	Creatine kinase (CK)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Lactate dehydrogenase (LDH)
Phosphate	Total Bilirubin
Glucose	Cholesterol
Triglycerides	Conjugated bilirubin
C-reactive protein (CRP)	Unconjugated bilirubin
Total Protein	Amylase
HbA1c*	TSH†
Serological Parameters (3.5 mL blood sample) †	

Hepatitis B Virus (HBV) Human Immunodeficiency Virus (HIV)	Hepatitis C Virus (HCV)
Urine Parameters	
Pregnancy test (and Serum human Chorionic Gonadotropin (S-hCG) in case of a positive result) [(1)] Drug screening	

* Only at the screening visit for diabetic participants
† Only at the screening visit, in case of serology confirmation an extra 8.5ml sample will be analyzed
[(1)] All positive urine pregnancy test results must be confirmed by a serum hCG test

Study medication must be halted in all patients who fail to have platelet counts checked at the scheduled timepoints. The study medication should not be resumed until testing has been completed and confirmed to be within an acceptable range.

At the discretion of the PI, additional and repeat testing may be performed in scheduled visits as well as in unscheduled safety visits.

Clinically significant out-of-range values must be recorded as an adverse event on an AE Form or as a serious adverse event (SAE) on a SAE form, if applicable.

7.3.6. Determination of Viral Testing and Tuberculosis Status

Blood samples will be collected at the Screening Visit (Visit 1) as shown in the Schedule of Assessments and Procedures (Table 1 and Section 7.7). A total of 3.5 mL blood sample will be collected for all the tests shown below.

The blood sample for viral testing will be analyzed by a central laboratory. The blood sampling and handling procedures are described in the study-specific Laboratory Specification Manual.

- ***Human Immunodeficiency Virus (HIV)***
  Determination of HIV status will be required before the participant is enrolled in the study. The status must be determined by medical history, signs, symptoms, and testing. Any significant findings will be recorded in the HIV Assessment section and the Medical History page of the eCRF, as necessary.

  An HIV antibody test will be performed. This test will only be used to determine participant eligibility for inclusion in the study.

- ***Hepatitis B and C Virus (HBV/HCV)***
  Determination of hepatitis B and C status will be required before the participant is enrolled in the study. The status must be determined by medical history, signs, symptoms, and testing. Any significant findings will be recorded in the HBV/HCV Assessment section and the Medical History page of the eCRF, as necessary.

  Hepatitis testing will include HBV surface antigen and HCV antibody testing. These tests will only be used to determine participant eligibility for inclusion in the study.

Tuberculosis (TB)

Determination of TB status will be required before the participant is enrolled in the study and will only be used to determine participant eligibility for inclusion in the study. The status must be

determined as usual clinical practice (i.e., by medical history, signs and symptoms). Any significant findings will be recorded in the TB Assessment section and the Medical History page of the eCRF, as necessary.

7.3.7. Urinalyses

- **Pregnancy test** in urine will be conducted only in females of reproductive age at Visit 1 (Screening Visit), Visit 2 (Baseline) and Visit 8 or EoS Visit. Pregnancy tests can be performed at any point during the study if pregnancy is suspected or as required by local regulations. All positive urine pregnancy test results must be confirmed by a serum test. Pregnancy tests are to be performed by a central laboratory.
- **Drug screening** in urine for illicit drugs will be conducted in all participants at Visit 1 (Screening Visit), and all the study visits from Baseline (Visit 2) to Visit 8 or EoS Visit, including Visit 9 (Safety follow-up). A positive drug screen test is not automatically a withdrawal criterion. However, a positive drug screen test should prompt the investigator to investigate the cause of such a positive test and further evaluate the patient in light of this finding. Before the patient is withdrawn, the sponsor should be consulted. Drug screening urinalyses will be conducted by a central laboratory.

7.4. Pharmacokinetic Assessments

Blood samples will be collected prior to IMP intake and under fasting conditions to assess the systemic vafidemstat levels at different visits as shown in the Schedule of Assessments and Procedures (Table 1) and Section 7.7. A total of 5 mL blood sample will be collected at each visit. The blood sample for pharmacokinetic assessments will be analyzed by a central laboratory. Samples may also be used for exploratory evaluation of vafidemstat metabolites. The blood sampling and handling procedures at site are described in the study-specific Laboratory Specification Manual. Blood laboratory kits for biological sampling will be supplied by a central laboratory.

For US Sites only, a sampling at around T_{max} to assess average levels and help drug monitoring will be conducted in a patient subpopulation (approximately 10 patients). If C_{max} values observed are in the range of those seen in healthy volunteers, no further samples should be necessary at T_{max}. For the patients of this selected subpopulation, one extra blood sample (5 mL) for PK assessments will be obtained 1 to 2 hours after IMP intake on Visits 4 and 6 (in addition to the pre-dose sample already scheduled on these visits as per the original protocol). Participants will have to sign a separate specific informed consent form.

7.5. Pharmacodynamics Assessments

7.5.1. Peripheral blood mononuclear cells (PBMC) LSD1 target engagement (TE)

Blood samples will be collected prior to IMP intake and under fasting conditions to assess LSD1-TE in PBMCs at different visits as shown in the Schedule of Assessments and Procedures (Table 1) and Section 7.7. A total of 10 mL of blood will be collected at each visit. The blood sample for pharmacodynamics assessments will be analyzed by a central laboratory. The blood sampling and handling procedures at site are described in the study-specific Laboratory Specification Manual. Blood laboratory kits for biological sampling will be supplied by a central laboratory.

7.6. Exploratory Assessments

Possible future exploratory analyses will help increasing the understanding of BPD etiology and the molecular basis for drug response. As the complex interactions between genes and disease are currently not characterized to a level that translates into a meaningful clinical advantage, the efforts described in this protocol are strictly research based, and individual results will not be added to the participants' medical records.

Since the analysis of these samples may occur after the finalization of the study and completion of the Clinical Study Report (CSR), the results from the exploratory analyses will not be part of the study specific database and therefore, they will not be included in the CSR.

Study participants will have no direct benefit from the exploratory analyses. As blood sampling for exploratory assessments is an integral part of the study, the main Patient Information Sheet covers these analyses.

The blood samples for exploratory assessments will be analyzed by Oryzon or by a third party contracted by Oryzon. Data derived from these blood samples may be shared with academic and public institutions and other companies. However, Oryzon will retain full control of the samples and their use in accordance with the information in the Patient Information Sheet. Furthermore, the results based on the analysis of the samples may be pooled across studies to increase the statistical power of the analyses.

A participant may, at any time and without stating any reason, specifically request the destruction of the participant's exploratory samples, irrespective of his or her continued participation in the study. The investigator, on behalf of the patient, must send to the sponsor a written request to destroy the exploratory samples. The investigator will receive written confirmation from Oryzon when the samples have been destroyed. Data from analyses performed before the request for destruction will be part of the database of the sponsor.

The blood samples for exploratory assessments will be identified using the patient's screening number and they will be stored in Oryzon´s repository at Oryzon´s laboratory facilities in Spain (Oryzon Genomics S.A., C/Sant Ferran 74 – 08940 Cornellà de Llobregat, Barcelona – Spain). These blood samples will be destroyed by Oryzon after a period of storage up to 15 years after last patient out in the trial.

7.6.1. Blood samples for biomarkers analysis

Blood samples for genomic, proteomic or any other bioanalytical methodology to assay exploratory biomarkers will be collected.

The maximum volume of blood to be collected during the study for this purpose will be 30 mL (7.5 ml per timepoint). The remaining back-up samples from Safety Labs, TE and PK once the primary analysis is completed, may also be used for biomarkers analysis.

Sampling and handling procedures at site are described in the study-specific Laboratory Specification Manual. Blood laboratory kits for biological sampling will be supplied by a central laboratory.

The samples will be shipped to Oryzon Genomics, Spain for storage and potential future analysis by a central laboratory.

7.6.2. Genotyping

Blood samples will be collected to investigate ADME-related genetic polymorphisms by DNA genotyping analysis and assess any potential impact on vafidemstat pharmacokinetics. This analysis does not include sequencing of any genomic material from study participants.

The maximum volume of blood to be collected during the study for this purpose will be 10 mL.

Sampling and handling procedures at site are described in the study-specific Laboratory Specification Manual. Blood laboratory kits for biological sampling will be supplied by a central laboratory.

The samples will be stored for potential future analysis by a central laboratory.

7.7. Schedule of Assessments and Procedures

The Schedule of Assessments and Procedures is shown in Table 1.

All study visits should take place preferably in the early morning.

All assessments from a specific visit might be completed over a maximum of two consecutive days. In this case, the first day should be considered as the visit day.

Study treatment will be dispensed at each study visit, from Visit 2 to Visit 8, in a box containing treatment for 14±2 days. At each visit, the first study drug intake, corresponding to the new treatment box dispensed on that visit, should take place at the clinical study center.

Although no serotoninergic syndrome has been reported thus far in the clinical development of vafidemstat, the study staff should educate the participant at Baseline visit and throughout the study around the symptoms which may be compatible with serotonin syndrome. Additionally, a follow-up call will be required approximately 6-8 hours after the first intake of vafidemstat, as well as at 24 hours and 48 hours to check in on the participant and ensure they are not experiencing any signs or symptoms of serotonin syndrome. The follow-up phone calls are only applicable if the participant is receiving concomitant treatment with antidepressants (selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclics, tetracyclics, and triazolopyridines).

Participants should be informed at screening and throughout the study that the ingestion of foods with a high tyramine content should be used with caution throughout the study. Study staff will provide the patients with the necessary dietary recommendations as it relates to this study requirement.

The order of the assessments/activities within a visit will be performed according to the Schedule of Assessments and Procedures. The following needs to be considered:

- Informed consent at the Screening visit must be obtained before any study specific procedure is implemented
- Assessments/activities that must be performed before IMP intake:
  - Vital signs and electrocardiogram (ECG) should be obtained for a participant in the same manner throughout the study (e.g., obtained from the same arm).
  - Blood extractions must ideally take place at the same time of the day and in fasting conditions (e.g., first thing in the morning preferably) in order to allow participants to ingest food before the other study assessments are conducted. In case the study visit is scheduled in the afternoon/evening, when fasting conditions are required, should last 6-8 hours. Participants must be instructed to take IMP in fasting conditions.

7.7.1. Visit 1 (Week -2, Day (-14 to -1) ± 7) - Screening Visit

Before participating in the study, participants will be informed, both verbally and in writing, about the purpose of the study, its procedures and any risks or discomforts involved in their participation. Informed consent will be obtained from participants at Visit 1 (Screening Visit) before any study specific procedure could take place. The screening period will last two weeks with a window of ± 7 days.

At Visit 1 (Screening Visit), the following activities and assessments will be performed:

- Informed consent
- Verification of inclusion and exclusion criteria
- Participant eligibility form
- Diagnosis of BPD based on DSM-5. The Mini-International Neuropsychiatric Interview (MINI) will be administered at screening in order to confirm BPD diagnosis, as well as to confirm participant does not meet other relevant exclusion criteria.
- Demographic information: date of birth, sex, race, height, weight and BMI
- Physical examination (including height and weight)
- Medical history
- Prior and concomitant medication
- Vital signs
- ECG
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Blood extraction under fasting conditions for viral testing (hepatitis C, hepatitis B and HIV). If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Tuberculosis status (by medical history, signs and symptoms)
- Urine pregnancy test (females of reproductive age)
- Urine drug screening
- Provide snack/meal
- COAs

The Screening Visit can be split between two days to make sure all the assessments can be performed. The first day will always be used as the date of the Screening Visit.

7.7.2. Visit 2 (Week 0, Day 1) - Baseline Visit

Only participants who fulfil all eligibility criteria (Section 4.1) and have been given approval by Sponsor will be randomized to the study. At Visit 2, the following activities and assessments will be performed:

<u>Prior to Randomization</u>

- Verification of inclusion and exclusion criteria
- Physical examination (including weight)

- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology and biochemistry
- Blood extraction under fasting conditions for PK assessments before the IMP intake
- Blood extraction under fasting conditions for LSD1-TE assessments before the IMP intake
- Blood extraction for genotyping. The blood sample could be obtained at any visit from Baseline Visit to the end of the study, however, baseline collection is recommended
- Blood extraction under fasting conditions for future investigations
- Urine pregnancy test (females of reproductive age)
- Urine drug screening

Randomization

- Adverse Events assessment
- Number of visits to healthcare services outside of the trial in the last month
- Dispensation of IMP and intake of the first capsule in fasting conditions
- Provide snack/meal
- COAs

7.7.3. Visit 3 (Week 2, Day 15±2)

At Visit 3, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Urine drug screening
- Assess IMP compliance
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.4. Visit 4 (Week 4, Day 29±2)

At Visits 4, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry
- Blood extraction under fasting conditions for PK assessments before the IMP intake
- Blood extraction under fasting conditions for LSD1-TE assessments before the IMP intake
- Urine drug screening
- Assess IMP compliance
- Number of visits to healthcare services outside of the trial in the last month
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.5. Visit 5 (Week 6, Day 43±2)

At Visit 5, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Urine drug screening
- Assess IMP compliance
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.6. Visit 6 (Week 8, Day 57±2)

At Visit 6, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)

- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry
- Blood extraction under fasting conditions for PK assessments before the IMP intake
- Blood extraction under fasting conditions for LSD1-TE assessments before the IMP intake
- Urine drug screening
- Assess IMP compliance
- Number of visits to healthcare services outside of the trial in the last month
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.7. Visit 7 (Week 10, Day 71±2)

At Visit 7, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Urine drug screening
- Assess IMP compliance
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit. If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.8. Visit 8 (Week 12, Day 85±2) – End of Study (early termination)

At Visit 8, the following activities and assessments will be performed:

- Adverse Events assessment
- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs

- ECG
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry
- Blood extraction under fasting conditions for PK assessments before the IMP intake
- Blood extraction under fasting conditions for LSD1-TE assessments before the IMP intake
- Blood extraction under fasting conditions for future investigations
- Urine pregnancy test (females of reproductive age)
- Urine drug screening
- Assess IMP compliance
- Number of visits to healthcare services outside of the trial in the last month
- Dispensation of IMP and intake in fasting conditions of the first capsule from the new treatment box dispensed at this visit (not applicable for non-completers participants – see definitions above)
- Provide snack/meal
- COAs

7.7.9. Visit 9 (Week 14, Day 99±2) – Run-out Safety Follow-up Visit – Participant blind placebo run-out period

At Visit 9, the following activities and assessments will be performed:

- Physical examination (including weight)
- Changes in concomitant medication since the last visit
- Vital signs
- Blood extraction under fasting conditions for laboratory safety assessment: hematology (including platelets) and biochemistry . If the study visit is scheduled in the afternoon/evening, fasting conditions will not be required.
- Urine drug screening
- Assess IMP compliance
- Adverse Events assessment
- Provide snack/meal
- COAs (Note: for the STAI, Form Y-1 only)

7.7.10. Unscheduled visits

Unscheduled visits will be allowed for safety reasons or in the event the medication needs replacing (i.e., in case of damaged blisters).

7.7.11. Classification of participants according to completion of study visits

According to the number of visits, participants can be classified as follows:

a. *Completers:* Participants completing Visit 9.

b. *Non-completers:* Participants that received at least one dose of study treatment, but prematurely discontinued the study before completion of Visit 9 for any reason other than withdrawal of the informed consent. These participants will be asked to complete an End of Study (EoS) Visit as soon as possible after withdrawal. Non-completers will not enter the 2-week participant-blind placebo run-out period.
    i. If there has been, at least, one week between the last intake of study drug and this EoS visit, no further Safety follow-up visit will be required.
    ii. If there has been less than one week between the last intake of study drug and EoS visit, participant will be asked to attend to a Safety-follow up visit, two weeks after the last intake of study drug, to perform safety assessments only.
c. *Non-completers who discontinue the study because they withdraw their consent:* Participants that received at least one dose of study treatment, but prematurely discontinued from the study before completion of Visit 9 due to withdrawal of informed consent. These participants, if possible, will be asked to attend to an EoS Visit.
    i. The visit must be scheduled as soon as possible after withdrawal.
    ii. If the participant withdraws consent during a visit but agrees to complete the visit, then, the investigator will complete an EoS Visit. All the data collected up to and including this visit will be used in the analysis.
    iii. If the participant withdraws consent and refuses to complete the EoS Visit, no new information will be collected. However, it is recommended, outside the scope of this study, to perform a safety assessment within 2 weeks after treatment discontinuation.

8. ADVERSE EVENTS

Safety parameters will be monitored by the PI and any impairment will be treated appropriately by the corresponding physicians and recorded in the CRF. In addition, safety will be also monitored by the DMC.

The safety assessment will be performed following International Conference on Harmonization (ICH) - Good Clinical Practice (GCP) Guidelines and according to the regulation currently in force for each country.

8.1. Definitions

8.1.1. Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Medical disorders present at the time of the first administration of IMP are only considered AEs if they worsen after this time. All baseline conditions should be recorded as part of the Medical History.

8.1.2. Adverse Reaction (AR)

An AR is any untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting PI or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as ARs. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

8.1.3. Unexpected Adverse Reaction

An unexpected AR is defined as an AR where the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized IMP or summary of product characteristics for an authorized product).

When the outcome of the AR is not consistent with the applicable product information this AR should be considered as unexpected.

8.1.4. Serious Adverse Event (SAE)

Any untoward medicinal occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important event or reaction

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed in the definition 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 hospitalization, or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

Life-threatening in the definition of a SAE or serious AR refers to an event in which the participant was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it was more severe.

8.2. Reporting of Adverse Events

All study participants will be carefully monitored for the occurrence of AEs during the study period from the signing of informed consent to the completion of the last Follow-up Visit. The Investigator will collect AEs with a non-leading question such as “have you experienced any new health problems or worsening of existing conditions” as well as reporting events directly observed or spontaneously volunteered by participants.

A clinical laboratory abnormality should be documented as an AE if meet the following conditions: the test finding is accompanied by clinical symptoms AND/OR the abnormality suggests a disease and/or organ toxicity AND/OR the abnormality is of a degree that requires additional diagnostic evaluation(s) or medical/surgical intervention AND/OR the abnormality is considered clinically significant by the clinician.

Clearly related signs, symptoms and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible.

All AEs including but not limited to events reported by the participant, or reported in answer to an open question by the Investigator or member of this team, which fall into any of the above definitions must be recorded as an AE in the eCRF and should include the following information:

- Brief description of the event (diagnosis)
- Start date (and time, if relevant)
- Stop date (and time, if relevant) (or resolution)
- Severity
- Action taken regarding study drug
- Opinion on causality
- Seriousness (as defined in section 8.1.4 for definition of SAE, Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction [SUSAR])
- Outcome

8.2.1.Severity

Severity describes the intensity of an event, and will be assessed as:

- *Mild:* The AE does not interfere in a significant manner with the participant’s normal functioning level. It may be an annoyance.

- *Moderate:* The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.
- *Severe:* The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the participant. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

If an AE changes in severity, the worst severity should be reported.

8.2.2. Causality

Causality will be assessed according to the WHO Causality Assessment as follows:

Related to IMP

- *Certain*: Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Re-challenge satisfactory, if necessary.
- *Probable/Likely*: Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable. Rechallenge not required.
- *Possible: Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.*

Not related to IMP

- *Unlikely*: Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.

Conditional/Not classifiable

- Event or laboratory test abnormality. More data for proper assessment needed, or Additional data under examination.

Unassessable/Unclassifiable

- A report suggesting an AR that cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

All AEs judged as having a reasonable suspected causal relationship to the IMP (i.e., possibly, probably, certain) as well as all AEs judged as unassessable/unclassifiable will be considered as related to IMP. Any AE that is considered to be related to the IMP is described as an AR.

8.2.3. Follow-up of Participants after Adverse Events

Any AE that is ongoing when after the End of Study Visit, should be followed up until the AE is resolved or the Investigator decides that the AE is stable and needs no further follow-up. For the last ongoing AE, any of these outcomes and the resolution date should be updated in the AE form in the eCRF.

8.2.4.Abnormal Laboratory Values/Vital Signs

Reporting of abnormalities as both laboratory/vital signs findings and AEs should be avoided.

A clinical laboratory abnormality should be documented as an AE if all the following conditions are met:

- The test finding is accompanied by clinical symptoms
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires additional diagnostic evaluation(s) or medical/surgical intervention.

If the laboratory test shows a relevant abnormality, it will be repeated to confirm it as soon as possible.

An asymptomatic abnormal vital sign finding should only be reported as an AE if it is clinically significant if it fulfils the criteria for an SAE or if it causes the participant to discontinue the study.

If an abnormal vital sign value is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated vital sign result should be considered additional information.

8.3. Reporting of Serious Adverse Events

The Investigator is responsible for ensuring that all SAEs are reported to the Sponsor immediately, but in any event no later than 24 hours of any center personnel becoming aware of the event. Initial reports should be followed as soon as possible by detailed written reports. The initial and follow-up reports should identify participants by unique code numbers assigned in the study. The participants' names, personal identification numbers, and/or addresses must not be included. The following information is mandatory for the initial report:

- Participant study ID
- Study treatment (blinded, if applicable)
- Start date (time, if relevant) of the study treatment
- Brief description of the event (diagnosis)
- Start date (time, if relevant) of the event
- Seriousness criteria
- Causality assessment

For reported deaths, the Investigator should supply the Sponsor and the IEC (if applicable) with any additional requested information (e.g., autopsy reports and terminal medical reports).

SAE REPORTING CONTACT DETAILS

[redacted]

SUSAR will be reported to CAs, IECs and PIs in accordance with EU legislation and local regulations. [redacted] will handle the submission of SUSARs.

8.4. Adverse Events of Special Interest

The following AEs (SOC and PT) or laboratory findings of special interest will be evaluated by PIs at all study visits and time points (as applicable):

- Investigations (SOC):
  - Platelet count decreased (PT)
  - Neutrophil count decrease (PT)

Platelet and neutrophils count decrease with minor hematological impact (i.e., at a given study visit, a decrease in the platelet or neutrophil count less than a 30% from baseline´s count) are not to be reported as an AE unless, in the opinion of the investigator, the decrease is clinically significant.

8.5. Precautions/Overdose

Overdose should be reported as an adverse event. The definition of overdose is as follows:

1. Compliance >120% assessed by the Study Coordinator on visit days (considering the previous 2 weeks)

   OR,

2. Daily compliance >200%, meaning if the participant takes 3 capsules or more within 24h

Administration of any dose that deviates from the scheduled regimen will be documented and reported by center personnel.

8.6. Pregnancy

Female participants will be instructed to notify the PI immediately if they become pregnant during the study. Male participants will be instructed to notify the PI immediately if their partner becomes pregnant. Pregnant participants will be withdrawn from further study treatment. The participants will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the study.

A pregnancy as such is not an AE, unless there is a possibility that vafidemstat has interfered with the efficiency of any contraceptive measures. However, the Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs (Section 8.3). The pregnancy report form should be used instead of the SAE form.

The pregnant participant or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

9. STATISTICAL METHODS

9.1. Statistical and Analytical Plans

The statistical analysis will be further detailed in a separate statistical analysis plan (SAP). The SAP will be finalized before the interim analysis and any unblinding.

All statistical analyses will be performed using the latest available version of SAS® (SAS Institute Inc., Cary, North Carolina, United States of America [USA]).

9.2. Data sets to be analyzed

With regards to analysis of data, the following analysis sets are defined:

- **Safety Analysis Set (SAF):** All participants who received at least one dose of the study IMP or Placebo.
- **Full Analysis Set (FAS):** All patients enrolled (randomized) in the study. Patients will be analyzed as randomized.
- **Per-Protocol Set (PPS):** All participants in the FAS without any major protocol deviations* as described in Section 10.9 and who also satisfy both of the following constraints:
    1. Have at least completed one CGI-S A/A assessment at specific weeks
    2. Have at least completed one BPDCL assessment at specific weeks

    **Important violations of eligibility criteria and other deviations from the protocol will be assessed in cooperation with the Sponsor. Important deviations from the protocol may lead to exclusion of a participant from the PPS. Individuals in the PPS will be analyzed as treated.*

9.3. Statistical Analysis

9.3.1. Use of different analysis sets

Both, SAF and PPS will be used for safety analysis, being SAF considered the primary safety analysis set population. Primary efficacy analysis will be performed using the FAS population. Efficacy will also be tested in the PPS population and used for supplementary and sensitivity analysis.

9.3.2. Handling of missing values

Missing value imputation will be performed as outlined in the SAP, and several additional options for imputing missing values will also be explored as part of the sensitivity analysis (see Section 9.3.11), including multiple imputation.

9.3.3. Summary Statistics

Descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum) will be provided for continuous variables. Frequency counts (n and percentage) will be provided for qualitative variables. Clinical rating scales may be summarized both as continuous and as qualitative variables, depending on the context. A confidence level of 95% will be used for all confidence intervals unless stated otherwise.

All summary statistics will be provided by randomized or actual treatment arm and by visit and time point (where applicable).

In the listings, participants will be identified using their participant number.

Details will be provided in the SAP.

9.3.4. Primary Efficacy Analysis

The primary efficacy analysis will be performed for the CGI-S A/A and the BPDCL scores (sum of responses for all items).

The estimand for the primary efficacy analysis is defined with the target population determined by the inclusion/exclusion criteria, the endpoints targeted are the primary efficacy endpoints for the study and mean changes from baseline to specific weeks as the population level summary. Intercurrent events that are expected to occur include early treatment discontinuation due to patient choice or due to adverse events both unrelated to the medication or study indication (e.g., Covid-19) and related to the study medication or indication, as well as the initiation and/or discontinuation of psychotherapy during the trial.

The mixed model repeated measures (MMRM) will include as fixed factors: site, visit, treatment arm, psychotherapy at baseline, baseline value of the response variable, the interaction between treatment and visit as well as visit interaction with the baseline value (last measurement prior to treatment initiation) for the endpoint and psychotherapy at baseline. The contrast that will be tested for significance is the difference between active treatment and placebo from baseline to specific week. The study is controlled at a 5% level. The Hochberg correction will be applied. If one endpoint is below the 2.5% level or if both endpoints are below the 5% level of significance the study is declared a success.

Possible alternative analysis methods will be investigated as part of the sensitivity analysis, see Section 9.3.11.

Boxplots will be presented for the changes from baseline to specific week in both endpoints by treatment arm.

Descriptive statistics will also be presented.

Full details on the primary analysis will be documented in the SAP and supersede what is outlined in the protocol.

9.3.5. Secondary Efficacy Analysis

The same MMRM as for the primary analysis will be calculated without a formal confirmatory significance test. At each visit, estimates for the adjusted changes from baseline in both the treatment and the placebo arm (adjusted for individual differences and differences in baseline and therapy status) as well as for the difference in changes between the two arms will be presented, including 95% confidence intervals (CI).

Subgroup analyses may be performed on the following variables:

- Country or center
- Psychotherapy at baseline
- Sex

Further details will be outlined in the SAP.

Descriptive summary statistics will be presented for both, absolute values and changes from baseline by visit and treatment arm.

Efficacy endpoints results will be plotted versus time individually and using means (absolute values and change from baseline) calculated by actual treatment arm.

9.3.6.Secondary Safety Analyses

Safety endpoints will be analyzed throughout the study from baseline to week 14, including:

- Number and frequency of Treatment Emergent Adverse Events (TEAEs) by severity
- Number and frequency of Serious TEAEs by severity
- Number and percentage of withdrawn participants due to TEAEs
- Frequency of physical examination parameters, vital signs, and ECG parameters of potential clinical concern
- Frequency of clinical laboratory parameters of potential clinical concern throughout the study
- Columbia – Suicide Severity Rating Scale (C-SSRS) results
- Number and frequency of concomitant medication intake throughout the study

The change from baseline to specific week will be analyzed for the following safety endpoints:

- Change from baseline to specific week in physical examinations, vital signs, and ECG parameters
- Change from baseline to specific week in clinical laboratory parameters

More details to specific endpoints are provided below.

Adverse Events

The total number of participants with at least one AE and the total number of AEs will be presented overall and by treatment arm and tabulated by MedDRA SOC and PT. In addition, AEs will be tabulated by worst severity and worst relationship to treatment.

The same tabulations will be provided for TEAEs, TEAEs of special interest, TEAEs leading to study drug discontinuation, serious TEAEs (STEAEs) and STEAEs related to study medication.

Listings of participants with STEAEs, deaths and STEAEs leading to discontinuation and individual narratives for these cases will be provided.

Physical Examinations

Physical examination results including assessment as “normal” or “abnormal” and clinical significance of abnormalities will be listed. New abnormalities do not present at baseline will be flagged.

Vital Signs

All abnormal vital signs including assessment of clinical significance will be listed by participant. Summary statistics for vital sign parameters will be provided (absolute and change from baseline) by actual treatment arm and visit.

Electrocardiograms

All abnormal ECG results will be listed by participant including assessment of clinical significance and description of any abnormality. ECG parameters (absolute values and changes from baseline) will be summarized by actual treatment arm and visit.

Columbia-Suicide Severity Rating Scale

The C-SSRS results will be listed and summarized descriptively by actual treatment arm and visit.

Laboratory Safety Assessments

All abnormal laboratories including assessment of clinical significance will be listed by participant. Laboratory parameters (absolute values and changes from baseline) will be summarized by actual treatment arm and visit.

Shift tables will be produced for post-baseline time points and overall results per each parameter Results will be defined as clinically significant abnormal > clinically non-significant abnormal > normal.

9.3.7. Exploratory Efficacy Analyses

The analysis of exploratory endpoints will be described in the SAP.

9.3.8. Demographic and Other Baseline Characteristics

All demographic and baseline characteristics, including medical history coded using MedDRA, will be summarized descriptively.

9.3.9. Exposure to treatment

Target engagement (TE) will be used to assess active treatment exposure. LSD1-TE observed levels will be compared with the expected TE levels as obtained in previous vafidemstat clinical trials. Chi-square test will be applied to measure the deviation of the observed data from the values that would be expected.

9.3.10. Prior and Concomitant Treatment

Prior and concomitant medications will be coded according to WHO Drug Dictionary.

Summaries of concomitant medication will be provided for the SAF population by actual treatment arm, displaying the number of percentage of participants being treated with each type of medication/therapy classified according to ATC level 2 (therapeutic main group) and ATC level 3 (pharmacological subgroup).

A similar summary will be provided for prior medication.

9.3.11. Sensitivity Analysis

Sensitivity analysis will be initially conducted for the primary analysis and will be described fully in the SAP.

As part of the sensitivity analysis, the pattern of missing data of the CGI-S A/A and BPDCL scores will be investigated, i.e., to detect a possible link with the treatment received and to check whether early changes from baseline after initial treatment are predictive of future drop-out or non-compliance.

The sensitivity analysis for the two primary efficacy endpoints will be performed using multiple imputation assuming missing at random as well as missing not at random. Additional sensitivity analyses may be performed and will be detailed in the SAP.

9.4. Determination of Sample Size

The sample size for the study was calculated assuming an estimand of the effect size between active treatment and placebo of 0.51 on both endpoints, considering the placebo effect will not exceed the 30%.

The Phase IIa REIMAGINE trial did not contain a placebo group to further help establish the estimand. Moreover, there is no ‘gold standard’ measure in BPD clinical development, thus, there is no historical clinical trial data on the COAs proposed in PORTICO to establish a more accurate estimand.

Controlling the overall type I error rate at 5% for the study, both endpoints will be tested at a two-sided alpha of 2.5% . A power of approximately 80% for each endpoint is achieved with 75 patients completing the study in each arm, active treatment and placebo. Accounting for a drop-out rate of 20%, 94 patients (total 188 patients) should be recruited per arm. A sample size adjustment will be considered at the interim analysis (see Section 9.6). The total sample size will not be increased to more than 300 completed patients.

9.5. Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Before unblinding, the original statistical analysis plan may be amended. All deviations after database lock will be documented in the CSR or in an SAP Addendum, including justifications for the deviation.

9.6. Interim Analysis

An interim analysis will be performed after 90 participants have completed the specific week assessments (expected 108 patients enrolled after accounting for 20% dropout). Individuals that had the opportunity to complete their specific week visit, but were lost to follow-up, will also be included in the analysis, however, will not be included in the 90-patient count required for initiation of the interim analysis. The objective of this interim analysis will be to reassess the sample size based on the observed variability and effect sizes. The interim analysis will be conducted as per the main efficacy analysis. Imputation and sensitivity analyses will not be performed. A sample size adjustment may be performed using the promising zone approach as described by Mehta and Pocock which allows the sample size to be adjusted based on an interim analysis only if the data are in a promising zone, i.e., the effect is trending toward success but not strong enough to indicate it will finish successfully without increasing the sample size (Mehta & Pocock, 2000). If the effect is strong (favorable zone) or too weak (unfavorable zone) the trial will be allowed to accumulate participants to the originally planned sample size (188 enrolled). If data are within the promising zone, the sample size will be increased in a stepwise fashion to keep the estimated power of the study between 80 and 90%. This step wise approach to increasing sample size at interim is implemented to avoid the possibility of back-calculating the observed effect size from the sample size increase, although variations in standard deviation and placebo decline rates from historical expectations already make this difficult. For both primary endpoints, a new sample size will be determined independently. This will yield two proposed new sample sizes, one per endpoint. The larger proposed increase will be used.

Additional details will be provided in the SAP which will be finalized prior to conduct of the interim analysis.

At the interim analysis, the safety data will also be reviewed by the DMC.

10.INVESTIGATOR/SPONSOR RESPONSIBILITIES

10.1. Ethical Aspects and regulatory Approval/Notification

10.1.1. Independent Ethics Committee (IEC) and Institutional Review Boards (IRBs)

This protocol and any amendments will be submitted to a properly constituted IEC, in accordance with the ICH guidelines, the applicable European Directives and local legal requirements, for approval/favorable opinion of the study. This study will be conducted only after approval/favorable opinion in writing of the protocol has been granted by the appropriate IEC or IRB and a copy of the approval has been received by Oryzon.

The Sponsor or the Contract Research Organization (CRO) will be responsible for submission of the protocol (blinded protocol and Clinical Study Protocol Addendum – Unmasked Information) and other appropriate documents to the IECs/IRBs. The blinding of the investigator should be ensured and any correspondence to and from the IECs/IRBs should be sent via the Sponsor or the CRO. Members of the IECs/IRBs will be requested not to communicate directly with the investigators on the unblinded design of the study.

In accordance with local requirements, this study (blinded protocol and Clinical Study Protocol Addendum – Unmasked Information) will be submitted to the regulatory authorities and IECs/IRBs for approval or notification. The blinded version of the study protocol will be uploaded to publicly available websites (e.g., ClinicalTrials.gov, EudraCT) per requirements.

The investigator must not screen any participants before receiving written approval from the IEC/IRBs and the Competent Authority.

If applicable, interim reports on the study and reviews of its progress will be submitted to the IEC by the PI at intervals stipulated in its guidelines.

10.1.2. Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, regulatory requirements, GCP and the ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association.

10.1.3. Participant Information and Consent

All participants will receive written and verbal information regarding the study at a prior interview. This information will emphasize that participation in the study is voluntary and that the participant and close relative/caregiver may withdraw from the study at any time and for any reason. All participants will be given the opportunity to ask questions about the study and will be given enough time to decide whether to participate in the study.

It is the personal responsibility of the PI to obtain written informed consent from the participant. No study-related procedures, including any screening procedures, may be performed before the PI has obtained written informed consent from the participant.

Prior to obtaining written informed consent in the Informed Consent Form (ICF), the PI or a designee must explain to potential participants, the aims, methods, and potential hazards of the study and any discomfort it may entail.

It is the responsibility of the PI to ensure that all questions about the study are answered to the satisfaction of the participants. Prior to enrolling a participant in the study, an *Informed Consent Form* must be signed and dated by the participant and the investigator on the same day. The participants will receive a copy of the written information (*Participant Information Sheet*) as well as a copy of the signed *Informed Consent Form*.

If parts of the informed consent process (such as giving information) may be delegated, the requirements for the delegates must be documented prior to the start of the study. National laws must always be adhered to when allowing potential delegation. Any delegation must be documented in the center delegation log.

The PI must identify vulnerable participants, that is, participants whose willingness to participate in a clinical study might be unduly influenced by the expectation, regardless of whether it is justified, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Participants thus identified must be excluded from participation in the study.

The blood samples may be shared with academic or public institutions; however, Oryzon will retain full control of the samples and their use in accordance with the information in the Participant Information Sheet and a Material Transfer Agreement. Furthermore, samples may be pooled across studies to increase the statistical power of the analyses.

In accordance with European General Data Protection Regulation (2016/679) the data will be processed in accordance with the specifications outlined by the local law to ensure that requirements regarding personal data protection are met. If an external organization will process data on behalf of Oryzon, a contractual procedure will be signed between Oryzon and the external organization to ensure compliance with the above-mentioned legislation.

If applicable, the participation of participants in this study will be reported to the appropriate local data protection agencies, in accordance with European General Data Protection Regulation (2016/679) and Country-specific guidelines and laws.

10.2. Participant Records and Source Data

It is the responsibility of the PI to record essential information in the medical records in accordance with national regulations and requirements. The following information should be included as a minimum:

- A statement that the participant is in a clinical study
- The identity of the study e.g., study code
- Participant screening number and/or participant number
- That informed consents for the participant were obtained and the date
- Diagnosis
- Dates of all visits during the study period
- Any information relating to AEs
- All treatments and medications prescribed/administered (including dosage)
- Date of study termination
- Patient health service identification number

The PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained. Sections of eCRFs will be monitored on a regular basis.

10.3. Access to Source Data and Documentation

The PI should guarantee access to source documents for the monitor and auditors as well as for inspection by appropriate competent authorities, and the IEC, if required.

10.4. Monitoring

The monitor will visit the study center on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, ICH GCP guidelines, regulatory requirements and any study specific documents such as CRF completion guidelines.

Monitoring visits will be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants AEs have been reported as required
- Data are being accurately recorded in the CRFs
- IMP is being stored correctly and drug accountability is being performed on an on-going basis
- Facilities are, and remain, acceptable throughout the study
- The PI and the center are receiving sufficient information and support throughout the study

Moreover, during monitoring visits the data recorded in the CRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual existence of the participant in the study i.e., source data verification.

10.4.1. Data Monitoring Committee (DMC)

A Data Monitoring Committee will be established by the sponsor to have access to unblinded information in order to assess at intervals the progress of the study, safety data and critical efficacy variables and recommend the sponsor whether to continue, modify or terminate the study. This DMC will have written operating procedures and maintain records of all its meetings.

10.5. Data Management

Data management and handling of data will be conducted according to the study specific Data Management Plan with ICH guidelines

An eCRF system will be used to capture data from the study. Data entry will be performed by the study center personnel. Validation and data queries will be handled by the [redacted] Data Management Team. The data will be subjected to validation according to [redacted] SOPs in order to ensure accuracy in the collected eCRF data.

Changes to the data in the eCRF will be made at the center by the study center personnel. The eCRF will have an audit trail with appropriate functionality for data capture, tracking and documentation of any queries or changes. Electronic signatures will be used to lock the data and identify the person entering or changing the data.

Before database closure, reconciliation will be performed between the SAEs entered in the safety database and the study database. After database closure, the database will be exported as SAS® data sets.

Any deviations, i.e., discrepancies and additions from the process defined in the Data Management Plan, will be described in a study specific Data Management Report.

10.6. Quality Assurance and Audit

Audits or inspections, including source data verification, may be performed by representatives of [redacted] the Sponsor, a RA/CA and/or an IEC/IRB.

10.7. COVID-19 Contingency Plan

Previous COVID-19 restrictions, and most specifically the limitations on the mobility of participants, investigators, and monitors, impacted the conduct of the clinical trials in 2020. These constraints limited participant's ability to complete required in-person clinic visits, as well as onsite monitoring activities.

Before first patient in (FPI), the Sponsor together with the CRO and the key vendors will assess the potential risk arising from potential new restrictions and will define a contingency plan. This contingency plan should aim to ensure the safety and wellbeing of the study participants, study-site staff and study monitors, as well as to minimize impact on study data integrity.

This contingency plan may include telemedicine visits (e.g., to complete study related procedures such as remote completion of clinical outcome assessments), two-factor authentication and Electronic Medical Records (EMR) for remote source data verification, at-home nurse services and/or direct shipment of IMP to participant´s homes.

The participant will be informed on the Patient Information Sheet about the possibility of such study modifications and the participant should consent at the study onset in case these changes become necessary.

10.8. Record Retention

The Investigator/institution should maintain essential documents (as defined in ICH E6 GCP, Section 4) as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of the documents.

Essential documents should be retained according to applicable regulatory requirements of the country(ies) where the product is approved, and/or where the Sponsor intends to apply for approval.

It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when the documents no longer need to be retained.

10.9. Protocol Deviations

The classification of protocol deviations in major or minor deviations will be mutually agreed between the Sponsor and [redacted] at the start of the study.

A major protocol deviation occurs when the participant, investigator, or Sponsor fails to adhere to significant protocol requirements affecting selection criteria, administration of study treatment and administration of prohibited medication, including failure:

- To abstain from illicit substance use for at least one-week before the Screening and throughout the trial, as verified by routine drug testing during the trial

- To avoid initiation of any prohibited concomitant medications or psychotherapy during the trial
- To enroll or participate in another investigational study or take any other investigational drug for 3 months prior to and throughout the trial

Failure to comply with GCP guidelines will also result in a major protocol deviation. The Sponsor will determine if a major protocol deviation results in withdrawal of a participant.

Deviations to the study protocol will be documented in a Protocol Deviation Log.

The Sponsor or delegate is responsible for immediately reporting major deviations according to applicable regulations, as well as deviations from the study protocol that substantially affect the integrity or the safety of the participants or the scientific validity of the study, to the CA.

Protocol deviations will be reviewed before interim analysis and database lock in order to allocate the participants into the different analysis sets.

10.10. Insurance

The Sponsor must provide insurance or must indemnify (legal and financial coverage) the Investigator/the institution against claims arising from the study, except for claims that arise from malpractice, negligence, or non-compliance with the protocol.

10.11. Report and Publication

After completion of the study, a clinical study report will be prepared according to the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3) by [redacted] in close collaboration with the Investigator and the Sponsor.

All information supplied by the Sponsor in connection with this study and all information generated during this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

If a PI wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the IMP and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript, including abstracts, prior to their submission to journals, meetings, or conferences. No submission to any journal, meeting or conference or the like, or any kind of publication or disclosure in any form may be undertaken without the prior written approval by the Sponsor.

The Sponsor may choose to publish or present data from this study. Authorship will follow ICMJE guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). The Sponsor has the right to use the results for registration and internal presentation and for promotion of the Sponsor's commercial interests.

11. REFERENCE LIST

Introduction: The Investigational Medicinal Product (IMP): Vafidemstat

Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. 2004 Dec 29;119(7):941–53.

Youdim MB. Rat liver mitochondrial monoamine oxidase, a flavin-containing enzyme. *Biochem J*. 1971 Jan;121(1):20P.

Maes T, Mascaró C, Ortega A, Lunardi S, Ciceri F, Somervaille TCP, et al. KDM1 histone lysine demethylases as targets for treatments of oncological and neurodegenerative disease. *Epigenomics*. 2015;7(4):609–26.

Sprüssel A, Schulte JH, Weber S, Necke M, Händschke K, Thor T, et al. Lysine-specific demethylase 1 restricts hematopoietic progenitor proliferation and is essential for terminal differentiation. *Leukemia*. 2012 Sep;26(9):2039–51.

Chao Wang. The role of pro-inflammatory S100A9 in Alzheimer's disease amyloid neuroinflammatory cascade. *Acta Neuropathol*. 2014;127:507–522.

Lin X-M, Zhong W-T, Wang C-L, Wang S-Q. [Expression of histone demethylase lysine specific demethylase 1 in acute leukemia and its clinical significance]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2011;19(6):1348–52.

Maes T, Mascaró C, Rotllant D, Lufino MMP, Estiarte A, Guibourt N, et al. Modulation of KDM1A with vafidemstat rescues memory deficit and behavioral alterations. *PLoS ONE*. 2020;15(5): e0233468. https://doi.org/10.1371/journal.pone.0233468

Cavalcanti F, Mestre L, Guaza C, Maes T. ORY-2001 reduces inflammatory cell infiltration in the Theiler's murine encephalomyelitis virus model and highlights the epigenetic axis in MS. Poster presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum; 2018 Feb 1-3; San Diego, CA, US.

Maes T, Cavalcanti F, González-Rey E, Delgado M, Mascaró C, Lufino M, Lunardi S, Buesa C. ORY-2001 Reduces Lymphocyte Egress and Demyelination in Experimental Autoimmune Encephalomyelitis and Highlights the Epigenetic Axis in Multiple Sclerosis. Poster presented at: Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum; 2017 Feb 23-25; Orlando, FL, US.

Maes T, Cavalcanti F, González-Rey E, Delgado M, Mascaró C, Lufino M, Xaus L, Buesa C. Characterization of the efficacy of ORY-2001, a novel epigenetic drug for the treatment of multiple sclerosis, during the effector phase of the EAE model. Poster presented at: European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; 2017 Oct 25-28; Paris, FR.

Maes T, Cavalcanti F, González-Rey E, Delgado M, Mascaró C, Rotllant D, Buesa C. LSD1 inhibition, a potential epigenetic therapeutic approach for the treatment of Multiple Sclerosis. Poster presented at: European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; 2016 Sept 14-17; London, UK.

Qin L, Ma K, Wang ZJ, et al. Social deficits in Shank3-deficient mouse models of autism are rescued by histone deacetylase (HDAC) inhibition [published correction appears in Nat Neurosci. 2018 Aug;21(8):1139]. *Nat Neurosci*. 2018;21(4):564-575. doi:10.1038/s41593-018-0110-8

Zhang F, Rein B, Zhong P, Shwani T, Conrow-Graham M, Wang Z-J, Yan Z. Synergistic inhibition of histone modifiers produces therapeutic effects in adult Shank3-deficient mice. *Transl Psychiatry*. 2021;11: 99. https://doi.org/10.1038/s41398-021-01233-w

Matsuda, S., Baba, R., Oki, H. *et al.* T-448, a specific inhibitor of LSD1 enzyme activity, improves learning function without causing thrombocytopenia in mice. *Neuropsychopharmacol*. 2019;44:1505–151. https://doi.org/10.1038/s41386-018-0300-9

Mukai J, Cannavò E, Crabtree GW, et al. Recapitulation and Reversal of Schizophrenia-Related Phenotypes in Setd1a-Deficient Mice. *Neuron*. 2019;104(3):471-487.e12. doi:10.1016/j.neuron.2019.09.014

Mayo Clinic. Thrombocytopenia (low platelet count) Causes [Internet]. Mayo Clinic. [cited 2017 Jul 11]. Available from: http://mayoclinic.org

Introduction: Disease Background

Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008;69:533–45.

Lenzenweger M, Lane M, Loranger A, Kessler R. Personality disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 2007;62:553–64.

Torgersen J. Epidemiology. In: Oldham J, Skodol, AE, Bender, DS, eds. Textbook of personality disorders. Washington, DC: American Psychiatric Publishing, 2005:129–41.

Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. *Am J Psychiatry*. 2009;166:530–39.

Gunderson JG et al. Revising the borderline diagnosis for DSM-V: an alternative proposal. *J Pers Disord*. 2010 Dec;24(6):694-708.

American Psychiatric Association. (2013). Borderline Personality Disorder. In Diagnostic and statistical manual of mental disorders (5th ed.)

Paris J, Zweig-Frank H. A 27-year follow-up of patients with borderline personality disorder. *Compr Psychiatry*. 2001;42(6):482-487.

Oldham JM. Borderline personality disorder and suicidality. *Am J Psychiatry*. 2006;163:20–26

Skodol A et al. Co-occurrence of mood and personality disorders: A report from the collaborative longitudinal personality disorders study (CLPS). *Depression and Anxiety*. 1999;10:175–182.

Zanarini MC, Frankenburg FR, Dubo ED, et al. Axis I comorbidity of borderline personality disorder. *Am J Psychiatry*. 1998;155(12):1733-1739.

Soloff PH, Lynch KG, Kelly TM, Malone KM, Mann JJ. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. *Am J Psychiatry*. 2000;157(4):601-608.

Bloo J, Arntz A, Schouten E. The borderline personality disorder checklist: Psychometric evaluation and factorial structure in clinical and nonclinical samples. *Annals of Psychology*. 2017;(2):311-226.

Zanarini M, Gunderson J, Frankenburg FR, Chauncey DL. The revised diagnostic interview for borderlines: Discriminating BPD from other Axis II disorders. *J Pers Disord*. 1989;3:10–18. Published Online January 2011 https://doi.org/10.1521/pedi.1989.3.1.10

Hurt S, Clarkin J, Widiger T, Fyer M, Sullivan T, Stone M, Frances, A. Evaluation of DSM-III decision rules for case detection using joint conditional probability structures. *J Pers Disord*. 1990;4(2):121–130.

Morey LC (1991). Personality Assessment Inventory: Professional manual. Odessa, FL: Psychological Assessment Resources.

Adams HE, Bernat JA, and Luscher KA (2001). Borderline personality disorder: An overview. In P. B. Sutker & H. E. Adams (Eds.), Comprehensive handbook of psychopathology (3rd ed., pp. 491–507). New York: Plenum.

Livesley WJ and Schröder ML. Dimensions of personality disorder: The DSM-III-R Cluster B diagnoses. *J Nerv Ment Dis*. 1991;179:320–328.

Clarkin JF, Hull JW, Hurt, SW. Factor structure of borderline personality disorder criteria. *J Pers Disord*. 1993;7:137–143.

Sanislow CA, Grilo CM, Morey LC, Bender DS, Skodol AE, Gunderson JG, Shea MT, Stout RL, Zanarini MC, McGlashan TH. Confirmatory factor analysis of DSM-IV criteria for borderline personality disorder: findings from the collaborative longitudinal personality disorders study. *Am J Psychiatry*. 2002 Feb;159(2):284-90.

Bradley R, Jenei J, Westen D. Etiology of borderline personality disorder: disentangling the contributions of intercorrelated antecedents. *J Nerv Ment Dis*. 2005;193(1):24-31.

Leichsenring F, Leibing E, Kruse J, New AS, Leweke F. Borderline personality disorder. *Lancet*. 2011;377:74–84.

Bulbena-Cabre A, Bassir Nia A, Perez-Rodriguez MM. Current Knowledge on Gene-Environment Interactions in Personality Disorders: an Update. *Curr Psychiatry Rep*. 2018;Aug 9;20(9):74.

Zanarini MC, Frankenburg FR, Hennen J, Silk KR. The Longitudinal Course of Borderline Psychopathology: 6-year Prospective Follow-Up of the Phenomenology of Borderline Personality Disorder. *Am J Psychiatry*. 2003; 160(2):274-283.

Introduction: Clinical Studies

Antonijoan RM, Ferrero-Cafiero JM, Coimbra J, Puntes M et al. First-in-human randomized trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of the KDM1A inhibitor vafidemstat. CNS Drugs. 2021 Mar;35 (3):331–344.

Introduction: Study Rationale

Grant BF, Chou SP, Goldstein RB, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV borderline personality disorder: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2008; 69: 533–45.

Lenzenweger M, Lane M, Loranger A, Kessler R. Personality disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 2007;62:553–64.

Torgersen J. Epidemiology. In: Oldham J, Skodol, AE, Bender, DS, eds. Textbook of personality disorders. Washington, DC: American Psychiatric Publishing, 2005:129–41.

Gunderson JG. Borderline personality disorder: ontogeny of a diagnosis. *Am J Psychiatry*. 2009;166:530–39.

Oldham JM. Borderline personality disorder and suicidality. *Am J Psychiatry*. 2006;163:20–26.

Skodol AE, Gunderson JG, Shea MT, et al. The Collaborative Longitudinal Personality Disorders Study (CLPS): overview and implications. *J Pers Disord*. 2005;19:487–504.

Soloff PH, Lynch KG, Kelly TM, Malone KM, Mann JJ. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. *Am J Psychiatry*. 2000;157(4):601-608.

NICE Clinical Guideline. Borderline personality disorder: recognition and management (CG78). Published: 28 January 2009. Appendix A: Evidence summary for 2018 surveillance of Borderline personality disorder: recognition and management (2009) NICE guideline CG78.

Skodol A et al. Co-occurrence of mood and personality disorders: A report from the collaborative longitudinal personality disorders study (CLPS). *Depression and Anxiety*. 1999;10:175–182.

Salvador-Carulla L, Bendeck M, Ferrer M, Andión O, Aragonès E, Casas M; BDP-Cost Group. Cost of Borderline Personality Disorder in Catalonia (Spain). *Eur Psychiatry*. 2014 Oct;29(8):490-7.

Stoffers J, Völlm BA, Rücker G, Timmer A, Huband N, Lieb K. Pharmacological Interventions for Borderline Personality Disorder. *Cochrane Database Syst Rev*. 2010 Jun 16;(6):CD005653

Gunderson, J. G., & Hoffman, P. D. (Eds.). (2005). Understanding and treating borderline personality disorder: A guide for professionals and families. American Psychiatric Publishing, Inc.

Zimmerman M, Gazarian D. Is research on borderline personality disorder underfunded by the National Institute of Health? . *Psychiatry Res*. 2014;220(3):941-944.

Study treatment: Investigational Medicinal Product

EU COMMISSION. Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014 - GMP Guidelines for IMPs-. EC EudraLex Volume 4, Annex 13. 2017.

https://www.gmp-compliance.org/guidemgr/files/guideline_adopted_1_en_act_part1_v3.pdf

US Regulations: CFR Title 21 – Part 210

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=210.1

Diagnostic and Efficacy Assessments Measures

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59 (Suppl 20):22-33;quiz 34-57.

Atkins AS, Tseng T, Vaughan A, Twamley EW, et al. Validation of the tablet-administered Brief Assessment of Cognition (BAC App). *Schizophr Res*. 2017;181:100-106.

Beck AT, Steer RA, Ball R, Ranieri WF. Comparison of the Beck Depression Inventories-1A and -II in psychiatric outpatients. *J Pers Assess*. 1996;67:588–97.

Pfohl B, Blum N, St. John D, McCormick B, Allen J, Black DW. Reliability and validity of the Borderline Evaluation of Severity Over Time (BEST): a self-rated scale to measure severity and change in persons with borderline personality disorder. *J Pers Disord*. 2009 June;23(3):281–293.

Bloo J, Arntz A, Schouten E. The borderline personality disorder checklist: Psychometric evaluation and factorial structure in clinical and nonclinical samples. *Annals of Psychology*. 2017;(2):311-226.

Calvo N, Valero S, Arntz A, Andión Ó, Matalíf JL, Navascues V, Ramos-Quiroga J, Casas M, Ferrer M. Validation of the Spanish version of the Borderline Personality Disorder Checklist (BPD Checklist) in a sample of BPD patients: Study of psychometric properties. *Eur J of Psychiat*. 2018;32(1): 26-35.

Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory. 1983. Palo Alto, CA: Consulting Psychologists Press.

Spielberger, CD. STAXI-2 State Trait Anger Expression Inventory-2, Professional manual. 1999. PAR, Florida

Lievaart M, Franken IH, Hovens JE. Anger Assessment in Clinical and Nonclinical Populations: Further Validation of the State-Trait Anger Expression Inventory-2. *J Clin Psychol*. 2016 Mar;72(3):263-78.

Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville, MD, U.S. Department of Health, Education, and Welfare.

Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont). 2007 Jul;4(7):28-37.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA.

De Mauleon A, Ismail Z, Miller D, Rosenberg PB, Cantet C, Andrieu S, Vellas B, Lyketsos CG, Soto M. Searching for the best outcome in clinical trials for Agitation symptom in AD: CMAI vs NPI-C. Results from the A3C study. Poster presented at: Clinical Trials on Alzheimer's Disease (CTAD) Conference; 2019 Dec 1-3; San Diego, CA, US.

Sano M, Soto M, Carrillo M, Cummings J, Hendrix S, Mintzer J, Porsteinsson A, Rosenberg P, Schneider L, Touchon J, Aisen P, Vellas B, Lyketsos C. Identifying Better Outcome Measures to Improve

Treatment of Agitation in Dementia: A Report from the EU/US/CTAD Task Force. *J Prev Alzheimers Dis*. 2018;5(2):98-102.

Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. *JAMA*. 2014;311(7):682-691.

Soto M, Andrieu S, Nourhashemi F, Ousset PJ, Ballard C, Robert P, Vellas B, Lyketsos CG, Rosenberg PB. Medication development for agitation and aggression in Alzheimer disease: review and discussion of recent randomized clinical trial design [published online ahead of print, 2014 Sep 16]. Int *Psychogeriatr*. 2014;1-17.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia–Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings from Three Multisite Studies with Adolescents and Adults. *American J of Psychiatry*. 2011;168: 1266–77.

Statistical Methods

Mehta CR, Pocock SJ. Adaptive Increase in Sample Size when Interim Results are Promising: A Practical Guide with Examples. *Statist. Med.* 2000;67:00:1-6.

12. CLINICAL STUDY PROTOCOL AGREEMENT FORM

I have read the clinical study protocol entitled: "A double blind, randomized, placebo-controlled, adaptive 14-week Phase IIb trial to evaluate the efficacy and safety of vafidemstat in an adult borderline personality disorder (BPD) population (PORTICO)" and verified that it contains all necessary information for conducting the study.

I hereby confirm that:

- I have carefully read and understood this clinical study protocol
- My personnel and I will conduct the study according to the study protocol and will comply with its requirements, including ethical and safety considerations

I understand that, should the Sponsor decide to prematurely terminate or suspend the study for whatever reason, then such decision will be communicated to me in writing. Conversely, if I decide to withdraw from execution of the study, I will immediately communicate such a decision to the Sponsor.

I agree not to publish any part of the results of the study carried out under this clinical study protocol without consulting the Sponsor.

Principal Investigator: _____

Date: _____

Signature: _____