CLINICAL TRIAL PROTOCOL

Study Title:	A Phase 1/2, Open-Label, Randomized Parallel Arm, Intra-patient Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Preliminary Efficacy of CNSA-001 (Sepiapterin) in Primary Tetrahydrobiopterin Deficient Patients with Hyperphenylalaninemia
Study Number:	PBD-001
Study Phase:	1/2
Product Name:	CNSA-001 (sepiapterin)
Dosage Form:	oral powder for suspension
IND Number:	132575
Indication:	Treatment of Hyperphenylalaninemia in Primary Tetrahydrobiopterin Deficient patients with PTPS or recessive GTP-CH deficiencies
Investigators:	Multicenter trial
Sponsor:	Censa Pharmaceuticals Inc. 65 William Street Suite #200 Wellesley, MA 02481
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]

	Date
Original Protocol:	14 August 2017
Amendment 1:	01 November 2017
Amendment 2:	01 March 2018
Amendment 3:	08 October 2018
Amendment 4:	10 May 2019
Amendment 5:	13 May 2020

Confidentiality Statement

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor.

SPONSOR SIGNATURES

Study Title:	A Phase 1/2, Open-Label, Randomized Parallel Arm, Intra-patient Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Preliminary Efficacy of CNSA-001 (Sepiapterin) in Primary Tetrahydrobiopterin Deficient Patients with Hyperphenylalaninemia
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This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: _____

[redacted]
Censa Pharmaceuticals, Inc.

Signed: _____ Date: _____

[redacted]
Censa Pharmaceuticals

INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 1/2, Open-Label, Randomized Parallel Arm, Intra-patient Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Preliminary Efficacy of CNSA-001 (Sepiapterin) in Primary Tetrahydrobiopterin Deficient Patients with Hyperphenylalaninemia
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I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

PROTOCOL AMENDMENT 5 (MAY 13, 2020)

Protocol PBD-001 is amended primarily for the following reasons:

- Included exploratory measure to assess changes in movement and sleep for euphenylalaniemic and hyperphenylalaninemic states and as assessed by an accelerometer device (GeneActiv, Activinsights Ltd.).

- Included exploratory measure to evaluate changes from baseline in cognitive assessments for children and adolescents ages 3-17 via the NIH Toolbox.

- Included a parent rated sleep assessment tool, the Child and Adolescent Sleep Checklist.

Major changes to the protocol are as follows:

- Synopsis, Section 2.3, Section 7.1.1, Section 7.2.1, Section 7.2.4, Section 7.6, Section 9.5. Appendix 1: Added language and activities specific to two new exploratory measures GENEActiv accelerometer device, the NIH Toolbox, and the Child and Adolescent Sleep Checklist.

- Sections 6.8.4, 6.8.5and 6.8.6 were added to describe the GENEActiv accelerometer device, the NIH Toolbox, and the Child and Adolescent Sleep Checklist, respectively.

- References were updated.

PROTOCOL AMENDMENT 4 (MAY 10, 2019)

Protocol PBD-001 is amended primarily for the following reasons:

- Included children above 12-months of age.
- Modified exclusion criteria for tachycardia rates and systolic blood pressure for children.
- Clarified discrepancy between inclusion criterion 2 and various sections regarding genetic testing not being required for inclusion into the study.
- Modified the laboratory value for hypophenylalaninemia to be consistent across patient ages.
- Modified the Abnormal Movement Seizure Journal to distinguish and collect both seizures and abnormal movement (dystonia).
- Urine sample collection for urinalysis and for the exploratory biomarkers (Sepiapterin, BH_4 and Neopterin) will not be collected from toddlers (unless toilet trained and able to provide sample).
- Updated the Schwartz formula for estimating creatinine clearance in children to the Schwartz-Lyon formula.

Major changes to the protocol are as follows:

- Synopsis, Section 2.1, Section 3.1, Section 4.2, Section 10.3: Decreased inclusion age to above 12-months based on DSMB and FDA feedback.
- Synopsis, Section 4.3, Section 11: Modified Exclusion Criterion No.13, adjusted the heart rate bpm and systolic blood pressure for children.
- Synopsis, Section 3.1, Section 4.2, Section 6.2, Section 7.1.1: Modified Inclusion Criterion No.2, clarified discrepancy between inclusion criterion 2 and section 6.2 and 7.1.1 regarding genetic testing.
- Section 6.13.1, Section 6.8.1: Modified early discontinuation for the occurrence of hypophenylalaninemia defined as < 30 μmol/L for all patients.
- Section 6.14: Modified the Abnormal Movement Seizure journal to distinguish and collect seizures and abnormal movement separately within the journal.
- Section 6.61, Section 6.82: Collection of urine samples from toddlers (unless toilet trained and able to provide sample) is not required.

- Appendix 2: changed the Schwartz Formula to the Schwartz-Lyon Formula for estimation of creatinine clearance.

PROTOCOL AMENDMENT 3 (OCTOBER 8, 2018)

Protocol PBD-001 is amended primarily for the following reasons:

1. Shortened the BH_4 Washout Period from 7 to 3 days duration and removed Inclusion Criterion #3: Blood Phenylalanine (Phe) level >360 µmol/L during the Screening or BH_4 Washout Periods. This change is being made for patient safety and ease of study conduct.
2. Made the Washout Period 3 Days ± 1 Day to better accommodate clinic hours of operations.
3. Corrected the title to more accurately reflect the trial design.
4. Removed the requirement for the Day 7 trough single PK draw and changed the 12-hour draw to 8 hours for ease of collection.
5. Clarified Inclusion Criteria 4, 5 and 8.
6. Added summary of safety data from completed Phase 1 single- and multiple-dose escalation study in healthy volunteers, Study PKU-001, inclusive of food effect data.
7. Added a new section describing rationale for selection of doses.
8. Added a new section describing the risk and benefits of study participation.
9. Added a new section describing Sponsor clinical trial insurance.

Major changes to the protocol are as follows:

- Synopsis, Section 3.1, Figure 1, Section 6.6.1, Section 6.8.1, Section 7.1.1, Section 7.1.2 and Appendix 1: Shortened the BH_4 Washout from 7 to 3 days duration.
- Synopsis and Section 4.2: Removed Inclusion Criterion # 3.
- Title Page, Sponsor's Signature, Investigator's Signature, Synopsis, Section 3.1 and Section 3.2: Title was changed to better reflect the actual design of intra-patient dose escalation versus intra-patient dose titration.
- Synopsis, Section 3.1, Section 6.9, Section 7.2.4, Section 7.4.4, Appendix 1 and Appendix 3: Removed the Day 7 trough single PK draw. Following data from a recently completed Phase 1 Study wherein accumulation was not observed and following feedback from investigational sites, this single blood draw was deemed unnecessary. The 12-hour collection was moved to 8 hours to ease collection.
- Synopsis, Section 4.2, and Appendix 2: Modified Inclusion Criteria 4, 5, and 8 to clarify that assent applied to adolescents and/or mentally impaired secondary to disease, 2 methods of contraception include a highly effective method plus barrier contraception, and creatinine clearance for adolescents will now use the Schwartz formula.
- Section 1.3, Section 1.4, Section 3.3 and Section 3.4: Added data from completed Phase 1 single- and multiple dose study in healthy volunteers, Study PKU-001. Inserted new dose rationale and risk benefit sections.

- Section 6.4, Section 7.1.1 and Appendix 1: Collection of height was added for Screening Period.
- Section 10.15: Statement of Sponsor Insurance provided.

PROTOCOL AMENDMENT 2 (MARCH 1, 2018)

Protocol PBD-001 is amended primarily for the following reasons:

1. Expanded geographic scope to include Germany.
2. Corrected the central bioanalytical laboratory sampling schedule in Appendix 3 and removed the sample tube summaries as these are in the Laboratory Manual.
3. Included local bioanalytical phenylalanine (Phe) monitoring by sites for safety.
4. Clarified that for patients taking tetrahydrobiopterin (BH_4) pre-study, the BH_4 Washout will last the full 7 days regardless of when Phe concentrations become elevated above 360 µmol/L.
5. Clarified inclusion criterion requiring confirmation of mutation via medical history.
6. Extended the duration of male contraception inclusion criterion from 30 to 90 days post-study to cover full cycle of spermatogenesis.
7. Adverse event grading was changed to use the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria throughout the study.
8. Corrected several typographical errors and inconsistencies.

Major changes to the protocol are as follows:

- Section 1.4: Added Kuvan® as an approved treatment of HPA in adults and pediatric patients with PBD in Europe.
- Synopsis, Section 3.1, Section 6.8.1, and Section 7.1.2: Clarified that all patients washing out of BH_4 will complete the full 7-day BH_4 Washout prior to being randomized into the study and patients may continue the BH_4 Washout until the Day -1 Phe concentration results have been obtained.
- Section 4.1: Germany added as a geographic region in which study will be conducted.
- Synopsis, Section 4.2, Section 6.2, Section 7.1.1, and Appendix 1: Modified Inclusion Criterion No. 2 to indicate that documentation of mutation could be obtained as part of medical history. Clarified no genetic testing or retesting is required.
- Synopsis and Section 4.2: Modified Inclusion Criterion No. 6 to indicate the duration of required contraception for males is 90 days after the last dose of study drug.
- Synopsis and Section 4.3: Modified Exclusion Criterion No. 7 to indicate the Investigator will determine if the patient has any condition or history that would interfere with the patient's ability to participate or increase the risk of participation for the patient.
- Synopsis and Section 4.3: Modified Exclusion Criterion No. 17 to indicate pregnant females are excluded from the study.
- Section 6.6.1, Section 6.8.1, Section 7, and Appendix 1: Included local measurement of Phe for safety monitoring of HypoPhe and HyperPhe and indicated those that are monitored by the bioanalytical laboratory for preliminary efficacy.

- Section 6.10, Section 6.10.6.2, Section 10.2, Section 10.3: Removed reference to Code of Federal Regulations (CFR).
- Section 6.10.1: Revised reporting timelines for serious adverse events (SAEs), pregnancies, and deaths, and clarified reporting of pregnancies.
- Section 6.10.2: Replaced adverse event severity grading with NCI CTCAE Version 4.03 criteria.
- Section 6.10.4: Revised adverse event (AE) and SAE expectedness to indicate all will be considered unexpected in this study.
- Section 6.10.5: Deleted section on determination of clinical significance by the Investigator.
- Section 6.10.6.1: Adverse event definitions updated.
- Section 6.13.2: Added subjects may be withdrawn from the study for AEs or SAEs.
- Section 10.2, Section 10.4, Section 10.5, Section 10.10: Added reference to the Independent Ethics Committee.
- Appendix 3: Table updated to accurately reflect tubes and samples, and to indicate tyrosine will be measured on Day 4 and EOS with Phe; summary was removed and placed into the Laboratory Manual.

Editorial changes to the protocol are as follows:

- Title Page: Added EudraCT Number.
- Corrected typographical errors and inconsistencies throughout.

PROTOCOL AMENDMENT 1 (NOVEMBER 1, 2017)

Protocol PBD-001 is amended primarily for the following reasons:

1. To add the use, collection and review of an abnormal movement seizure journal starting at Screening through End of Study visits.
2. To include a lower limit of normal for Phe concentrations and provide appropriate rescue therapy and the ability to obtain an unscheduled Phe collection.
3. To include an age-based stopping rule for hypophenylalaninemia.
4. To ensure all blood Phe samples collected for preliminary efficacy assessment during Period 1 and Period 2 are analyzed by the Bioanalytical Laboratory, Medical Neurogenetics Laboratories.
5. To add a provision to permit adjusting PK sampling timepoints/duration once the PK data become available from the Period 1 treatment.
6. To permit Study Day 4 to occur ±1 Day. This permits sites that are closed on weekends to accommodate Day 4 visits on either Day 3 or Day 5 in order to be within the requirements of the protocol.
7. To permit the use of filter paper for Phe collection on Study Days -5 and -3 during the BH_4 Washout Period in an effort to minimize burden placed on patients' participation in the study.
8. Appendix 3, "Study Drug Preparation and Dispensing Instructions," was removed from the protocol in an effort to remove confusion on how to prepare and dose CNSA-001 Powder for Oral Suspension. A separate Pharmacy Manual and Patient Instruction Guide for dose preparation will be provided.

Major changes to the protocol are as follows:

- Synopsis, Section 3.1, Section 6.14, Section 7.1.1, Section 7.1.2, Section 7.2.1, Section 7.2.2, Section 7.2.3, Section 7.2.4, Section 7.3, Section 7.4.1, Section 7.4.2, Section 7.4.3, Section 7.4.4, Section 7.6 and Appendix 1: Added dispensing/collection/review of abnormal movement seizure journal.

- Section 6.8.1, Section 6.13.1, and Appendix 1: Added lower limit of Phe and rescue therapy for hypophenylalaninemia (Section 6.8.1), unscheduled Phe collection (Appendix 1), and criteria for discontinuation of study drug to hypophenylalaninemia (Section 6.13.1).

- Section 6.8.1, Section 7.2.2, Section 7.2.3, Section 7.4.2, Section, 7.4.3, Appendix 1 and Appendix 3: Added ±1 day variance for Day 4 visit to permit sites to avoid weekend visits.

- Synopsis, Section 3.1, Section 6.6.1, Section 6.8.1, Section 7.1.2, and Appendix 1 footnote: Added potential for Day -5 and Day -3 Phe collections to be obtained using filter paper.

- Section 5.2, Section 6.7 and Appendix 3 (original protocol): Clarified that details on preparation of study drug and dosing guidelines will be provided in a Pharmacy Manual separate from the protocol and deleted this information in Appendix 3.

- Synopsis, Section 3.1, Section 6.9, Section 7.4.1, Section 7.4.2, Section 7.4.4, Appendix 1, and Appendix 3 (formerly Appendix 4): Clarified that pharmacokinetic sampling timepoints/duration may be adjusted once the PK data are available from Treatment Period 1.

- Section 6.6.2.1, Section 7.2.1, Section 7.2.2, Section 7.2.3, Section 7.2.4, Section 7.4.1, Section 7.4.2, Section 7.4.3, Section 7.4.4, Section 7.6, Appendix 1, and Appendix 3 (formerly Appendix 4): Clarified that blood Phe levels collected during treatment Period 1 and Period 2 will be analyzed by the bioanalytical laboratory.

Editorial Changes to the Protocol are as follows:

- Revised text in Section 5.9 to include only the total amount of the active ingredient (sepiapterin).

- Renamed Appendix 4 (Pharmacokinetic Samples) as Appendix 3 (Pharmacokinetic, Efficacy, and Exploratory Biomarker Samples).

- Renamed Table 6 (PK Sampling Time for Plasma/Whole Blood and Urine Samples) to Table 2 (PK, Preliminary Efficacy, Biomarker, and Exploratory Biomarker Sampling Times for Plasma/Whole Blood and Urine Samples)

- Deleted original protocol Tables 2, 3, 4, and 5 when Appendix 3 content was deleted.

SYNOPSIS

Sponsor:
Censa Pharmaceuticals

Name of Finished Product:
CNSA-001

Name of Active Ingredient:
sepiapterin

Name of Inactive Ingredient(s):
microcrystalline cellulose, colloidal silicon dioxide, croscarmellose, and ascorbic acid

Study Title:
A Phase 1/2, Open-Label, Randomized Parallel Arm, Intra-patient Dose Escalation Study to Evaluate the Safety, Pharmacokinetics and Preliminary Efficacy of CNSA-001 (Sepiapterin) in Primary Tetrahydrobiopterin Deficient Patients with Hyperphenylalaninemia

Study Number:
PBD-001

Study Phase: 1/2

Primary Objective(s):

- To assess the safety and tolerability of 4 dose levels of CNSA-001 in primary tetrahydrobiopterin deficiency (PBD) patients with 6-pyruvoyl-tetrahydropterin synthase (PTPS) or recessive guanosine triphosphate cyclohydrolase 1 (GTP-CH) deficiency

Secondary Objective(s):
The secondary objective(s) of this study are:

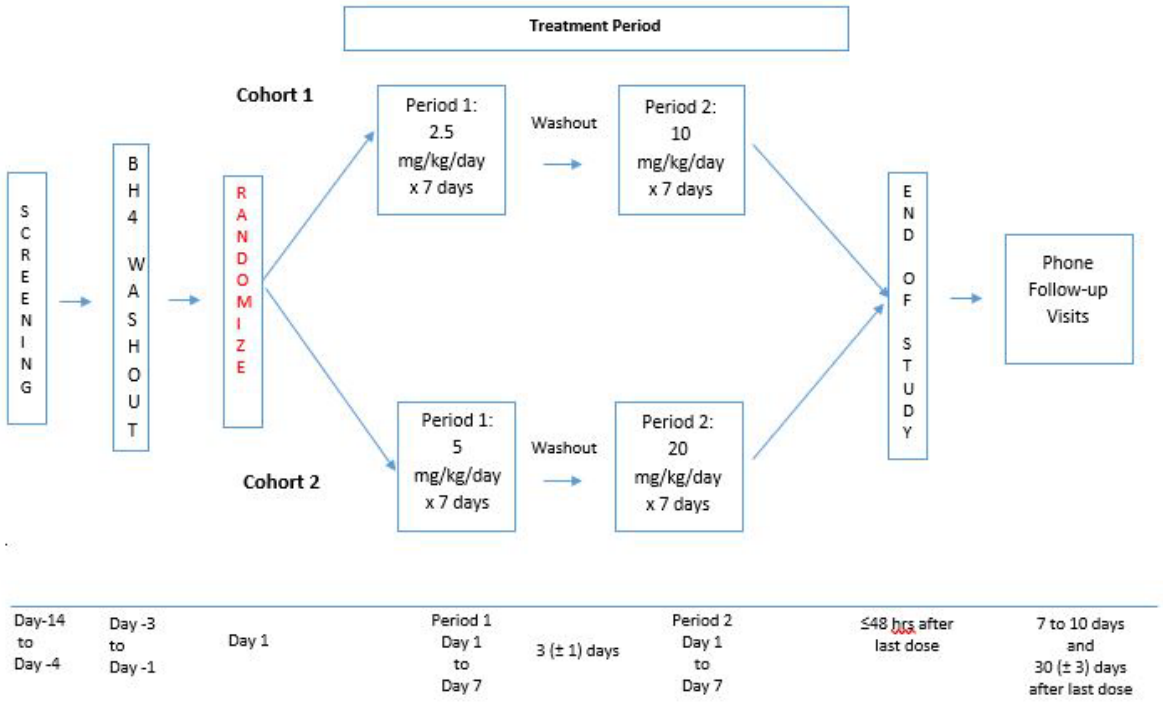
- To assess the pharmacokinetic profile of CNSA-001 and its effect on tetrahydrobiopterin (BH_4), phenylalanine (Phe), and tyrosine (Tyr) in PBD patients with PTPS or recessive GTP-CH deficiency.
- To evaluate the preliminary efficacy of CNSA-001 in reducing blood Phe levels in PBD patients with PTPS or recessive GTP-CH deficiency after 7 days of treatment.

Exploratory Objective:

- To assess the change from baseline in other exploratory biomarkers of this disease such as serum prolactin, whole blood serotonin, and urine sepiapterin, BH_4, and neopterin levels.
- To assess the change from baseline in Cambridge Neuropsychological Test Automated Battery (CANTAB) tests, including the Reaction Time (RTI), the Spatial Span (SSP), the Spatial Working Memory (SWM) and Rapid Visual Information Processing (RVP).
- To assess changes in movement and sleep for euphenylalaniemic and hyperphenylalaninemic states as assessed by an accelerometer device (GeneActiv, Activinsights Ltd.).
- To evaluate changes from baseline in cognitive assessments via the NIH Cognition Toolbox.
- To evaluate changes from baseline in the Child and Adolescent Sleep Checklist (CASC).

Study Design:
This is a Phase 1/2, multicenter, randomized, open-label, intra-patient dose escalation study designed to evaluate the safety, pharmacokinetics, and preliminary evidence of efficacy of CNSA-001 in male and female patients with PBD. This Phase 1/2 study will enroll patients with confirmed defects in de novo biopterin biosynthesis due to PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies. Genetic testing is not required. Approximately 6 to 10 patients will be enrolled in this study at 5 to 6 study centers.
The study design is summarized in the study schema. A schedule of study events and assessments

to be performed is provided in Appendix 1.



Screening Period (Day -14 to Day -4):
An informed consent or assent (if applicable) form must be signed before any study-related procedures are performed. After consenting to the study, PBD patients will undergo Screening procedures which include medical/surgical history, demographics, vital signs, ECG, physical examination, and clinical laboratory tests (chemistry, hematology, urinalysis). Blood Phe levels will be measured at Screening and compared to the 3 most recent historical Phe concentrations. Patients who are eligible based on Screening tests will proceed to the BH_4 Washout Period. Patients will be asked to keep an abnormal movement seizure journal while on study.

BH_4 Washout Period (Day -3 to Day -1):
Eligible patients who are taking BH_4 [Kuvan® (sapropterin dihydrochloride)] will discontinue the medication during the BH_4 Washout Period and will remain off this medication during the entire study. Patients will be instructed to maintain a consistent diet (with respect to protein and Phe intake) and 3-day diet records will be collected during BH_4 Washout and throughout the study. On Days -3 and -1 during the BH_4 Washout Period, blood will be collected for determination of Phe concentrations. To minimize burden on patients, Phe collection on Days -3 and -1 may be obtained via filter paper with overnight shipping to the site's designated laboratory.

Treatment Period 1 and Period 2:
Patients will receive treatment with CNSA-001 for a total of 14 days [i.e., two 7-day treatment periods separated by a 3 (±1) day washout]. Patients will be randomized into one of 2 cohorts, with each cohort assessing 2 dose levels of CNSA-001 via intra-patient dose escalation.

- **Cohort 1**, patients will receive 2.5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 10 mg/kg/day for 7 days in Period 2 (14 days total treatment)
- **Cohort 2**, patients will receive 5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 20 mg/kg/day for 7 days in Period 2 (14 days total treatment).

Patients will be eligible for dose escalation during Period 2 only if they meet the criteria for intra-patient dose escalation (see Section 6.12).

Initially, only adult patient(s) (≥18 years) will be enrolled. The first adult patient will be enrolled into Cohort 1 and then a second adult patient will be enrolled into Cohort 2 of the study, with subsequent patients being randomized into either cohort. After the first adult patient(s) have completed the study, the Data Safety Monitoring Board (DSMB) will review safety and pharmacokinetic/ pharmacodynamic (PK/PD) data, including preliminary efficacy, for the adult patient(s). If the data display no safety issues and provide for the prospect of clinical benefit in patients ≥12 months to <18 years old, then the eligibility criterion for age at time of enrollment will be expanded to include children (≥12 months). The safety, pharmacokinetic, and pharmacodynamic data on the dosed adult patient(s) will be submitted for review to the United States (US) Food and Drug Administration for review prior to enrolling patients <18 years old.

During the study, patients will continue receiving their other current medications for PBD (including L-dopa/carbidopa, 5HTP, melatonin, MAO inhibitors, and dopamine receptor agonists as prescribed) except for BH_4 supplementation (if they were taking BH_4) and will be monitored clinically as per standard of care for PBD to optimize treatment.

Safety and tolerability will primarily be assessed by adverse events (AEs), vital signs, and clinical laboratory tests (including chemistry, hematology, and urinalysis), physical examinations, and 12 lead electrocardiograms (ECGs).

Preliminary efficacy will be assessed by the reduction in plasma Phe levels. Other secondary measures will include whole blood serotonin, serum prolactin and BH_4, and urine sepiapterin, BH_4 and neopterin.

Blood samples will be collected to characterize the pharmacokinetics of sepiapterin and its effect on serum BH_4, Phe, and Tyr at the following time points for each dose level: on Day 1 at pre-dose (within 30 min of dosing), +0.5 hr (±3 min), +1 hr (±5 min), +2 hr (±6 min), +4 hr (±20 min), +6 hr (±30 min), +8 hr (±60 min, prior to Day 1 evening dose), and +24 hours (±2 hr, prior to Day 2 morning dose) after the first dose of study drug.

Patients will receive treatment with CNSA-001 for a total of 14 days [i.e., two 7-day treatment periods separated by a 3 (±1) day washout], unless they meet criteria for discontinuing CNSA-001 treatment. Permanent discontinuation of CNSA-001 treatment may be triggered by safety reasons or lack of efficacy (see Section 6.13.1).

Patients who discontinue CNSA-001 treatment early will complete the End of Study (EOS) assessments. After completion of the EOS assessments, patients should immediately revert to pre-study standard of care for their PBD, including BH_4 if they were taking it previously.

Phone follow-up visits to assess for AEs and serious adverse events (SAEs) will occur 7 to 10 days and 30 (±3) days after the last dose of study drug.

Study Population:

Approximately 6 to 10 patients will be enrolled in this study and treated with CNSA-001 (3 to 5 patients per arm).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Individuals eligible to participate in this study include patients with PBD who meet all the following inclusion criteria:

1. Male or Female patients 18 years old and above and 12 months old and above for the remaining patients (age reduction pending analysis of safety, PK, and response, in the adult patient(s) by the DSMB and FDA)
2. Confirmed diagnosis of PBD as evidenced by medical history of biallelic pathogenic mutations in PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies. Genetic testing is not required.
3. Informed consent and assent [if necessary (i.e., for children and/or patients that are mentally impaired secondary to disease)] with parental consent
4. Females must be either postmenopausal for ≥1 year, or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use at least 2 of the following methods of contraception (including adolescents 12 to 18 years old) from Screening through 30 days after the last dose of study drug:
    - Hormonal contraception (stable dose for 3 months) or
    - IUD/IU Hormone-releasing System, plus
    - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom) with spermicidal foam/gel/cream/suppository

   Males and females who are abstinent will not be required to use a 2nd contraceptive method unless they become sexually active.
5. Males with female partners of childbearing potential must agree to use barrier contraceptive (i.e., condom) with spermicidal foam from Screening through 90 days after the last dose of study drug. Males must also refrain from sperm donations during this time period.
6. Females with a negative pregnancy test at Screening and on Day 1 prior to dosing
7. Creatinine clearance (CrCl) >90 mL/min as estimated using the Cockcroft-Gault equation (≥18 years) or Schwartz-Lyon equation (≥ 12 months < 18 years) (Appendix 2)
8. The patient is clinically stable on therapy for management of their signs and symptoms of PBD as determined by the Investigator
9. The patient is willing and able to comply with the protocol
10. No tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco) for 2 weeks prior to the Screening visit and willingness to abstain from these products through the last dose of study drug

Individuals are not eligible to participate in this study if they have or meet any of the following exclusion criteria:

1. PBD caused by biallelic pathogenic mutations in pterin-4a-carbinolamine dehydratase (PCD), sepiapterin reductase (SR), dihydropteridine reductase (DHPR), or single dominant mutations in GTP-CH
2. Significant chronic medical illness other than PBD, as determined by the Investigator
3. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, etc.) that could affect the absorption of study drug
4. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
5. Inability to tolerate oral medication
6. History of allergies or adverse reactions to BH_4 or related compounds, or any excipients in the study drug formulation
7. Any clinically significant medical or psychiatric condition or medical history, that in the opinion of the Investigator, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient

8. Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV)
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) laboratory values >2 × the upper limit of normal (ULN)
10. Any other clinically significant laboratory abnormality unrelated to PBD at the Screening visit or prior to the administration of the first dose of study drug, as determined by the Investigator
11. Clinically significant cardiac arrhythmia at Screening or prior to the first dose of study drug
12. QTcF (QT with Fredericia's correction) ≥460 msec in males and ≥480 msec in females (based on the mean of triplicate measurements taken at Screening)
13. Resting heart rate ≤40 or ≥110 bpm for ages 12 and older, ≥ 130 bpm for ages 3 to 12, ≥ 150 bpm for ages 1-2 years or resting blood pressure <85/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug
14. Current participation in any other investigational drug study or participation within 30 days prior to Screening
15. History of alcohol or drug abuse within last 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
16. Currently taking an antifolate including, but not limited to, methotrexate, pemetrexed, or trimetrexate
17. A female who is nursing or who is pregnant or planning to become pregnant
18. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study

Test Product; Dose; and Mode of Administration:
The test product is CNSA-001 (sepiapterin) oral powder for suspension. Patients will be randomized to one of 2 cohorts that will test 2 doses each, adjusted for body weight (i.e., either oral doses of 2.5 and 10 mg/kg/day CNSA-001 in Cohort 1 or 5 and 20 mg/kg/day CNSA-001 in Cohort 2). All dosing will be divided and administered twice daily with breakfast and dinner.

Reference Therapy; Dose; and Mode of Administration: None

Duration of Treatment:
Patients will receive CNSA-001 during the treatment period for a duration of 7 days during Period 1 followed by a 3 (±1) day washout and then intra-patient escalation to a second dose level for an additional 7 days during Period 2 (i.e., 14 days of total treatment).

Safety Assessments:
Safety and tolerability of CNSA-001 will be measured by assessing the incidence of treatment-emergent adverse events (TEAEs), including assessment of severity of TEAEs, clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs).

Pharmacokinetic Variables:
The blood concentrations of sepiapterin, BH_4, Phe, and Tyr will be summarized and listed. The following non-compartmental PK parameters for sepiapterin, BH_4, Phe, and Tyr will be estimated and summarized along with graphical presentation of the concentration data:

Parameter	Definition
$AUC_{0\text{-inf}}$	Area under the curve from time 0 to infinity using trapezoidal method (linear-up/log-down method) and extrapolation to infinite time
$AUC_{0\text{-last}}$	Area under the curve from time 0 to the time of the last quantifiable concentration using linear-up/log-down method trapezoidal method
C_{max}	Maximum observed concentration
T_{max}	Time to C_{max}
$t_{1/2}$	Half-life

K_e	Elimination rate constant

Efficacy Variables:

The preliminary efficacy measure will be reduction in plasma Phe levels as defined by the change of plasma Phe concentrations from baseline (Day 1, pre-dose). All changes from baseline will be calculated from Day 1 of the treatment period to Day 7 of the treatment period.

Secondary measures may include the following summary statistics (at each visit) as well as summary statistics changes from baseline to Day 7:

- Percent of patients with Phe concentrations in acceptable treatment range of 130 to 360 µmol/L at Day 7
- Percent of patients with Phe concentrations <130 µmol/L at Day 7

Exploratory Measures Include:

- Urine sepiapterin, neopterin, and BH_4
- Serum prolactin
- Whole blood serotonin
- Computerized testing (CANTAB) at Screening and Day 1 (pre-dose) and Day 7 of each treatment period
- Changes in movement and sleep as assessed by an accelerometer device (GeneActiv, Activinsights Ltd.).
- Cognitive assessments via the NIH Cognition Toolbox.
- Sleep assessment via the CASC.

Statistical Methods:

Three study populations will be assessed:

1. Safety population: all patients who receive any amount of study drug
2. The Efficacy population: all patients who were randomized, received any amount of study drug, and had available pre-dose Phe Concentrations on Day 1 and at least one post-Day 1 visit within a period. All efficacy analyses will be conducted in this population.
3. PK Population: all patients who received at least one dose of study drug and had at least 1 blood sample collected for analysis of sepiapterin, BH_4, Phe, or Tyr concentrations.

Safety will be assessed in the Safety population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs (events that begin after first dose of study drug) will be tabulated by dose cohort, period, system organ class, and MedDRA preferred term. The dose cohort for each AE is identified based on the last dose of study drug taken at or before the start of the AE. Severity of AEs and SAEs will be summarized similarly. AEs leading to premature discontinuation from the study drug and serious TEAEs will be presented in a table or a listing. Clinical laboratory test results and vital signs will be summarized at each visit as well as changes from baseline within each cohort and period.

Efficacy will be assessed in the Efficacy population. Phe concentrations at each visit and changes from baseline will be summarized using summary statistics (number of patients, mean, standard deviation, median, range) within each dose cohort and period. Treatment induced Phe level is not powered for this study and caution is needed in the interpretation of results.

Secondary and exploratory outcome measures will also be summarized using descriptive statistics in the Efficacy population.

All PK variables will be summarized by dose and will also be listed. Concentration time plots will be created as well for sepiapterin, BH_4, Phe, and Tyr in the PK Population.

Details of the statistical analysis will be provided in a separate Statistical Analysis Plan.

Date of Original Protocol: 14 August 2017

Date of Most Recent Protocol Amendment (if applicable): 13 May 2020

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AM	Morning
AP	Alkaline phosphatase
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the time-concentration curve
BH_4	Tetrahydrobiopterin
BMI	Body mass index
BUN	Blood urea nitrogen
CASC	Child and Adolescent Sleep Checklist
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBC	Complete blood count
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Clinical Monitoring Plan
COMT	catechol-O-methyl transferase
CRF	Case report form
CRO	Contract Research Organization
CSF	Cerebrospinal fluid
CV	Coefficient of variation
DHPR	Dihydropteridine reductase
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practices
GTP-CH	Guanosine triphosphate cyclohydrolase 1
HCT	Hematocrit
HGB	Hemoglobin
HCB	Human chorionic gonadotropin
HEENT	Head, eyes, ears, nose and throat
HIPAA	Health Information Portability and Accountability Act
HPA	Hyperphenylalaninemia
IB	Investigator's Brochure
IBS	Irritable bowel syndrome
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IQ	Intelligence Quotient
IRB	Institutional Review Board
ITT	Intent-to-treat
LAR	Legally Authorized Representative
LDH	lactic dehydrogenase
MAO	Monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
PBD	Primary tetrahydrobiopterin deficiency
PCD	Pterin-4a-carbinolamine dehydratase
PCr	Plasma Creatinine
PD	Pharmacodynamic
PE	Physical examination

Phe	Phenylalanine
PK	Pharmacokinetic
PKU	Phenylketonuria
PTPS	6-pyruvoyl-tetrahydropterin synthase
QC	Quality control
RBC	Red blood cell (count)
RTI	Reaction time
RVP	Rapid visual information processing
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
SSP	Spatial span
SR	Sepiapterin reductase
SWM	Spatial working memory
T_{max}	Time to maximum plasma concentration
$t_{1/2}$	Half-life
Tyr	Tyrosine
US	United States
WBC	White blood cell (count)
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Primary Tetrahydrobiopterin Deficiency

Primary tetrahydrobiopterin deficiency (PBD) is caused by deficiency of GTP cyclohydrolase I (GTP-CH), 6-pyruvoyl-tetrahydropterin synthase (PTPS), or sepiapterin reductase (SR) that impair the biosynthesis of tetrahydrobiopterin (BH_4) or by defects in BH_4 recycling (pterin-4a-carbinolamine dehydratase [PCD] or dihydropteridine reductase [DHPR] deficiency) (Tada et al, 1969; Tada et al, 1980; Bartholome, 1974; Abeling et al, 2006). PBD accounts for 1 to 3% of all cases of hyperphenylalaninemia (HPA), with virtually all of the remaining cases due to phenylalanine hydroxylase deficiency. HPA occurs in 1:10,000 to 1:15,000 live births (Dhondt, 1991; Hardelid et al, 2008; Donlon et al, 2004). The estimated frequency of PTPS deficiency is 1:320,000 while GTP-CH deficiency affects <1:1,000,000 newborns (http://www.orpha.net/consor/cgi-bin/index.php) accessed 8/29/16).

A worldwide registry started more than 20 years ago contains data on approximately 1,118 patients with primary BH_4 deficiency (BioDefDb at BIOPKU.org accessed 2/16/17). Based on this evidence, currently there are approximately 100 patients with PTPS or GTP-CH deficiency in the United States (US).

BH_4 is an essential cofactor for phenylalanine hydroxylase (Kaufman, 1958), tyrosine hydroxylase (Nagatsu et al, 1964), tryptophan hydroxylase (Ichiyama et al, 1970), (Loyenberg, 1967), fatty acid glycerylether oxygenase (Tietz et al, 1964), and nitric oxide (NO) synthase (Kwon et al, 1989), (Mayer et al, 1991).

In PBD, impaired hydroxylation of Phenylalanine (Phe) to Tyrosine (Tyr) results in HPA. The reduced synthesis of Tyr and impaired activities of Tyr and tryptophan hydroxylases results in reduced formation of neurotransmitters and consequent neuromotor deficits (Butler et al, 1981). A synthetic form of BH_4, sapropterin dihydrochloride (Kuvan®; NDA 022181 and NDA 205065; Biomarin Pharmaceutical, Inc.), has been successful in addressing HPA, but not the neurotransmitter deficiency in the brain (Ohashi A et al, 2016).

Phenotypically, BH_4 deficiency presents with HPA and deficiency of the neurotransmitter precursors, L-dopa and 5-hydroxytryptophan, and thus may be detected through newborn screening programs which measure Phe in order to detect phenylalanine hydroxylase deficiency (the exception being SR deficient patients who have normal Phe concentrations).

Untreated patients with PBD typically present with developmental delay and other severe neurological symptoms early in life (Smith et al, 1975; Danks et al, 1975). Infants affected by PTPS deficiency, the most common form of BH_4 deficiency, are usually small for gestational age (Smith and Dhont, 1985) and can have poor sucking, impaired tone and microcephaly in the neonatal period. Later they present characteristic extrapyramidal symptoms due to deficiency of dopamine in the basal ganglia including truncal hypotonia, increased limb tone, postural instability, hypokinesia, choreatic or dystonic limb movements, gait difficulties, hypersalivation due to swallowing difficulties, and oculogyric crises. Ataxia, hyperreflexia, hypothermia as well as episodes of hyperthermia (in the absence of infections), drowsiness, irritability, disturbed sleep patterns, and convulsions (grand mal or myoclonic) are often seen

(Nyan and Ozand, 1998; Blau and Dhondt, 1996). The clinical course of illness in DHPR deficiency is similar to that seen in severe forms of PTPS deficiency with the addition of brain calcifications in the cortex, basal ganglia, and thalamus (Kaufman, 1975).

PBDs are screened in all infants with HPA by measuring pterins in urine and DHPR activity in blood spots. A BH_4 loading test in vivo is sometimes performed in European Countries (Dhondt JL, 1991; Blau, 2006).

1.2 Current Treatment of PBD

Treatment of BH_4 deficiency consists of reducing Phe concentrations in blood either by oral administration of BH_4 (in GTP-CH and PTPS deficiency) and/or low Phe diet (mainly in DHPR deficiency) and administration of the neurotransmitter precursors L-dopa and 5-hydroxytryptophan (5HTP) (Ponzone, 2006). Folinic acid is given to DHPR-deficient patients and also in some PTPS-deficient patients with low 5-methyltetrahydrofolate (5MTHF) concentrations in cerebrospinal fluid (CSF). Monoamine oxidase (MAO) or catechol-O-methyl transferase (COMT) inhibitors are sometimes added to the therapeutic regimen (Jaggi et al, 2008), and more recently dopamine receptor agonists are sometimes utilized (Porta et al, 2015). A synthetic form of BH_4, sapropterin dihydrochloride, is approved (Kuvan®; NDA 022181 and NDA 205065; Biomarin Pharmaceutical, Inc.) for the treatment of HPA due to BH_4-responsive phenylketonuria (PKU) but is not approved for PBD in the US. Therapy with BH_4, alone or in combination with neurotransmitter precursors and folinic acid, has been shown to decrease blood Phe concentrations and improve neuromotor function in patients with PBD (Shintaku, 2002; Kitagawa et al, 1990). Reports of long-term follow-up of patients with BH_4 deficiency are scarce (Dudesek et al, 2001; Chien et al, 2001; Wang et al, 2006). Therapeutic strategies vary by treating physician and clinic, are far from clinically based evidence, and include pharmacologic agents none of which have marketing approval for this indication in the US (Shintaku, 2002).

Although there is no approved treatment for PBD in the US, in Japan a formulation of BH_4 (Biopten®, Asubio Pharma) has been marketed for this indication since 1992. In Europe, BH_4 Deficiency was included as part of the labeled indication for Kuvan® (sapropterin dihydrochloride) when it was approved to treat PKU in 2008.

Two clinical trials have evaluated the safety and efficacy of sapropterin in BH_4 deficient patients. The first study evaluated the effectiveness of sapropterin 2.5% granules (Biopten) to decrease blood Phe concentrations in patients with BH_4 deficiency (PTPS, DHPR, or GTP-CH deficiency). This open-label trial which was used to support Biopten (sapropterin 2.5% granules) registration in Japan, was conducted between 1987 and 1989, and enrolled and treated 16 patients with BH_4 deficiency. For all 16 patients, blood Phe concentrations were lower after treatment with sapropterin and were maintained within the normal range during the treatment period (Kitigawa et al, 1990). A post-marketing surveillance study of the use of Biopten in the treatment of BH_4 deficiency was conducted in Japan over a 10-year data collection period, from March 1992 to March 2002. Global improvement based on blood Phe concentrations and physical/mental development before and during Biopten treatment was assessed as an efficacy endpoint. Ninety-three percent (93%; 25/27) of patients were described as having a global improvement of “markedly improved”, “improved”, or “slightly

improved." One patient with DHPR deficiency was described as having a global improvement of "unchanged" and another was classified as "exacerbated." These 2 patients had also developed neurological symptoms before treatment with sapropterin, and symptoms of epilepsy increased during the surveillance period.

A second study evaluating the effects of Kuvan® in PBD was conducted: Safety and Efficacy Study of Phenoptin in Patients with Hyperphenylalaninemia Due to BH_4 Deficiency, ClinicalTrials.gov Identifier NCT00355264. Wasserstein et al, 2008 reported interim results of presumably the same study at the American Society of Human Genetics 2008 meeting: Interim results of a Phase II, multicenter, open-label study of sapropterin dihydrochloride in patients with hyperphenylalaninemia related to primary BH_4 deficiency. Sapropterin was well tolerated. There were no deaths, serious adverse events (SAEs) or withdrawals caused by the drug, and blood Phe concentrations remained stable.

1.3 CNSA-001 (Sepiapterin)

CNSA-001 contains the new molecular entity, sepiapterin. Sepiapterin is [redacted] with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.

The chemical structure is:

[redacted]

Sepiapterin is a natural precursor of BH_4 via the pterin salvage pathway (Curtius et al, 1979; Mayer, 1995). The major goals of treatment for PBD are to impact signs and symptoms by elevating tissue levels of BH_4, lowering Phe levels, and replacing potentially deficient neurotransmitters. Support for the use of sepiapterin for the treatment of PBD comes from experience with BH_4. Sepiapterin is converted intracellularly to BH_4. The use of BH_4 for the treatment of PBD has been well documented in the literature and is approved for BH_4 Deficiency in Japan (Biopten) and the European Union (Kuvan®). Sepiapterin is expected to function as well as or better than BH_4, however, until now, manufacturing sepiapterin at a scale to conduct appropriate clinical studies has been prohibitive.

CNSA-001 is the first viable formulation of sepiapterin, shown to increase intracellular BH_4, and intended for the treatment of HPA in patients with PBD. CNSA-001 was studied in a single and multiple ascending-dose study in healthy volunteers, the Phase 1 study, Study PKU-001 (Smith et al, 2019). A total of 60 subjects were exposed to single or multiple doses of CNSA-001. Part A of this study assessed the safety and pharmacokinetics of CNSA-001 at 6 dose levels inclusive of an assessment of food effect (i.e., 2.5 mg/kg, 7.5 mg/kg, 20 mg/kg, 40 mg/kg, 80 mg/kg, and 10 mg/kg [to assess food effect]). Additionally, Kuvan was administered at equivalent doses for the first 3 dose levels (2.5 mg/kg, 7.5 mg/kg, and 20

mg/kg). Dose-dependent correlations between CNSA-001 and plasma BH_4 concentrations were observed with each successive dose level. Administration with a standard high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 calories) meal resulted in approximately 80% higher plasma BH_4 concentrations (area under the concentration time curve from 0 to the last measurement [AUC0-last] and maximum concentration [Cmax]) than in subjects who had fasted before receipt of CNSA-001. Treatment-emergent adverse events (TEAEs) in Part A of Study PKU-001 were reported in 26 subjects (44.1%, 26/59). The TEAEs for CNSA-001 were generally mild and consistent with reported adverse events (AEs) for Kuvan® and placebo. The frequency of TEAEs did not appear to increase with increasing dose. The TEAEs that were judged to be related to study treatment were reported in 17 subjects: 11 subjects (26.2%, 11/42) who received CNSA-001, 4 subjects (44.4%, 4/9) who received Kuvan®, and 2 subjects (25.0%, 2/8) who received placebo. No TEAEs were severe or serious or led to discontinuation of study drug. Headache and dizziness were the most common TEAEs, but these TEAEs occurred at a similar frequency as with placebo.

Part B of Study PKU-001 assessed multiple ascending doses CNSA-001 in healthy volunteers. Data indicate CNSA-001 was well tolerated following daily doses of 5, 20, and 60 mg/kg/day for 7 days and that TEAEs were reported in 14 subjects (58.3%, 14/24). The TEAEs in subjects who received CNSA 001 were mild or moderate and consistent with the TEAEs in subjects who received placebo: TEAEs were experienced by 10 subjects (55.6%, 10/18) who received CNSA-001 at doses from 5 mg/kg to 60 mg/kg daily for 7 days and by 4 subjects (66.7%, 4/6) who received placebo. No TEAEs were severe, serious, or led to discontinuation. Of the 10 TEAEs reported in subjects who received CNSA-001, only 4 were judged to be related to study drug, and, of the 4 TEAEs reported in subjects who received placebo, only 1 was judged to be related to study drug. Somnolence, fatigue, headache, and procedural pain (secondary to performance of 2 sequential lumbar punctures 7 days apart) were the most common TEAEs reported, and they occurred at a similar frequency when compared with placebo with the exception of fatigue and headache, which were each reported in 2 subjects who received CNSA-001 (11.1%, 2/18).

There have been 5 published case reports of PBD patients that received sepiapterin and demonstrated similar positive effects on blood Phe concentrations as seen with BH_4 treatment (Niederwieser et al, 1982; Curtius et al, 1979; Hase et al, 1982; Dhondt et al, 1985; Giudici et al, 1991).

1.4 Rationale for Study

Primary BH_4 deficiency is an ultra-rare, genetically-linked disease that affects approximately 100 to 200 patients in the US. Of these, 70% are associated with defects in the PTPS and GTP-CH enzymes that are responsible for the de novo synthesis of BH_4. As CNSA-001 is part of the salvage pathway for BH_4 synthesis, it is anticipated that patients with PTPS or recessive GTP-CH defects will produce BH_4 via the salvage pathway when administered CNSA-001. Both in vitro and in vivo data suggest that exogenous administration of sepiapterin demonstrates preferential uptake into various tissues resulting in superior BH_4 production versus BH_4 supplementation (Sawabe et al, 2008).

Although Kuvan® (sapropterin dihydrochloride) is approved in Europe for the treatment of HPA in adults and pediatric patients of all ages with PBD who have been shown to be responsive to such treatment, there is a need for additional treatment options. There is currently no approved treatment for HPA in PBD in the US and, therefore, represents an unmet medical need. The excellent safety record of sapropterin as well as the completed Phase 1 study of CNSA-001, Study PKU-001, and human case studies of sepiapterin demonstrating Phe lowering justify this study (Niederwieser et al, 1982; Curtius et al, 1979; Hase et al, 1982; Dhondt et al, 1985; Giudici et al, 1991).

2 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objective of this study is:

- To assess the safety and tolerability of 4 dose levels of CNSA-001 in PBD patients with PTPS or recessive GTP-CH deficiency.

2.2 Secondary Objective(s)

The secondary objective(s) of this study are:

- To assess the pharmacokinetic profile of CNSA-001 and its effect on BH_4, Phe, and Tyr in PBD patients with PTPS or recessive GTP-CH deficiency.
- To evaluate the preliminary efficacy of CNSA-001 in reducing blood Phe levels in PBD patients with PTPS or recessive GTP-CH deficiency after 7 days of treatment.

2.3 Exploratory Objective

- To assess the change from baseline in other exploratory biomarkers of this disease such as serum prolactin, whole blood serotonin, and urine sepiapterin, BH_4, and neopterin levels.
- To assess the change from baseline in a CANTAB test battery including the Reaction Time (RTI), the Spatial Span (SSP), the Spatial Working Memory (SWM) and Rapid Visual Information Processing (RVP).
- To assess changes in movement and sleep for euphenylalaniemic and hyperphenylalaninemic states as assessed by an accelerometer device (GeneActiv, Activinsights Ltd.).
- To evaluate changes from baseline in cognitive assessments via the NIH Cognition Toolbox.
- To evaluate changes form baseline in sleep via the CASC.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 1/2, multicenter, randomized, open-label, intra-patient dose escalation study designed to evaluate the safety, pharmacokinetics, and preliminary evidence of efficacy of CNSA-001 in male and female patients with PBD. This Phase 1/2 study will enroll patients with confirmed defects in de novo biopterin biosynthesis due to PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies. Genetic testing is not required. Six (6) to 10 patients will be enrolled in this study at 5 to 6 study centers.

Screening Period (Day -14 to Day -4):

An informed consent or assent (if applicable) form must be signed before any study-related procedures are performed. After consenting to the study, PBD patients will undergo Screening procedures which include medical/surgical history, demographics, vital signs, 12-lead electrocardiogram (ECG), physical examination, and clinical laboratory tests (chemistry, hematology, urinalysis). Blood Phe levels will be measured at Screening and compared to the 3 most recent historical Phe concentrations. Patients who are eligible based on Screening tests will proceed to the BH_4 Washout Period. Patients will be asked to keep an abnormal movement seizure journal while on study.

BH_4 Washout Period (Day -3 to Day -1):

Eligible patients who are taking BH_4 [Kuvan® (sapropterin dihydrochloride)] will discontinue the medication during the BH_4 Washout Period and will remain off this medication during the entire study. Patients will be instructed to maintain a consistent diet (with respect to protein and Phe intake) and 3-day diet records will be collected during BH_4 Washout Period and throughout the study. On Days -3, and -1 during the BH_4 Washout Period, blood will be collected for determination of Phe concentrations. To minimize burden on patients, Phe collection on Days -3 and -1 may be obtained via filter paper with overnight shipping to the site's designated laboratory.

Treatment Period 1 and Period 2:

Patients will receive treatment with CNSA-001 twice daily for a total of 14 days [i.e., two 7-day treatment periods separated by a 3 (±1) day washout]. Patients will be randomized into one of 2 cohorts, with each cohort assessing 2 dose levels of CNSA-001 via intra-patient dose escalation.

- **Cohort 1**, patients will receive 2.5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 10 mg/kg/day for 7 days in Period 2 (14 days total treatment)
- **Cohort 2**, patients will receive 5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 20 mg/kg/day for 7 days in Period 2 (14 days total treatment).

Patients will be eligible for dose escalation during Period 2 if they meet the criteria for intra-patient dose escalation (see Section 6.12).

Initially, only adult patient(s) (≥18 years) will be enrolled. The first adult patient will be enrolled into Cohort 1 and then a second adult patient will be enrolled into Cohort 2 of the study, with subsequent patients being randomized into either cohort. After the first adult patient(s) have completed the study, the Data Safety Monitoring Board (DSMB) (see Section 10.8) will review safety and PK/PD data, including preliminary efficacy, for the adult patient(s). If the data display no safety issues and provide for the prospect of clinical benefit in patients ≥12 months to <18 years old, then the eligibility criterion for age at time of enrollment will be expanded to include children (≥12 months). The safety, pharmacokinetic, and pharmacodynamic data on the dosed adult patient(s) will be submitted for review to the US FDA for review prior to enrolling patients <18 years old.

During the study, patients will continue their other current medications for PBD (including L-dopa/carbidopa, 5HTP, melatonin, MAO inhibitors, and dopamine receptor agonists as prescribed) except for BH_4 supplementation (if they were taking BH_4) and will be monitored clinically as per standard of care for PBD to optimize treatment.

Evaluations while in the study will include safety and tolerability, PK, and preliminary efficacy evaluation. Safety and tolerability will primarily be assessed by adverse events (AEs), vital signs, clinical laboratory tests (including chemistry, hematology), physical examinations, and urinalysis, and 12-lead ECGs. Preliminary efficacy will be assessed by the reduction in plasma Phe levels. Other secondary measures will include whole blood serotonin, serum prolactin and BH_4, and urine sepiapterin, BH_4 and neopterin.

Sampling for pharmacokinetic analysis (with evaluation of sepiapterin and its effect on serum BH_4, Phe, and Tyr levels) will occur at the following time points for each dose level: on Day 1 at pre-dose (within 30 min of dosing), +0.5 hr (±3 min), +1 hr (±5 min), +2 hr (±6 min), +4 hr (±20 min), +6 hr (±30 min), +8 hr (±60 min, prior to Day 1 evening dose), and +24 hours (±2 hr, prior to Day 2 morning dose) after the first dose of study drug.

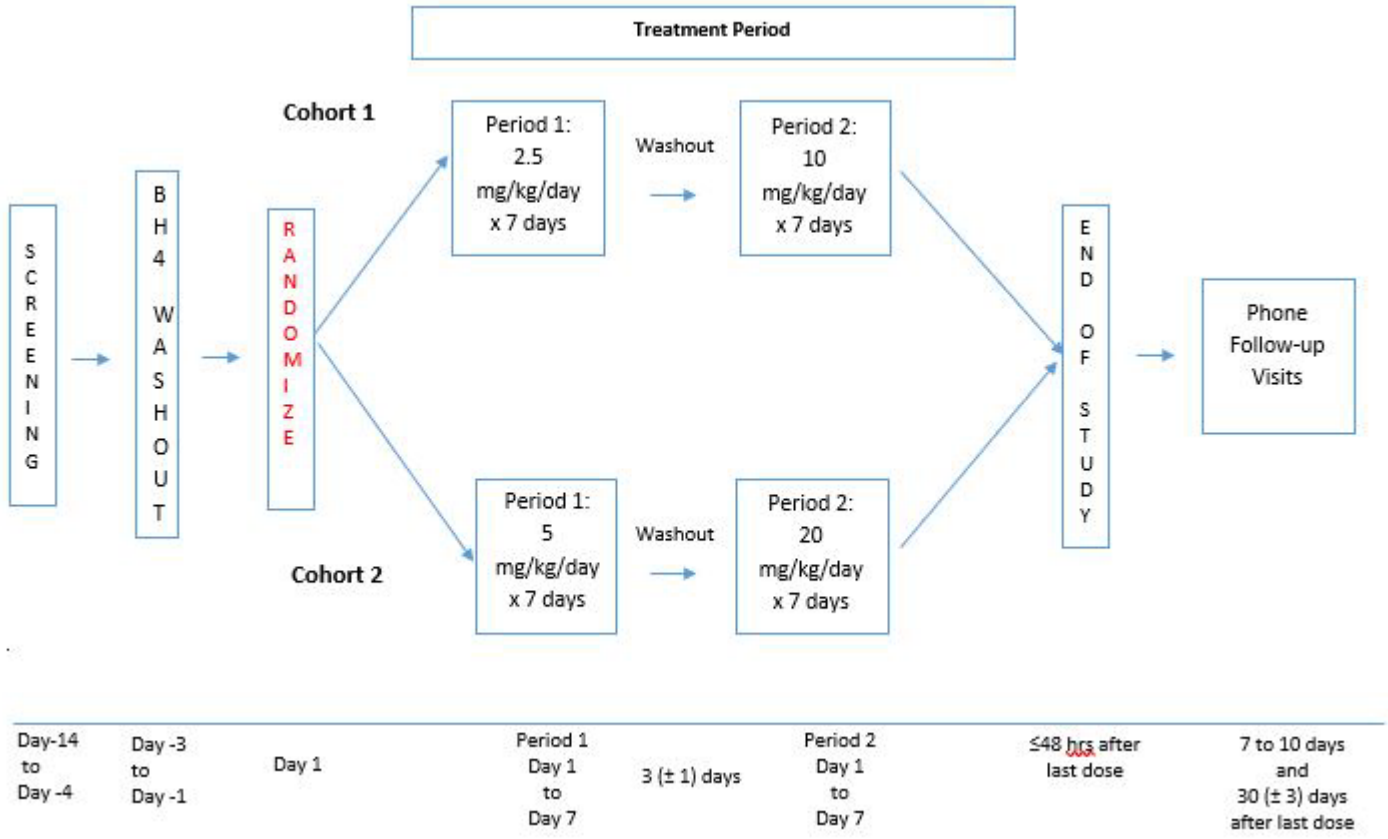
Patients will receive treatment with CNSA-001 for a total of 14 days [i.e., two 7-day treatment periods separated by a 3 (±1) day washout], unless they meet criteria for discontinuing CNSA-001 treatment. Permanent discontinuation of CNSA-001 treatment may be triggered by safety reasons or lack of efficacy (see Section 6.13.1).

Patients who discontinue CNSA-001 treatment early will complete the End of Study (EOS) assessments. After completion of the EOS assessments, patients should immediately revert to pre-study standard of care for their PBD, including BH_4 if they were taking it previously.

Phone follow-up visits to assess for AEs and SAEs will occur 7 to 10 days and 30 (± 3) days after the last dose of study drug.

A schedule of study events and assessments to be performed is provided in Appendix 1. The study design is summarized in Figure 1.

Figure 1. Study Schema



3.2 Rationale for Study Design and Control Group

Primary BH_4 deficiency is an ultra-rare, genetically-linked disease that affects approximately 100 to 200 patients in the US. Of these, 70% are associated with defects in the PTPS and GTP-CH enzymes that are responsible for the de novo synthesis of BH_4. As CNSA-001 is part of the salvage pathway for BH_4 synthesis, it is anticipated that patients with PTPS or recessive GTP-CH defects will produce BH_4 via the salvage pathway when administered CNSA-001. Because of the extremely small numbers of available patients, effort to maximize the data obtained from each individual patient was considered. Accordingly, an intra-patient dose escalation will be employed to obtain safety, tolerability, PK and preliminary efficacy at 4 different dose levels while utilizing a minimum number of patients.

Patients will be asked to stop taking BH_4 supplementation while participating in this study. HPA is anticipated for a short period of time during Screening and in between dosing periods. Short-term increases in plasma Phe will be closely monitored. Phe >360 µmol/L represents the lower limit of acceptable Phe concentrations in patients with HPA. If patients experience an increase in their Phe of more than 360 µmol/L from baseline (Day 1 pre-dose value) within the initial 48 hours of treatment, then they will be removed from the study and immediately placed back on pre-study treatment for HPA. Because of the concern for prolonged HPA, a placebo control will not be used in this study.

3.3 Rationale for Selection of Doses

Results from completed Phase 1 study (Study PKU-001) entitled, "A Phase 1 Exploratory Placebo and Active-Controlled, Double-Blind, Single- and Multiple-Dose Escalation, Pharmacokinetic, Pharmacodynamic and Food Effect Study of CNSA-001 in Healthy Volunteers" indicate that CNSA-001 is safe and well tolerated at doses ranging from 2.5 to 80 mg/kg/day as single doses and 5 to 60 mg/kg/day as multiple daily dosing over 7 days (Section 1.3; Smith et al. 2019). In total, 60 subjects received either single (n = 42) or multiple doses (n = 18) of CNSA-001 in Study PKU-001. This study also assessed pharmacokinetic properties of CNSA-001 and Kuvan® (sapropterin dihydrochloride). Both sepiapterin and BH_4 were assessed as PK analytes in plasma. Following oral administration of CNSA-001, sepiapterin was rapidly converted to BH_4. Plasma concentrations of BH_4 following CNSA-001 treatment were 1.5 to 3.6 times higher (AUC0-last and Cmax) on a dose/dose equivalency when compared with Kuvan. Based on these data, it is anticipated that the starting dose of 2.5 mg/kg/day will produce sufficient quantity of BH_4 to demonstrate efficacy in this patient population. Subsequent doses of 5, 10 and 20 mg/kg/day were selected as half-log increases in doses, a typical practice in early phase 1 studies and may aid in assessing dose response. Additionally, this range of doses represents the same range of doses used commercially by Kuvan. Lastly, these doses were found to be safe and well tolerated in the completed Phase 1 study PKU-001.

In nonclinical studies conducted in mice, rats, and marmoset monkeys, rapid conversion of CNSA-001 to BH_4 intracellularly in liver, kidney, and brain was observed. In two 14-day GLP toxicology studies conducted in rat and marmoset monkey with CNSA-001 at doses of 100, 300 and 1000 mg/kg/day, no adverse effect was observed on any assessment and the No-Observed-Adverse-Effect-Level (NOAEL) for both species was 1000 mg/kg/day. This

correlates to a Human Equivalent Dose of 161.3 mg/kg/day and reflects a safety margin of approximately 64.5 based on a minimum expected therapeutic dose of 2.5 mg/kg in humans, the starting dose for healthy volunteers in Study PKU-001 and for patients with PBD in study PBD-001.

3.4 Risks and Benefits for Participating in Study PBD-001

Results from completed Phase 1 study (Study PKU-001) are summarized in Section 1.3. Administration of CNSA-001 was found safe and well tolerated at single doses ranging from 2.5 to 80 mg/kg/day and following multiple doses ranging from 5 to 60 mg/kg/day for 7 days. In this study, safety was evaluated by adverse events (AEs) reporting, vital signs and 12-lead ECGs, physical examination and weight, medical and laboratory assessments. Headache, dizziness and fatigue were the most common TEAEs reported but occurred at a similar frequency when compared with placebo. Shifts in liver function enzyme parameters from baseline observed during the study were small, either from grade 1 to no grade or vice versa. All post baseline vital signs were normal or slightly below normal for heart rate (<50 bpm) and diastolic blood pressure (<50 mm Hg). No clinically significant increases in heart wave interval between Q and T with Fridericia's correction (QTcF) values were observed.

As indicated in Section 3.2, patients will be asked to stop taking BH_4 supplementation while participating in this study and will likely experience associated increases in phenylalanine. All other treatments for their primary BH_4 deficiency will remain unchanged. For two brief periods, patients will not have access to any pharmacological treatment for HPA [BH_4 washout Period: 3 days duration, and CNSA-001 Washout between Treatment Periods 1 and 2: 3 (±1) days duration]. Major clinical/neurological signs of HPA such as effects in coloration of the skin, hair, and eyes, psychomotor function, and mental retardation are long-term observations. As these patients will only be off of BH_4 supplementation for a short period of time, the concern for significant clinical/neurological effects will be minimized. Over short-term periods, HPA may result in slowed reaction time or impaired mental acuity, similar to the effects following alcohol consumption. Accordingly, this study has incorporated very short-term periods for washout of BH_4 to minimize potential long-term effects of HPA. Additionally, patients will be requested to maintain an abnormal movement seizure diary throughout the study to assist with monitoring patient safety and reporting of potential adverse events (Section 6.14). Rescue therapy with BH_4 has also been incorporated should patients experience lack of efficacy with CNSA-001 treatment.

Another potential risk is hypophenylalaninemia as a result of CNSA-001 treatment. Hypophenylalaninemia is extremely rare. However, the Kuvan prescribing information states, "in clinical trials, some patients have experienced low blood Phe levels. Children younger than 7 years treated with Kuvan doses of 20 mg/kg per day are at increased risk for low levels of blood Phe compared with patients 7 years and older" congestion (Kuvan Prescribing Information, BioMarin 07/2015)." Long term deficit of phenylalanine may result in poor mental and physical development. To ensure that no long-term deficit in phenylalanine results with study treatment in Study PBD-001, a rescue meal will be provided.

As indicated in Sections 3.3, oral administration of CNSA-001 in Study PKU-001 resulted in rapid conversion or sepiapterin to BH_4 with subsequent plasma concentrations of BH_4 following CNSA-001 treatment being 1.5 to 3.6 times higher (AUC0-last and Cmax) on a dose/dose equivalency when compared with Kuvan. Based on these data, it is anticipated that all of the proposed dose levels in PBD-001 will produce enough BH_4 to demonstrate efficacy in this patient population.

There have been 5 published case reports of Primary BH_4 Deficiency patients that received sepiapterin, the active ingredient of CNSA-001 (Niederwieser et al, 1982; Curtius et al, 1979; Hase et al, 1982; Dhondt et al, 1985; Giudici et al, 1991). These case reports demonstrated rapid and sustained reduction in serum Phe levels within 2–4 hours following oral administration of sepiapterin. Each patient received a single dose of sepiapterin ranging between 0.6 and ~3.3 mg/kg, with no noted adverse events. The ages of patients treated were between 0 (i.e., several days postnatal) and 3.5 years of age.

CNSA-001 has been administered to 60 subjects in a phase 1 study, PKU-001 and was determined to be safe and well tolerated. CNSA-001 represents a potential new treatment for HPA in PBD patients.

3.5 Study Duration and Dates

The study is expected to begin enrollment in October 2018. The study duration for each patient is anticipated to be approximately 10 weeks.

4 STUDY POPULATION SELECTION

4.1 Study Population

Six (6) to 10 PBD patients will be enrolled in this study and treated with CNSA-001 (3 to 5 patients per arm). It is expected that 5 to 6 study sites will be required to enroll patients for this orphan population. The study will be conducted globally.

4.2 Inclusion Criteria

Individuals eligible to participate in this study include patients with PBD who meet all of the following criteria:

1. Male or Female patients 18 years old and above and 12 months old and above for the remaining patients (age reduction pending analysis of safety, PK, and response, in the adult patient(s) by the DSMB and FDA)
2. Confirmed diagnosis of PBD as evidenced by medical history of biallelic pathogenic mutations in PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies. Genetic testing is not required.
3. Informed consent and assent [if necessary (i.e., for children and/or patients that are mentally impaired secondary to disease)] with parental consent
4. Females must be either postmenopausal for ≥1 year, or surgically sterile (tubal ligation, hysterectomy, or bilateral oophorectomy) for at least 6 months or, if of childbearing potential and not abstinent, willing to use at least 2 of the following methods of contraception (including adolescents 12 to 18 years old) from Screening through 30 days after the last dose of study drug:
    - Hormonal contraception (stable dose for 3 months) or
    - IUD/IU Hormone-releasing System, plus
    - Barrier contraceptive method (diaphragm, cervical cap, contraceptive sponge, condom) with spermicidal foam/gel/cream/suppository

    Males and females who are abstinent will not be required to use a 2nd contraceptive method unless they become sexually active.
5. Males with female partners of childbearing potential must agree to use barrier contraceptive (i.e., condom) with spermicidal foam from Screening through 90 days after the last dose of study drug. Males must also refrain from sperm donations during this time period.
6. Females with a negative pregnancy test at Screening and on Day 1 prior to dosing
7. Creatinine clearance (CrCl) >90 mL/min as estimated using the Cockcroft-Gault equation (≥18 years) or Schwartz-Lyon equation (≥ 12 months < 18 years) (Appendix 2)
8. The patient is clinically stable on therapy for management of their signs and symptoms of PBD as determined by the Investigator

9. The patient is willing and able to comply with the protocol
10. No tobacco use (e.g., cigarettes, e-cigarettes, cigars, smokeless tobacco) for 2 weeks prior to the Screening visit and willingness to abstain from these products through the last dose of study drug

4.3 Exclusion Criteria

Individuals are not eligible to participate in this study if they have or meet any of the following criteria:

1. PBD caused by biallelic pathogenic mutations in PCD, SR, DHPR, or single dominant mutations in GTP-CH
2. Significant chronic medical illness other than PBD, as determined by the Investigator
3. Gastrointestinal disease (such as irritable bowel syndrome, inflammatory bowel disease, chronic gastritis, peptic ulcer disease, etc.) that could affect the absorption of study drug
4. History of gastric surgery, including Roux-en-Y gastric bypass surgery or an antrectomy with vagotomy, or gastrectomy
5. Inability to tolerate oral medication
6. History of allergies or adverse reactions to BH_4 or related compounds, or any excipients in the study drug formulation
7. Any clinically significant medical or psychiatric condition or medical history, that in the opinion of the Investigator, would interfere with the patient's ability to participate in the study or increase the risk of participation for that patient
8. Known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV)
9. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) laboratory values >2 × the upper limit of normal (ULN)
10. Any other clinically significant laboratory abnormality unrelated to PBD at the Screening visit or prior to the administration of the first dose of study drug, as determined by the Investigator
11. Clinically significant cardiac arrhythmia at Screening or prior to the first dose of study drug
12. QTcF (QT with Fredericia's correction) ≥460 msec in males and ≥480 msec in females (based on the mean of triplicate measurements taken at Screening)
13. Resting heart rate ≤40 or ≥110 bpm for ages 12 and older, ≥ 130 bpm for ages 3 to 12, ≥ 150 bpm for ages 1-2 years or resting blood pressure <85/40 mmHg or >150/90 mmHg at Screening or prior to the first administration of study drug
14. Current participation in any other investigational drug study or participation within 30 days prior to Screening

15. History of alcohol or drug abuse within last 6 months prior to Screening or current evidence of substance dependence as determined by the Investigator
16. Currently taking an antifolate including, but not limited to, methotrexate, pemetrexed, or trimetrexate
17. A female who is nursing or who is pregnant or planning to become pregnant
18. The patient, in the opinion of the Investigator, is unwilling or unable to adhere to the requirements of the study

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

CNSA-001 contains the new chemical entity, sepiapterin. Sepiapterin is [redacted] with a molecular weight of 237.2 and a molecular formula of $C_9H_{11}N_5O_3$.
The chemical structure is:

[redacted]

The test product is CNSA-001 (sepiapterin) oral powder for suspension.

5.1.2 Placebo or Control

There is no placebo or control product.

Patients will be randomized to one of 2 cohorts that will test 2 dose levels each, adjusted for body weight:

- **Cohort 1**, patients will receive 2.5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 10 mg/kg/day for 7 days in Period 2 (14 days total treatment)
- **Cohort 2**, patients will receive 5 mg/kg/day for 7 days in Period 1, undergo a 3 (±1) day washout period, then escalate to 20 mg/kg/day for 7 days in Period 2 (14 days total treatment).

All dosing will be divided and administered twice daily with breakfast and dinner.

Details on preparation of study drug (i.e. suspension for oral administration) and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

5.3 Selection and Timing of Dose for Each Patient

Patients will receive CNSA-001 twice daily during the treatment period for a duration of 7 days followed by a 3 (±1) day washout and then intra-patient escalation to a second dose level for an additional 7 days (i.e., 14 days of total treatment). Patients will be allowed to

dose-escalate during Period 2, only if none of the criteria in Section 6.12 are met. If a patient meets any of the criteria prohibiting dose escalation, the patient will discontinue further study treatment and will complete the EOS assessments (See Section 7.6).

5.4 Method of Assigning Patients to Treatment Groups

Patients who fulfill the eligibility criteria, provide informed consent, and complete the BH_4 Washout Period, will be enrolled into the study and randomized to study treatment. Patients will be randomized to one of 2 cohorts, both receiving active treatment (see Figure 1).

5.5 Blinding

This Phase 1/2 study is an open-label study; therefore, neither patients nor the Investigator are blinded to study treatment.

5.6 Concomitant Therapy

Patients will continue their other current medications for PBD (including L-dopa/carbidopa, 5HTP, melatonin, MAO inhibitors, and dopamine receptor agonists as prescribed) except for BH_4 supplementation (if they were taking BH_4) and will be monitored clinically as per standard of care for PBD to optimize treatment.

Patients will not be permitted to take any drugs known to inhibit folate synthesis (e.g., methotrexate, pemetrexed, trimetrexate).

During the study, the Investigator can prescribe additional medications as long as they are not prohibited medications (as described above). Study staff will record on the case report form (CRF) all prescription and over-the-counter medications that a patient takes during the study (from the time of informed consent until the EOS visit).

5.7 Restrictions

5.7.1 Prior Therapy

Study staff will record on the CRF all prescription and over-the-counter medications that a patient took during the 30-day period before Screening. Any patients taking BH_4 therapy prior to study entry will undergo a “washout” period during Screening before they can qualify for randomization.

5.7.2 Fluid and Food Intake

Patients will be instructed to maintain a consistent diet, with respect to protein and Phe intake, and 3-day diet records will be obtained throughout the study. Diet records will be reviewed by a qualified dietician at each site. Total Phe concentrations for the 3-day period will be calculated by the dietician and entered in the electronic CRF (eCRF).

5.7.3 Total Blood Volume

The total volume of blood obtained from an individual study participant is expected to be approximately 125 mL, including pharmacokinetic and biomarker samples and clinical laboratory tests.

5.7.4 Patient Activity Restrictions

Patients will not be confined during the study and will not require any activity restrictions.

5.8 Treatment Compliance

Study staff will instruct patients to return all used and unused study drug bottles at each study visit. Compliance with the dosing regimen will be assessed by reconciliation of used and unused study drug bottles and study drug vials (prior to reconstitution). The quantities dispensed, returned, used, and lost will be recorded on the dispensing log provided for the study.

5.9 Packaging and Labeling

CNSA-001 drug product packaging consists of CNSA-001 vials (vials sufficient for each dose level), 1 bottle of Medisca® Oral Mix, (473mL), an empty vial with cap for suspending CNSA-001 in Medisca Oral Mix, and a dosing syringe. CNSA-001 Oral Powder for Suspension is packaged in 10 mL amber glass vials with black child proof caps. Each glass vial contains 175 mg of the active ingredient, sepiapterin. The suspending agent, Medisca® Oral Mix (473 mL), is included. A dosing syringe is included for accurate measurement of dose volumes.

Each vial of CNSA-001 Oral Powder for Suspension will contain the product name, strength, content, and company name. Each vial label will contain the words, “Caution: New Drug—Limited by Federal (or US) law to investigational use.’’

5.10 Storage and Accountability

All drug product required for completion of this study will be provided by Censa Pharmaceuticals. It is the responsibility of the pharmacy staff or study staff to ensure that a current record of drug inventory and drug accountability is maintained. Inventory and accountability records must be readily available for inspection by the study monitor and are open to inspection at any time by applicable regulatory authorities.

5.11 Investigational Product Retention at Study Site

Upon the completion of the study and once inventoried by the study site and the Sponsor’s clinical research monitor, all used vials of drug product will be destroyed. Any unused vials of drug product may be either destroyed or returned to the Sponsor following discussion with the Sponsor. If drug product is destroyed, a certificate of destruction will be provided to the Sponsor by the appropriate facility performing the destruction.

6 STUDY PROCEDURES

6.1 Informed Consent

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to conducting study-related procedures.

For pediatric participants, full informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. Where appropriate, pediatric participants should assent to enroll in a study (age of assent to be determined by Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs) or be consistent with local legal requirements).

See Section 10.4 for more information on the informed consent process.

6.2 Medical History and Demographic Data

A detailed medical history will be obtained at Screening. The history includes specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; head, eyes, ears, nose, and throat (HEENT); lymphatic; cardiovascular; respiratory; gastrointestinal; musculoskeletal; and neurological. The number and reasons for hospitalizations during the previous year should be recorded. The 3 most recent historical Phe concentrations will be collected as part of the medical history. Documentation by medical history of biallelic pathogenic mutations in PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies should also be recorded as part of the medical history. No genetic testing or retesting is required.

Demographic data will include age, gender, and self-reported race/ethnicity.

6.3 Physical Examination

A physical examination will be performed at Screening and on the Day 1 and Day 7 study visits during treatment Periods 1 and 2, and at the EOS visit. On Day 1 of each treatment period, a physical examination will be performed before the patient receives the first dose of study drug. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological parameters.

6.4 Vital Signs

Vital signs, including blood pressure, pulse, respiratory rate, and oral temperature, will be measured at Screening and on Day 1, Day 2 and Day 7 during each period, and at the EOS visit. Patients will have a 5-minute rest in a supine position before vital signs are assessed. On Day 1 of each treatment period, vital signs will be performed before the patient receives the first dose of study drug and post-dose at 2 hours (before 2-hour blood collection for PK). Weight will only be collected at Screening and on Day 1 of each treatment period. Height will only be collected at Screening.

6.5 ECGs

Twelve-lead ECGs will be obtained at the Screening visit, and on Day 1 (pre-dose) and Day 7 of each treatment period. ECGs will be performed in triplicate, with each read taken 1 minute apart. The following parameters will be collected and recorded in the e-CRF: RR interval, PR interval, QRS interval, QT interval, and QTc interval. In addition, the tracing should be reported as normal, abnormal clinically significant, or abnormal not clinically significant. If abnormalities are noted on the ECG, these should be recorded in the eCRF.

6.6 Clinical Laboratory Tests

6.6.1 Local Laboratory Parameters

Clinical laboratory tests will be performed by a qualified local laboratory. Blood and urine samples for clinical chemistry, hematology, and urinalysis will be collected at Screening and on Day 1 (before the morning dose) and Day 7 study visits of each period and at EOS if early termination. Patients should be fasted prior to collection of samples (minimum of 8 hours prior to sample collection. Urine samples will not be collected from toddlers unless they are toilet trained and a sample can be obtained.

The following laboratory parameters will be analyzed by the local laboratory:

Hematology:
- Hematocrit (HCT)
- Hemoglobin (HGB)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)

Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Pregnancy Testing:
- Serum human chorionic gonadotropin (HCG) at Screening
- Urine human chorionic gonadotropin (HCG) prior to Periods 1 and 2 and EOS

Serum Chemistry:
- Albumin (ALB)
- Alkaline phosphatase (AP)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- Gamma glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Uric acid

Exploratory Biomarker:
- Prolactin

Blood Phe levels will be analyzed by a local laboratory at the Screening visit and during the BH_4 Washout Period (Days -3, and -1), and during Treatment Period 1 and Period 2 on Day 1 (pre-dose), Day 2 (pre-dose), Day 4 (±1 day), Day 7, and EOS to monitor for safety (see Section 6.8.1). To minimize burden on patients, Phe collection on Days -3 and -1 during the BH_4 Washout Period may be obtained via filter paper with overnight shipping to the site's designated laboratory.

6.6.2 Bioanalytical Laboratory Parameters

6.6.2.1 Sample Collection, Storage, and Shipping

The following pharmacokinetic, preliminary efficacy (i.e., Phe), and secondary biomarkers will be analyzed by a qualified bioanalytical laboratory. Blood, plasma and urine samples for analysis will be sent to Medical Neurogenetics Laboratories. Urine samples will not be collected from toddlers unless they are toilet trained and a sample can be obtained. See Appendix 3 for details on sample collection and shipping for bioanalytical samples.

Analyte	Source	Endpoint
Sepiapterin	Plasma	Pharmacokinetic
BH_4	Plasma	Pharmacokinetic
Phenylalanine	Plasma	Pharmacokinetic/Preliminary Efficacy
Tyrosine	Plasma	Pharmacokinetic
Serotonin	Whole blood	Exploratory Biomarker
Sepiapterin	Urine	Exploratory Biomarker
BH_4	Urine	Exploratory Biomarker
Neopterin	Urine	Exploratory Biomarker

Blood Phe levels collected during treatment Period 1 and Period 2 on Days 1 (pre-dose), 2 (pre-dose), 4 (±1), 7 and EOS visit will be analyzed by the bioanalytical laboratory upon completion of the study (see Section 6.8.1).

6.7 Dispensing Study Drug

Dosing of CNSA-001 is based on the patient's weight. When dispensing CNSA-001, the patient's weight obtained on Day 1 of each dosing period will be used to calculate the exact mg of active ingredient, sepiapterin, required for each patient's daily dose. For example, if the patient's weight was 70 kg on Day 1 of dosing, and this patient was randomized to receive 2.5 mg/kg/day, then the total mg/day required of active ingredient, sepiapterin, would be 175 mg or one vial of CNSA-001.

Patients will take both doses of CNSA-001 on Day 1 and the morning dose of CNSA-001 on Day 2 while in the clinic; for all other dosing days, patients should take their morning dose prior to coming to the clinic for assessments.

Study drug will be dispensed at each Day 2 study visit and will include enough study drug for dosing until the Day 7 study visit. This will include enough CNSA-001 for the remainder of the treatment period plus one additional day (e.g., to account for holidays, weekends, or difficulties in scheduling study visits). Patients will be instructed on how to mix CNSA-001 powder for oral suspension and how much volume to take.

Details on preparation of study drug and dosing guidelines will be provided in a pharmacy manual for the site and an instruction guide for patients.

6.8 Efficacy Assessments

6.8.1 Blood Phenylalanine Levels

Phe levels will be measured at Screening and compared to the 3 most recent historical Phe concentrations. These values will be recorded as part of the patient's medical history.

Eligible patients who are taking BH_4 [Kuvan® (sapropterin dihydrochloride)] will stop taking BH_4 following the Screening visit and 3 days prior to randomization. On Days -3 and -1, blood will be collected for determination of Phe concentrations. To minimize burden on patients, Phe collection on Days -3 and -1 may be obtained via filter paper with overnight shipping to the site's designated laboratory.

During the treatment periods, blood Phe levels will be measured at each study visit (Day 1 and Day 2 [pre-dose], Day 4 (±1) and Day 7 [after the morning dose]), and at the EOS visit. Analysis of Phe levels during the treatment periods will be conducted at the site's designated laboratory in real-time to monitor for safety, and at the bioanalytical laboratory for assessment of preliminary efficacy and may use the same sample collected for pharmacokinetic Phe concentrations. If blood Phe concentrations have increased from baseline by >360 µmol/L after the initial 48 hours of treatment, patients should discontinue CNSA-001 treatment and will be withdrawn from the study. Patients who are withdrawn from the study will have EOS assessments collected (see Section 7.6). If blood Phe concentrations have decreased below the lower limit of normal defined as ≤30 µmol/L anytime while on treatment, patients will be asked to provide an unscheduled blood Phe sample. Immediately following this sample, they will be asked to consume a rescue therapy consisting of extra protein starting at 0.25 g/kg per day given as eggs, meat or cheese, etc. depending on patient preference. If a patient experiences hypophenylalaninemia as defined above, stopping rules may apply (see Section 6.13.1).

Blood samples for Phe as a measure of preliminary efficacy should be collected as pre-fed or no earlier than 3 hours following the patient's last meal and at approximately the same time of day at each visit (after the morning dose). The bioanalytical laboratory will analyze samples for blood Phe levels collected for efficacy (see Section 6.6.2.1).

6.8.2 Other Biomarker Levels

Exploratory biomarkers to be measured during the study will include serum prolactin, whole blood serotonin, and urine sepiapterin, BH_4 and neopterin levels. Urine collection should be the first void of the day. Urine samples will not be collected from toddlers unless they are toilet trained and a sample can be obtained.

Serum prolactin samples will be analyzed by a local laboratory and urine sepiapterin, BH_4 neopterin, and whole blood serotonin samples will be analyzed by the bioanalytical laboratory, MNG Laboratories. Directions for sample collections for those samples sent to the bioanalytical laboratory will be provided in Appendix 3.

6.8.3 Cambridge Neuropsychological Test Automated Battery (CANTAB) Test Battery

Phenylalanine accumulation has been demonstrated to cause impairments in psychomotor processing and executive functions (Palermo et al, 2017). The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a highly sensitive set of cognitive assessments designed to detect impairments in executive cognitive functioning.

Cognitive assessments to explore the potential effects of CNSA-001 on specific brain functions will be administered during Screening and on Day 1 (pre-dose) and Day 7 of each treatment period. The CANTAB test battery will include 4 short assessments designed to measure key cognitive domains of reaction time, memory and attention. The CANTAB test battery will include the RTI, the SSP, the SWM, and the RVP.

- The CANTAB RTI task is a processing and psychomotor speed task that will take on average 6 minutes to complete.
- The CANTAB SSP task is a measure of visual working memory and executive function and will take on average 8 minutes to complete.
- The CANTAB SWM task is a simultaneous measure of executive functioning (more specifically strategic thinking), alongside working memory and will take on average 6 minutes to complete.
- The CANTAB RVP task is a measure of sustained attention, requiring participants to continually scan an array of flashing digits and identify specific target sequences and will take on average 8 minutes to complete.

6.8.4 GENEActiv Accelerometer Device

The wrist-worn GENEActiv accelerometer is a highly sensitive device that records changes in physical activity and sleep patterns of behavior. It is postulated that data from the GENEActiv device may support valid comparisons in patient's changes of behavior, physical activity and sleep when patients are on and off CNSA-001 therapy.

Patients will be asked to wear a GENEActiv accelerometer continuously for up to two 14-day periods starting no earlier than Day -7 during screening through to the End of Study visit.

6.8.5 The NIH Toolbox – Cognition Domain

The NIH Toolbox® for Assessment of Neurological and Behavioral Function (NIH Toolbox) is an open-sourced set of computerized tests (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/cognition) (Weintraub et al. 2013). The Toolbox was specifically designed to measure neuropsychological and behavioral functions over time and to measure key constructs across developmental stages. This facilitates the potential evaluation of treatment effectiveness of CNSA-001, as well. This study will use an age-based battery of assessments from the *Cognitive Domain* of the NIH

Toolbox. All tests will be administered via an iPad on either Day-1 or Day 1 predose (i.e., at baseline) and on Day 7 of each Treatment Period.

The following tests comprise the Fluid Cognition Composite Score.

For children and adolescents ages 3-17, the following subtests will be administered:

6.8.5.1 NIH Toolbox Flanker Inhibitory Control and Attention Test (3 minutes)

The Flanker task measures both a participant's attention and inhibitory control (Zelazo et al. 2013). The test requires the participant to focus on a given stimulus while inhibiting attention to stimuli (arrows for ages 8-85) flanking it. Sometimes the middle stimulus is pointing in the same direction as the "flankers" (congruent) and sometimes in the opposite direction (incongruent). Scoring is based on a combination of accuracy and reaction time.

6.8.5.2 NIH Toolbox Picture Sequence Memory Test (7 minutes)

Picture Sequence Memory Test assesses episodic memory (Bauer et al. 2013). It measures cognitive processes involved in the acquisition, storage, and retrieval of new information. It involves recalling increasingly lengthy series of illustrated objects and activities that are presented in a particular order on the computer screen. The participants are asked to recall the sequence of pictures that is demonstrated over two learning trials; sequence length varies from 6-18 pictures, depending on age.

6.8.5.3 NIH Toolbox Picture Vocabulary Test (4 minutes)

The Picture Vocabulary Test measures receptive vocabulary administered in a computer-adaptive test (CAT) format (Gershon et al. 2013). Respondents select the picture that most closely matches the meaning of the word.

6.8.5.4 NIH Toolbox Dimensional Card Sort (4 minutes)

The Dimensional Change Card Sort Test is a measure of cognitive flexibility. Two target pictures are presented that vary along two dimensions (e.g., shape and color). The task involves deciding whether the two pictures are the same or different (depending on whether the "rule" is to sort by color or shape). This task measures the capacity to plan, organize, and monitor the execution of behaviors that are strategically directed in a goal-oriented manner. Errors and reaction time are recorded (Zelazo et al. 2013).

For children and adolescents ages 7-17 the following additional tests will be administered:

6.8.5.5 NIH Toolbox List Sorting Working Memory Test (7 minutes)

The List Sorting Working Memory Test assesses working memory and requires the participant to sequence different visually- and orally-presented stimuli (Tulsky et al. 2013). Pictures of different foods and animals are displayed with both a sound clip and written text that name the item. The task has two different conditions: 1-List and 2-List. In the 1-List

condition, participants are required to order a series of objects (either food or animals) in size order from smallest to largest. In the 2-List condition, participants are presented both food and animals and are asked to report the food in size order, followed by the animals in size order.

6.8.5.6 NIH Toolbox Pattern Comparison Processing Speed Test (3 minutes)

The Pattern Comparison Processing Speed Test measures speed of processing by asking participants to discern whether two side-by-side pictures are the same or not (Carlozzi et al. 2013). Participants' raw score is the number of items correct in a 90-second period. The items are designed to be simple to most purely measure processing speed.

6.8.6 Child and Adolescent Sleep Checklist (CASC)

The Child and Adolescent Sleep Checklist is a 24-item parent questionnaire to identify sleep problems in children, ages 3-18 years (Oka et al. 2009). Parents or caregivers are asked to recall the child's sleep during the last 7 days when providing responses to questions. Responses to the questions about sleep habits are scored from 0 (never or don't know) to 3 (always), yielding an overall score of 0-72. Scores above 18 indicate sleep problems. In addition, there are four categories of scores: Bedtime problems (Q1-Q6; 6 questions), sleep breathing and unstable sleep (Q7-Q12; 6 questions), parasomnia and sleep movement (Q13-Q18; 6 questions), and daytime problems (Q19-Q24; 6 questions). The CASC takes about 10 minutes to complete.

A parent or caregiver of patients between the ages of 3-18 years will be asked to complete the CASC at Day 1 and Day 7 or each treatment period.

6.9 Pharmacokinetic Assessments

Sampling for pharmacokinetic analysis (with evaluation of sepiapterin and its effect on BH_4, Phe and Tyr levels) will occur at the following time points for each dose level: on Day 1 at pre-dose (within 30 min of dosing), +0.5 hr (±3 min), +1 hr (±5 min), +2 hr (±6 min), +4 hr (±20 min), +6 hr (±30 min), +8 hr (±60 min, prior to Day 1 evening dose), and +24 hours (±2 hr, prior to Day 2 morning dose) after the first dose of study drug.

The concentration of CNSA-001 (sepiapterin), BH_4, Phe, and Tyr in plasma samples will be analyzed by MNG Laboratories using a validated LC/MS/MS method. The following non-compartmental PK parameters will be estimated and summarized along with graphical presentation of the concentration data:

Parameter	**Definition**
$AUC_{0\text{-inf}}$	Area under the curve from time 0 to infinity using trapezoidal method (linear-up/log-down method) and extrapolation to infinite time
$AUC_{0\text{-last}}$	Area under the curve from time 0 to the time of the last quantifiable concentration using linear-up/log-down method trapezoidal method
C_{max}	Maximum observed concentration

Parameter	Definition
T_{max}	Time to C_{max}
$t_{1/2}$	Half-life
K_e	Elimination rate constant

6.10 Adverse Events Assessments

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

The occurrence of an AE or SAE (see Section 6.10.6) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes, but not limited to, the event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All treatment-related AEs or AEs leading to discontinuation will be followed to adequate resolution as determined by the Investigator.

Any medical condition that is present at the time that the participant is screened will be considered as medical history and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

6.10.1 Reporting Timelines

The Investigator will record all reportable events with start dates occurring any time after informed consent and continue through clinical trial completion or, in the case of withdrawal, until the outcome is determined. AEs will be assessed at each visit and/or through telephone contact with the patient. A neutral question, such as "How have you been feeling since your last visit?" may be asked.

All SAEs should be reported after the patient signs the informed consent and followed until resolution, stabilization or until the Investigator provides sufficient evidence that no further information can be obtained.

All SAEs and pregnancies occurring while the patient is on the study or within 30 (±3) days after the patient received their last dose of study drug must be reported within 24 hours of knowledge of the event by study personnel whether or not considered to be related to study drug.

Deaths that occur ≥ 30 (±3) days after the patient's last study dose must be reported within 24 hours of knowledge of the event if deemed related to study drug by the Investigator

Although pregnancy is not always considered an AE or SAE by regulatory definition, for this study pregnancies must be processed following SAE timelines (e.g., within 24 hours of knowledge of the pregnancy) for data transmission purposes. In the event that a pregnancy complication occurs or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE, as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the patient is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE as appropriate.

Any pregnancy and/or suspected pregnancy that occurs during the study in a female patient should be reported using Pregnancy Reporting Form within 24 hours of knowledge of the event by study personnel. Any pregnancy and/or suspected pregnancy will be followed for outcome.

The Investigator must notify the Sponsor after the pregnancy is confirmed following SAE reporting timelines. If the patient has received the investigational drug prior to becoming pregnant, the patient will continue the efficacy assessment and follow-up periods and measures of safety and efficacy will be obtained.

The patient will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent Pregnancy Report Form. Furthermore, any SAE occurring as outcome of the pregnancy must be reported according to the procedures outlined for SAE reporting.

6.10.2 Severity

Adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (NCI, 2010) severity grading scheme as defined in Table 1.

Table 1: Severity Grading of Adverse Events (NCI CTCAE Criteria version 4.03)

Grade	Severity	Definitions
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
4	Life-threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL = activities of daily living; AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Medical conditions/diseases present before consenting the patient are only considered adverse events if they worsen after receiving any study drug. All laboratory values are to be reviewed by the Investigator and medically relevant abnormal values will be graded according to the CTCAE Version 4.03 as well (NCI, 2010).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea but may not be considered an SAE. Alternatively, a stroke that results in only a limited degree of disability may be considered only a mild stroke but would be considered an SAE.

6.10.3 Relationship

The Investigator's assessment of causality must be provided for all AEs (serious and non-serious). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. For purposes of consistency, guidelines for assessing causality are provided below:

Not Related	The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician. No relationship between the experience and the administration of study drug; related to other etiologies such as concomitant medications or patient's clinical state.
Unlikely to be Related	A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
Possibly Related	There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
Probably Related	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals,

	and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Definitely Related	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided, if available.

6.10.4 Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigators' Brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the protocol.

The drug safety medical reviewer (or designee) will be responsible for determining whether an AE or SAE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent (e.g., IB).

6.10.5 Clinical Laboratory Adverse Events

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention. However, each laboratory abnormality (e.g., clinically significant changes detected in hematology, serum chemistry panel, urinalysis, and urine microscopic evaluations) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to study drug interruption or discontinuation, must be recorded as an AE, or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (e.g., vital signs) performed that are associated with signs or symptoms must be recorded as AEs or SAEs if they meet the definition of an AE (or SAE) as described below.

6.10.6 Serious Adverse Events

6.10.6.1 Definition

An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or sponsor, it results in any of the following outcomes: death, life threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the Investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in these other situations.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘‘reasonable possibility’’ means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

For countries outside of the US, the associated ICH adverse and serious adverse event guidelines will be followed, and local regulatory guidance will apply.

6.10.6.2 Suspected Unexpected Serious Adverse Reaction (SUSAR)

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment that is both serious and unexpected. Before submitting an IND safety report, the Sponsor needs to ensure that the event meets all 3 of the definitions:

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all 3 of the definitions, it should not be submitted as an IND safety report.

6.10.6.3 Reporting Serious Adverse Events

The Investigator will report all SAEs within 24 hours of knowledge of the event whether or not considered to be related to study drug to the designated drug safety team using the SAE Report Form provided (following timelines included in Section 6.10.1).

Although not all information required for a complete SAE Report Form may be readily available at the time of the event, the Investigator must include sufficient information on the SAE Report Form to allow for a complete medical assessment. This should include at a minimum the patient number, site number, detailed description of the event, seriousness criteria, causality/relationship to study drug, and Investigator signature.

The designated drug safety team will acknowledge the receipt of the SAE via email to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the drug safety team as requested (e.g., concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the SAE Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the IRB/IEC of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

Treatment-related SAEs or events leading to discontinuation will be followed for outcome information until resolution or stabilization. Other supporting documentation of the event may be requested by Censa Pharmaceuticals or designee and should be provided as soon as possible. The Medical Monitor should be contacted when the Investigator considers an SAE to be treatment-related.

6.10.7 Treatment-Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are AEs that start at the time of or after the first dose of study drug. AEs that worsen at or after the time of first dose of study drug are also considered treatment-emergent. All AEs that occur on or after the informed consent form has been signed, including all treatment-emergent AE, through 7 days after the last dose of study drug (30 days after last dose of study drug for SAEs) will be recorded in the eCRF.

6.11 Prior and Concomitant Medication Assessments

All prescription and over-the-counter medications taken by a patient starting from the 30-day period before Screening through the last study visit will be recorded. Any concomitant medications added or discontinued during the study will be recorded at each visit.

6.12 Intra-Patient Dose Escalation Criteria

A determination regarding intra-patient dose escalation will be made in consultation by the Investigator with the Sponsor and the Medical Monitor if either of the following criteria are met:

- The presence of any Grade 3 or greater AE (per Common Terminology Criteria for AEs [CTCAE] v4.03) or SAE, regardless of relationship to study drug, which occurs prior to Day 1 of Dosing Period 2.
- The presence of any Grade 3 or greater (per CTCAE v4.03) laboratory abnormality, regardless of Investigator assessment of clinical significance or relationship to study drug, which occurs prior to Day 1 of Dosing Period 2, including any unscheduled laboratory results.

If neither of the above criteria are met, if no study halting rules have been met, and if none of the criteria in Section 6.13.1 for premature discontinuation of study drug have been met, dose escalation for the patient may continue as per the protocol.

6.13 Removal of Patients from the Trial or Study Drug

6.13.1 Early Discontinuation from Study Drug Administration

Premature discontinuation of study drug administration is defined as the discontinuation of study drug for an individual patient before the required full course of study drug is completed. Reasons for premature discontinuation from study drug administration should be recorded on the appropriate page(s) of the eCRF and may include, but are not limited to the following:

- Safety reasons:
  - Occurrence of an AE, SAE, or clinically significant laboratory abnormality that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from study drug administration.
  - Occurrence of hypophenylalaninemia defined as ≤30 µmol/L that cannot be corrected with a rescue therapy consisting of extra protein starting at 0.25 g/kg per day given as eggs, meat or cheese, etc., depending on patient preference, and in the opinion of the Investigator warrants the patient's permanent discontinuation from study drug administration.
  - In the judgment of the Investigator, the patient experiences a general or specific change(s) that renders the patient unsuitable for continued study drug administration.
  - There is a need for concomitant medication that makes the patient ineligible for further study drug administration.
  - Pregnancy

- Reasons Specific to Underlying PBD
  - Symptoms or findings that, in the opinion of the Investigator, indicate a worsening of the patient's underlying PBD that renders continued study drug administration inadvisable.
  - Increase of > 360 μmol/L in Phe concentration from baseline after the initial 48 hours of treatment and prior to the end of the dosing period.

Given the requirement for testing for pregnancy in women of childbearing potential at Screening and the requirement for highly effective methods for contraception during the study, it is unlikely that pregnancies will occur during study conduct. However, study drug will be discontinued should suspected or confirmed pregnancy or nursing during the study drug administration period occur.

Patients who discontinue study treatment early due to any of the above reasons should immediately revert to pre-study standard of care for their PBD.

6.13.2 Withdrawal from the Study

Patients may withdraw from the study for any reason or be withdrawn at the request of the Investigator or Sponsor. The reason for a patient's withdrawal must be recorded on the appropriate page(s) of the eCRF. Reasons for withdrawal from the study may include, but are not limited to:

- Withdrawal of consent
- Adverse events or SAEs
- Significant patient noncompliance, defined as refusal or inability to adhere to the protocol requirements
- The Investigator determines that it is in the best interest of the patient to withdraw from study participation, due to a reason other than safety

Each patient who withdraws from the study after receipt of any amount of study drug will be asked to undergo EOS assessments. However, patients may withdraw consent to participate in this study at any time without penalty. Withdrawn patients will not be replaced.

6.13.3 Study Halting Criteria

Dosing of patients randomized in the study and randomization of additional patients will be halted if any of the following occur:

- The presence of an SAE in 1 patient that is considered to be related to the study drug by the Investigator.
- The presence of the same system organ class (e,g., gastrointestinal, cardiac) Grade 3 or greater AE or laboratory abnormality for which no other alternative etiology can be identified (per CTCAE v4.03), considered related to study drug, in 2 or more patients, regardless of dose group or period.

- The presence of ALT or AST ≥3 × ULN, alkaline phosphatase (AP) ≥2 × ULN, AND bilirubin ≥2 × ULN (Hy's Law criteria) in 1 patient if no alternative etiology can be identified.
- Any other clinical observation that the Investigator or the Medical Monitor considers a safety issue such that additional doses of CNSA-001 should not be administered to subsequent patients.

Randomization and dosing of subsequent patients can be restarted if, after an assessment of any of the above findings by the DSMB, it is determined that there is no additional safety risk to the study patients.

6.14 Abnormal Movement Seizure Journal

Seizures and dystonic movements (abnormal movements) can occur in PBD but are difficult to distinguish clinically. Upon signing informed consent, patients will be required to keep a seizure journal to indicate date and time of abnormal dystonic movement and seizures. Patients will be required to record the duration (i.e., start and stop) of each abnormal movement and seizure in the journal. The journal will be reviewed at every visit.

6.15 Appropriateness of Measurements

Safety will be measured by routine clinical and laboratory procedures, physical examination, collection of vital signs, and recording of AEs and SAEs.

The measure of preliminary efficacy, blood Phe level, was selected as the endpoint measure for assessing response to a 1-week course of oral CNSA-001 treatment. The choice was based on consultation with the US FDA and data associating blood Phe with intelligence quotient (IQ) testing and the National Institutes of Health (NIH) consensus statement indicating that metabolic control of blood Phe is necessary across the lifespan of individuals with PBD (NIH 2000).

7 STUDY ACTIVITIES

7.1 Screening Visit (Days –14 to -1)

7.1.1 Screening Procedures (Day -14 to Day -4)

The following assessments will be performed/collected during the Screening Period from Day -14 to Day -4:

- Before performing any study-related procedures, obtain informed consent/pediatric assent and a properly signed Informed Consent Form (ICF) (Section 10.4)
- Confirm patient meets inclusion/exclusion criteria (see Section 4.2 and Section 4.3)
- Obtain/confirm gene mutation analysis, enzyme activity analysis, or CSF biochemical profile consistent for PBD and record as part of the Medical History (no genetic testing or retesting is required)
- Obtain demographic data (age, gender, race/ethnicity)
- Obtain medical history: Include the 3 most recent historical Phe concentrations. Also include specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; HEENT; lymphatic; cardiovascular; respiratory; gastrointestinal; musculoskeletal; and neurological.
- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature). Patients will have a 5-minute rest in a supine position before vital signs are assessed. Obtain patient weight and height.
- Obtain 12-lead ECG in triplicate. Each read can be taken 1 minute apart
- Conduct a complete physical examination, including assessments of the skin, head, eyes, ears, nose, throat, neck, thyroid, lungs, heart, abdomen, lymph nodes, extremities
- Collect blood sample for clinical chemistry panel (albumin, alkaline phosphatase [AP], alanine amino transferase [ALT], aspartate aminotransferase [AST], blood urea nitrogen [BUN], calcium, carbon dioxide [CO_2], chloride, creatinine, gamma glutamyl transferase [GGT], glucose, lactate dehydrogenase [LDH], phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, uric acid), and prolactin
- Collect blood sample for hematology panel (hematocrit, hemoglobin, platelet count, red blood cell [RBC], white blood cell [WBC], and WBC differential)
- Collect urine sample for urinalysis (appearance, bilirubin, color, glucose, ketones, microscopic examination of sediment, occult blood, pH, protein, specific gravity, urobilinogen)
- Obtain serum pregnancy test for all women who are not postmenopausal and for adolescents who have started menstruation

- Record all prior prescription and over-the-counter medications (including herbal medications) taken within 30 days before the Screening visit
- Assess AEs from the time of informed consent
- Collect blood samples for Phe concentration (prior to BH_4 Washout) to be analyzed by the site's local laboratory.
- Collect urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day.
- Collect blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Perform CANTAB test battery
- Provide an GENEActive accelerometer for the patient to wear continuously (i.e., 24 hours/day) for 14 days no earlier than Day-7 (see Section 6.8.4 and Appendix 1)
- Provide patients with abnormal movement seizure journal and ask to record any seizures.
- Instruct patients to stop BH_4 treatment 24 hours prior to returning for BH_4 Washout Period

7.1.2 BH_4 Washout (Day -3 to Day -1)

The following assessments will be performed/collected during the BH_4 Washout Period before randomization
(Day -3 to Day -1) for patients found eligible during Screening and who are taking BH_4:

- Collect blood samples for Phe concentrations during the BH_4 Washout Period at approximately the same time each day on Day -3 and Day -1. Blood sample collection should be performed pre-fed or at least 3 hours following last meal. To minimize burden on patients, Phe collection on Days -3 and -1 may be obtained via filter paper with overnight shipping to the site's designated laboratory. Blood Phe levels during the BH_4 Washout period should be analyzed by the site's local laboratory.
- Instruct patient to maintain a consistent diet (with respect to protein and Phe intake) throughout the study. Ask patient to record 3-day diet records during the BH_4 Washout Period.
- Assess AEs since the last visit
- Instruct patient to complete the abnormal movement seizure journal and to return it on their Day 1 visit.
- Record all prescription and over-the-counter medications taken by the patient
- Administer the NIH Toolbox Cognitive Domain test battery (on Day -1) or wait to administer on Day 1 of Treatment Period 1 (see Section 6.8.5)

7.2 Treatment Period 1 (Day 1 to Day 7)

7.2.1 Period 1, Day 1 Procedures

- The following assessments are to be collected prior to dosing on Day 1:
  - Confirm patient continues to meet inclusion/exclusion criteria
  - Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature) and patient weight
  - Obtain 12-lead ECG in triplicate. Each read can be taken 1 minute apart.
  - Conduct a complete physical examination
  - Perform CANTAB test battery
  - Administer the NIH Toolbox Cognitive Domain test battery unless already completed on Day -1 (see Section 6.8.5)
  - Collect blood sample for clinical chemistry and prolactin
  - Collect blood sample for hematology panel
  - Collect urine sample for urinalysis
  - Obtain urine pregnancy test for all women who are not postmenopausal and for adolescents who have started menstruation
  - Collect pre-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
  - Collect pre-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
  - Collect pre-dose blood samples for exploratory biomarker whole blood serotonin to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
  - Collect pre-dose blood samples (within 30 min of dosing) for pharmacokinetic parameters (sepiapterin, BH_4, Phe, and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.
- Determine patient's cohort and assigned treatment based on the randomization list:
  - Cohort 1: sepiapterin 2.5 mg/kg/day in Period 1 and 10 mg/kg/day in Period 2
  - Cohort 2: sepiapterin 5 mg/kg/day in Period 1 and 20 mg/kg/day in Period 2
- Administer first dose of Period 1 study drug to patient
- Collect post-dose blood samples for pharmacokinetic parameters (sepiapterin, Phe, BH_4, and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3) at the following timepoints: +0.5 hr (±3 min), +1 hr (±5 min), +2 hr

(±6 min), +4 hr (±20 min), +6 hr (±30 min), and +8 hr (±60 min) after the first dose of study drug. *NOTE: +8-hour sample should be prior to the evening dose on Day 1.*

- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature) 2 hours after the first dose of study drug in Period 1 (prior to the Hour 2 PK sample collection)
- Administer evening dose of Period 1 study drug to patient (after +8-hour PK sample has been collected)
- Provide the CASC for the parent or caregiver to complete and collect (see Section 6.8.6)
- Collect/review the 3-day diet record for the BH_4 Washout (dietician to review and record calculated Phe values consumed during washout)
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess AEs since the last visit

7.2.2 Period 1, Day 2 Procedures

- The following assessments are to be collected prior to the morning dose on Day 2:
  - Collect pre-dose blood sample for pharmacokinetic parameters (sepiapterin, BH_4, Phe, and tyrosine) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). *NOTE: Sample should be collected 24 (± 2) hr from the time of the first dose of study drug.* Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.
  - Collect pre-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
  - Collect pre-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
  - Collect pre-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Administer morning dose of study drug to patient
- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature)
- Dispense sufficient study drug for dosing until the Day 7 study visit and instruct patient on how to administer study drug (see Section 5.2)
- Dispense dosing diary and instruct patient on how to complete it
- Provide a new 3-day diet record to the patient and instruct them to bring it back on Day 7

- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Set up time for patient to have blood and urine samples for preliminary efficacy and exploratory biomarkers on Day 4 (± 1 day)
- Instruct patient to take their morning dose of study drug prior to the Day 4 (±1 day) laboratory visit, and to not eat another meal for at least 3 hours prior to the visit.
- Set up time for patient to return to the clinic on Day 7 and ask them to bring all diaries and study drug supplies with them to the visit
- Instruct patient to take their morning dose of study drug prior to the Day 7 visit

7.2.3 Period 1, Day 4 (±1 Day) Procedures

- Collect post-dose blood sample for pharmacokinetic parameters (Phe and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.
- Collect post-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect post-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
- Collect post-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3).
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Instruct patient to continue taking study drug twice daily until Day 7 visit
- Remind patient to take their morning dose of study drug prior to the Day 7 visit and to bring their dosing diary and diet record to the Day 7 visit

7.2.4 Period 1, Day 7 Procedures

- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature)
- Obtain 12-lead ECG in triplicate. Each read can be taken 1 minute apart
- Conduct a complete physical examination
- Collect blood sample for clinical chemistry and prolactin
- Collect blood sample for hematology panel
- Collect urine sample for urinalysis
- Perform CANTAB test battery
- Administer the NIH Toolbox Cognitive Domain test battery (see Section 6.8.5)
- Provide the CASC for the parent or caregiver to complete and collect (see Section 6.8.6)
- Collect post-dose blood sample for Phe concentrations for preliminary efficacy. Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect post-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect post-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3).
- Collect post-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Collect the dosing diaries for the treatment period
- Collect the 3-day diet record for the treatment period and have dietician review and record calculated Phe values consumed for the week
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Collect the GENEActive accelerometer and provide a new GENEActive accelerometer for the patient to wear continuously (i.e., 24 hours/day) to the End of Study Visit (see Section 6.8.4 and Appendix 1)
- Collect any unused study drug, except for the evening dose needed for Day 7

- Check and record study drug compliance for the treatment period
- Ask patient to stop taking study drug and continue refraining from all BH_4 treatments for the washout period [3 (±1) days] after taking the evening dose of study drug on Day 7
- Set up time for patient to return to the clinic for Period 2 after completing the washout period
- Provide a new 3-day diet record to the patient and instruct they bring it back at the beginning of Period 2.

7.3 Washout Period [3 (±1) Days]

During the washout period, patient is to refrain from taking all BH_4 treatments [i.e., Kuvan® (sapropterin dihydrochloride)] and any leftover study drug the patient may have not returned to the study site. The washout period should last for 3 (±1) days. Instruct patient to maintain a consistent diet (with respect to protein and Phe intake) throughout the washout period. Patients should maintain a 3-day diet record during washout period. Patients should also document any abnormal seizure movements during the Washout Period in abnormal movement seizure journal.

7.4 Treatment Period 2 (Day 1 to Day 7)

7.4.1 Period 2, Day 1 Procedures

- The following assessments are to be collected prior to dosing on Day 1:
  - Confirm patient continues to meet inclusion/exclusion criteria
  - Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature) and patient weight
  - Obtain 12-lead ECG in triplicate. Each read can be taken 1 minute apart
  - Conduct a complete physical examination
  - Perform CANTAB test battery
  - Administer the NIH Toolbox Cognitive Domain test battery (see Section 6.8.5)
  - Collect blood sample for clinical chemistry and prolactin
  - Collect blood sample for hematology panel
  - Collect urine sample for urinalysis
  - Obtain urine pregnancy test for all women who are not postmenopausal and for adolescents who have started menstruation
  - Collect pre-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.

- Collect pre-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
- Collect pre-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Collect pre-dose blood samples (within 30 min of dosing) for pharmacokinetic parameters (sepiapterin, BH_4, Phe, and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Pharmacokinetic sampling timepoints/duration may be adjusted once the PK data become available from the Treatment Period 1. Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.

- Confirm patient meets safety parameters for dose escalation (see Section 6.12), then determine dose for Period 2 based on cohort determined at Day 1 of Period 1:
  - Cohort 1: CNSA-001 2.5 mg/kg/day in Period 1 and 10 mg/kg/day in Period 2
  - Cohort 2: CNSA-001 5 mg/kg/day in Period 1 and 20 mg/kg/day in Period 2
- Administer first dose of Period 2 study drug to patient
- Collect post-dose blood samples for pharmacokinetic parameters (sepiapterin, Phe, BH_4, and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3) at the following timepoints: +0.5 hr (± 3 min), +1 hr (± 5 min), +2 hr (±6 min), +4 hr (± 20 min), +6 hr (± 30 min), and +8 hr (± 60 min) after the first dose of study drug. Pharmacokinetic sampling timepoints/duration may be adjusted once the PK data become available from the Treatment Period 1. *NOTE: +8-hour sample should be prior to the evening dose on Day 1.*
- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature) 2 hours after the first dose of Period 2 (prior to the Hour 2 PK sample collection)
- Administer evening dose of Period 2 study drug to patient (after +8-hour PK sample has been collected)
- Provide the CASC for the parent or caregiver to complete and collect (see Section 6.8.6)
- Collect/review the 3-day diet record for the washout (dietician to review and record calculated Phe values consumed during the washout)
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Record all prescription and over-the-counter medications (including herbal medications) taken since starting study drug
- Assess AEs since the last visit

7.4.2 Period 2, Day 2 Procedures

- The following assessments are to be collected prior to the morning dose on Day 2:
  - Collect pre-dose blood samples for pharmacokinetic parameters (sepiapterin, BH_4, Phe, and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Pharmacokinetic sampling timepoints/duration may be adjusted once the PK data become available from the Treatment Period 1. *NOTE: Sample should be collected 24 (± 2) hr from the time of the first dose of study drug.* Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.
  - Collect pre-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
  - Collect pre-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
  - Collect pre-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Administer morning dose of study drug to patient
- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature)
- Dispense sufficient study drug for dosing until the Day 7 study visit and instruct patient on how to administer study drug (see Section 5.2)
- Dispense dosing diary and instruct patient on how to complete it
- Provide a new 3-day diet record to the patient and instruct they bring it back at Day 7
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Set up time for patient to have blood and urine samples for preliminary efficacy and exploratory biomarkers on Day 4 (± 1 day)
- Instruct patient to take their morning dose of study drug prior to the Day 4 (±1 day) laboratory visit, and to not eat another meal for at least 3 hours prior to the visit
- Set up time for patients to return to the clinic on Day 7 and ask them to bring all diaries and study drug supplies with them to the visit

- Instruct patient to take their morning dose of study drug prior to the Day 7 visit

7.4.3 Period 2, Day 4 (±1 Day) Procedures

- Collect post-dose blood sample for pharmacokinetic parameters (Phe and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Phe concentrations for preliminary efficacy parameter may be obtained from the Phe pharmacokinetic sample.
- Collect post-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect pre-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3). Urine collection should be the first void of the day, if possible.
- Collect post-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Instruct patient to continue taking study drug twice daily until Day 7 visit
- Remind patient to take the morning dose of study drug prior to the Day 7 visit and to bring their dosing diary and diet record to the Day 7 visit

7.4.4 Period 2, Day 7 Procedures

- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature)
- Obtain 12-lead ECG in triplicate. Each read can be taken 1 minute apart
- Conduct a complete physical examination
- Collect blood sample for clinical chemistry and prolactin
- Collect blood sample for hematology panel
- Collect urine sample for urinalysis
- Perform CANTAB test battery
- Administer the NIH Toolbox Cognitive Domain test battery (see Section 6.8.5)

- Provide the CASC for the parent or caregiver to complete and collect (see Section 6.8.6)
- Collect post-dose blood sample for Phe concentrations for preliminary efficacy. Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect post-dose blood samples for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Collect post-dose urine sample for exploratory biomarkers (sepiapterin, BH_4, and neopterin) to be sent to local laboratory or bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3).
- Collect post-dose blood samples for exploratory biomarker whole blood serotonin to be sent to bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3)
- Record all prescription and over-the-counter medications (including herbal medications) taken since the last visit
- Assess/record AEs since last visit
- Collect the dosing diaries for the treatment period
- Collect the 3-day diet record for the treatment period and have dietician review and record the calculated Phe values consumed for the week
- Collect/review the abnormal movement seizure journal and provide patients with a new abnormal seizure journal.
- Collect any unused study drug, except for the evening dose needed for Day 7
- Check and record study drug compliance for the treatment period
- Set up time for patient to return to the clinic for the EOS visit

7.5 Early Termination Procedures

If a patient is required to withdraw early from the study (see Section 6.13), the patient should return to the study site within 24 hours of withdrawal and complete all of the procedures outlined for the EOS visit (Section 7.6).

7.6 End of Study Visit

Patients are to complete the EOS visit within 48 hours of the last dose of study drug. During the EOS visit, the following assessments will be completed:

- Collect blood sample for pharmacokinetic parameters (Phe and Tyr) to be sent to the bioanalytical laboratory for analysis (see Section 6.6.2 and Appendix 3).

- Collect blood sample for safety monitoring of Phe to be sent to the site's local laboratory for analysis (see Section 6.8.1). Phe collection should be performed pre-fed or at least 3 hours following last meal.
- Obtain vital signs (blood pressure, pulse, respiratory rate, and oral temperature)
- Conduct complete physical examination (not needed if performed at Day 7 of Treatment Period 2)
- Obtain blood sample for clinical chemistry and prolactin (not needed if performed at Day 7 of Treatment Period 2)
- Obtain blood sample for hematology panel (not needed if performed at Day 7 of Treatment Period 2)
- Obtain urine sample for urinalysis (not needed if performed at Day 7 of Treatment Period 2)
- Obtain urine pregnancy test for all women who are not postmenopausal and for adolescents who have started menstruation
- Record/review all prescription and over-the-counter medications (including herbal medications) taken during the study (since signing the informed consent)
- Assess/record/review all AEs that occurred during the study (since signing the informed consent)
- Collect all dosing diaries for all study periods (if not already collected)
- Collect all 3-day diet records for all study periods (if not already collected)
- Collect/review the abnormal movement seizure journal.
- Collect the GENEActive accelerometer
- Collect all unused study drug
- Check/record study drug compliance for the entire study
- Instruct patient on restarting BH_4 therapy if taken prior to entering the study

7.7 Phone Follow-up Visits

7.7.1 Phone Follow-up 7 to 10 Days After Last Dose

- Call the patient to see if patient experienced any AEs during the 7 days after the last dose of study drug
- Record AEs in the eCRF, if applicable

7.7.2 Phone Follow-up 30 (± 3) Days after Last Dose

- Call the patient to see if patient experienced any SAEs during the 30 days after the last dose of study drug
- Record SAEs in the eCRF, if applicable

8 QUALITY CONTROL AND ASSURANCE

Regular monitoring and an independent audit, if conducted, must be performed according to International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP). See also Section 10.6.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by Censa Pharmaceuticals, and inspection by local and regulatory authorities.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums, and maximums for continuous variables will be provided. Exploratory analyses may also be performed. Listings of individual patient data will be produced. Additional details can be found in the statistical analysis plan (SAP).

9.2 Determination of Sample Size

The primary objective of this study is to evaluate the safety of 4 doses of CNSA-001. The sample size for this study is not based on statistical considerations, and a sample size of 6-10 patients (with 2 doses administered per patient) is considered adequate for this orphan population. Also, the treatment induced changes in Phe level is not powered for this study and caution is needed in the interpretation of efficacy results.

9.3 Analysis Populations

Three study populations will be analyzed:

- The Safety population: all patients who were randomized and received any amount of study drug. All safety summaries will be conducted in this population.

- The Efficacy population: all patients who were randomized, received any amount of study drug, and had available pre-dose Phe Concentrations at Day 1 and at least one post-Day 1 visit within a period. All efficacy analyses will be conducted in this population.

- PK Population: all patients who received at least one dose of study drug and had at least 1 quantifiable post-dose blood sample collected for analysis of sepiapterin, BH_4, Phe, or Tyr concentrations.

9.4 Demographics and Baseline Characteristics

Enrollment, protocol deviations, demographics (age, sex, race/ethnicity), medical history, and ECG parameters will be summarized using descriptive statistics. Discontinuations from study drug and the study will be summarized for all patients as well as by cohort and the last dose of study drug received.

9.5 Statistical Analysis of Efficacy Variables

Efficacy will be assessed in the Efficacy population. Phe concentrations at each visit and changes from baseline (Day 1, pre-dose) to each post-Day 1 assessment will be summarized using summary statistics within each dose cohort and period.

Other Secondary measures will include the following descriptive statistics (at each visit) as well as summary statistics changes from Day 1 to each post-Day 1 visit (as applicable) for:

- Percent of patients with Phe concentrations in acceptable treatment range of 130 to 360 µmol/L at Day 7
- Percent of patients with Phe concentrations <130 µmol/L at Day 7

Exploratory measures include:

- Urine sepiapterin, neopterin, and BH_4
- Serum prolactin
- Whole blood serotonin
- Computerized testing (CANTAB) at Screening, Day 1 (pre-dose), and Day 7 of each treatment period will also be summarized
- Movement and sleep assessment via the GENEActiv accelerometer
- NIH Toolbox Cognitive Domain test battery
- Parent or caregiver assessment of sleep (CASC)

9.6 Safety Analysis

Safety will be assessed in the Safety population. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). The number and percentage of patients with TEAEs (events that begin after first dose of study drug) will be tabulated by dose cohort, period, system organ class, and MedDRA preferred term. The dose cohort for each AE is identified based on the last dose of study drug taken at or before the start of the AE. Severity of AEs and SAEs will be summarized similarly. AEs leading to premature discontinuation from the study drug and serious TEAEs will be presented in a table or a listing. Clinical laboratory test results and vital signs, as well as corresponding changes from baseline, will be summarized at each visit, within each cohort and period.

9.7 Statistical Analysis of Pharmacokinetic Variables

All analysis of PK variables will be assessed in the PK population.

The blood concentrations of sepiapterin, BH_4, Phe, and Tyr will be summarized and listed. The following non-compartmental PK parameters for sepiapterin, BH_4, Phe, and Tyr will be estimated and summarized along with graphical presentation of the concentration data vs. time:

Parameter	Definition
$AUC_{0\text{-inf}}$	Area under the curve from time 0 to infinity using trapezoidal method (linear-up/log-down method) and extrapolation to infinite time
$AUC_{0\text{-last}}$	Area under the curve from time 0 to the time of the last quantifiable concentration using trapezoidal method (linear-up/log-down method)
C_{max}	Maximum observed concentration

Parameter	Definition
T_{max}	Time to C_{max}
$t_{1/2}$	Half-life
K_e	Elimination rate constant

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Table 2 summarizes the administrative structure for this study.

Table 2 Administrative Structure for PBD-001 Study

Lead Principal Investigator	[redacted]
Clinical Research Organization	InClin, Inc 2000 Alameda De Las Pulgas, Ste 242 San Mateo, CA 94403 Phone: [redacted]
Bioanalytical Laboratory	Medical Neurogenetics Laboratories 5424 Glenridge Dr Atlanta, GA 30342 Phone: [redacted]

10.2 Institutional Review Board or Independent Ethics Committee Approval

The Investigator will submit this protocol, any protocol modifications, and the patient consent form to be utilized in this study, to the appropriate IRB/IEC for review and approval. This committee must operate in accordance with ICH GCPs. Documentation of approval of the protocol and the informed consent document must be forwarded to Censa Pharmaceuticals (or designee) prior to initiation of this study.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to his/her IRB/IEC. The Investigator will not make any changes in the protocol without IRB/IEC approval except as necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB/IEC as required by the IRB/IEC. If the study remains in progress for >1 year, the Investigator must obtain annual renewal and re-approval from the IRB/IEC. Documentation of renewal must be submitted to Censa Pharmaceuticals (or designee). The Investigator will provide notice to the IRB/IEC of completion of participation in the study.

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol; GCPs, including ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines;

applicable regional regulatory requirements (e.g., ICH E6, 41(2) AMG); and in accordance with the ethical principles of the Declaration of Helsinki.

To this end, minors (study participants ages ≥ 12 months ≤ 18 years of age) have been included into this study and their needs (i.e., potential for direct benefit from treatment, no alternative means to obtain the data in a different population with dissimilar genetic mutation or disease, and burden to participate has been minimized or is at most, temporary) have been considered and determined justified in accordance with the requirements outlined in the Declaration of Helsinki.

10.4 Patient Information and Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion in understandable terms of the purposes, procedures, risks and possible benefits of participation, and rights of study patients will be conducted with patients, and, as appropriate, their legally authorized representatives (LARs; henceforth in the discussion of informed consent, study patient means "patient and/or LAR") and their family members. The study patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. Study patients will be asked to carefully review a ICF approved by Censa Pharmaceuticals and the IRB/IEC. After any needed discussion and consideration of study participation and before undergoing any procedures specifically for the study, the participant will sign the ICF. The ICF will be retained in the study patient's study records, and a copy of the ICF will be given to the study patient.

Individuals may decline to participate in the study and withdraw consent at any time or for any reason throughout the course of the study without AEs on the quality of their medical care.

10.5 Confidentiality

The Investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. This extends to testing of biological samples and genetic tests in addition to the clinical information relating to participants. Only an identification code (i.e., not names) should be recorded on any form or document submitted to Censa Pharmaceuticals, the Contract Research Organization (CRO), or the IRB/IEC. The Investigator must keep logs on screened and enrolled patients. In addition, the Investigator must have a list where the identity of all treated patients can be found.

The Investigator agrees that all information received from Censa Pharmaceuticals, including, but not limited to, the IB, this protocol, CRFs, and any other information related to the protocol-specified treatment of the study, remain the sole and exclusive property of Censa Pharmaceuticals during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Censa Pharmaceuticals. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by

any employee or agent of the study center to any third party or otherwise into the public domain.

The study monitor, other authorized representatives of Censa Pharmaceuticals, and representatives of the IRB/IEC may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, and hospital) and pharmacy records for the participants in this study. The clinical study site's research staff will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB/IEC and Institutional regulations.

10.6 Study Monitoring

A clinical monitor authorized to represent Censa Pharmaceuticals will conduct site visits to inspect study data, patients' medical records, and eCRFs in accordance with ICH guidelines GCPs, and applicable regulations and guidelines. The clinical monitor will also monitor ongoing drug accountability and adherence to protocol procedures. Details of clinical site monitoring are specified in a Clinical Monitoring Plan (CMP).

Independent audits may be conducted to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

The Investigator will allow representatives of the Censa Pharmaceuticals and regulatory authorities to inspect facilities and records relevant to this study.

10.7 Case Report Forms and Study Records

The eCRFs will be supplied by Censa Pharmaceuticals or designee for the recording of all information and study data as specified by this protocol. Original eCRF data should be handled in accordance with instructions from Censa Pharmaceuticals or designee. All eCRFs must be completed by the clinical study site's research staff authorized to do so by the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data reported in the eCRF derived from source documents should be consistent with the source documents. Source documents are defined as records of documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific email correspondence, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by Censa Pharmaceuticals or designee and by regulatory authorities. The original ICF for each participating patient shall be filed with records kept by the Investigator, and copies shall be given to the patient.

Once all data queries and issues have been resolved for each patient the Investigator will electronically sign each patient's eCRF. This signature will indicate that the data have been thoroughly inspected and will thereby certify the contents of the eCRF.

Clinical data will be entered into a 21 CFR Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered by the clinical study site's research staff directly from the source documents.

10.8 Data Monitoring Committee

The safety of study patients will be monitored by a DSMB. The function and membership of the DSMB will be described in the DSMB Charter but at minimum will consist of a physician familiar with PBD, a statistician, and the Medical Monitor.

10.9 Protocol Violations/Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. Because of deviations, corrective actions are to be developed by the site and implemented promptly. This is consistent with the following sections in ICH E6:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

10.10 Access to Source Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission for national or international registration. If required, national or international authorities will be provided with the name of the Investigator and his or her address, full disclosure of his or her qualifications, any potential conflicts of interests, payments, and extent of involvement.

During site visits, the clinical monitor will review original patient records, drug accountability records, and additional documents as needed. During the course of the study, Censa Pharmaceutical's or designee's Quality Assurance personnel may conduct an on-site audit visit. The Investigator will provide direct access to and allow verification and copying of all trial related documents (e.g., source data) for trial related monitoring, audits, IRB/IEC reviews, and regulatory inspections.

10.11 Data Generation and Analysis

Some or all of the obligations of implementing or conducting this study may be transferred from Censa Pharmaceuticals to the CRO.

A case report, comprised of individual eCRFs, will be completed for every patient who signs an ICF (or for whom an ICF is signed by a LAR) and is enrolled into the study.

All original source documentation (laboratory results, treatment records, audit query responses, etc.) will be retained by the Investigator or institution unless specified otherwise by the protocol. The results as they become available will be entered on the appropriate eCRFs. Legible reproductions of the original laboratory reports for selected tests or variables will be submitted to Censa Pharmaceuticals or CRO as requested.

eCRFs will be reviewed by a clinical monitor who will evaluate the completeness and accuracy of the data. Queries will be generated for omissions, corrections, and clarifications. Data may also be reviewed in-house by a clinical auditor and data management or other personnel.

Data analyses will be performed after database lock, when all queries have been resolved.

10.12 Retention of Data

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of Censa Pharmaceuticals, if applicable. It is the responsibility of Censa Pharmaceuticals to inform the Investigator when these documents no longer need to be retained.

10.13 Financial Disclosure

Each Investigator must submit to Censa Pharmaceuticals (or designee) financial disclosure information according to national law and/or local regulations.

10.14 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of Censa Pharmaceuticals and are confidential. Authorship on any publication of the results from this study will be based on contributions to study design, patient enrollment, data analysis, interpretation of results, and drafting and editing of any publication in accordance with published authorship ethical guidelines for publication of research studies. Independent analysis and/or publication of these data by the Investigator(s) or any member of their staff is not permitted without the prior, written consent of Censa Pharmaceuticals.

10.15 Clinical Trial Insurance

Censa Pharmaceuticals will ensure that clinical trial insurance sufficient to meet local and national requirements for the conduct of clinical research in patients is obtained prior to the conduct of this study and remains in effect for the duration of this study.

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Appendix 1 Schedule of Events

Evaluation	Screen Period	BH_4 Washout	Treatment Period									End of Study (≤ 48 hrs after last dose)	Phone Follow-up	
			Period 1				Washout	Period 2						
	Day-14 to Day -4	Day -3 to Day -1	Day 1	Day 2	Day 4 (±1)	Day 7	3 (±1) days	Day 1	Day 2	Day 4 (±1)	Day 7		7 - 10 days after last dose	30 (±3) days after last dose
Informed consent	X													
Confirm inclusion/exclusion criteria eligibility	X		X[a]					X[a]						
Confirm mutation analysis for PBD genes [b]	X													
Demographics	X													
Medical history [c]	X													
Vital signs, height, and weight [d]	X		X[a]	X		X		X[a]	X		X	X		
ECGs [e]	X		X[a]			X		X[a]			X			
Physical examination [f]	X		X[a]			X		X[a]			X	X[g]		
Clinical laboratory tests and serum prolactin [h]	X		X[a]			X		X[a]			X	X[g]		
Serum/urine pregnancy test [i]	X		X[a]					X[a]				X		
Prior/Concomitant meds [j]	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Phe concentrations [l]	X	X	X[a]	X[a]	X	X		X[a]	X[a]	X	X	X		
Consistent diet/ 3-day diet record [m]		X	X	→		X	X	X	→		X	X[g]		
Seizure journal	X	X	X	X	X	X	X	X	X	X	X	X		
Discontinue BH_4 [n]		X	→											
PK: Sepiapterin, BH_4, and Phe/Tyr [o]			X[a]	X[a]	X	X		X[a]	X[a]	X	X	X		
Biomarkers in urine [p]	X		X[a]	X[a]	X	X		X[a]	X[a]	X	X			
Whole blood serotonin	X		X[a]	X[a]	X	X		X[a]	X[a]	X	X			
CANTAB testing [q]	X		X[a]			X		X[a]			X			
Don GENEActive Accelerometer[u]	X	X	X	X	X	X	X	X	X	X	X	X		
NIH ToolBox Test Battery		X[a,v]	X[a,v]			X		X			X			
Administer the CASC			X			X		X			X			
Administer study drug [r]			→					→						

Evaluation	Screen Period	BH_4 Washout	Treatment Period									End of Study (≤ 48 hrs after last dose)	Phone Follow-up	
			Period 1				Washout	Period 2						
	Day-14 to Day -4	Day -3 to Day -1	Day 1	Day 2	Day 4 (±1)	Day 7	3 (±1) days	Day 1	Day 2	Day 4 (±1)	Day 7		7 - 10 days after last dose	30 (±3) days after last dose
Dispense study drug [s]				X					X					
Dispense Dosing Diary [t]				X					X					
Collect Study Drug, Dosing Diary, Assess Compliance						X					X	X		
Resume BH_4 therapy												X	X	X

a. To be completed prior to initial dosing.

b. Confirmed diagnosis of PBD as evidenced by medical history of biallelic pathogenic mutations in PTPS or recessive GTP-CH genes, abnormal enzyme activity of the PTPS or GTP-CH enzymes, or a CSF biochemical profile indicative of PTPS or GTP-CH deficiencies. No genetic testing or retesting is required.

c. Includes specific information related to any prior or existing medical conditions or surgical procedures involving the following systems: dermatologic; HEENT; lymphatic; cardiovascular; respiratory; gastrointestinal; musculoskeletal; and neurological. Also, includes documentation of 3 most recent historical Phe concentrations.

d. Includes blood pressure, pulse, respiratory rate, and oral temperature. Patients will have a 5-minute rest in a supine position before vital signs are assessed. Weight will only be collected at Screening and on Day 1 of each treatment period. Height will only be collected at Screening. Vital signs will be collected both pre-dose and 2-hours post-dose (before 2-hour blood collection for PK) on Day 1 of each treatment period; for all other timepoints they will be taken at any time during the visit.

e. 12-lead ECGs to be performed at Screening, and on Day 1 (pre-dose) and Day 7 of each treatment period. ECGs will be performed in triplicate, with each read taken 1 minute apart.

f. The examination will assess general appearance, as well as dermatologic, HEENT, lymphatic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological parameters.

g. Can be performed either on Day 7 visit of Treatment Period 2 or at the EOS Visit. Does not need to be conducted at both.

h. Includes clinical chemistry panel (albumin, AP, ALT, AST, BUN, calcium, CO2, chloride, creatinine, GGT, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, direct bilirubin, total cholesterol, total protein, uric acid), and serum prolactin; hematology panel (hematocrit, hemoglobin, platelet count, RBC, WBC, and WBC differential); and urinalysis (appearance, bilirubin, color, glucose, ketones, microscopic examination of sediment, occult blood, pH, protein, specific gravity, and urobilinogen).

i. Serum and urine pregnancy test required for all women who are not postmenopausal and for adolescents who have started menstruation; serum testing to occur during the Screening Period and urine testing to occur prior to dosing on Day 1 of Periods 1 and 2 and EOS. A positive urine test must be confirmed with a serum test.

j. Record all Rx and OTC medications starting from 30 days prior to Screening through last study visit.

k. Adverse events are to be collected from the time of informed consent until 7 days after the last dose of study drug (30 days after last dose for SAEs).

l. Blood Phe concentrations collected during Screening (prior to BH4 Washout) and during BH4 Washout Period on Days -3 and -1 will be analyzed by the site's local laboratory. To minimize burden on patients, Phe collection on Days -3 and -1 during the Washout Period may be obtained via filter paper with overnight shipping to the site's designated laboratory. All other blood Phe concentrations will be used for safety monitoring and analyzed by the site's local laboratory and are collected on Day 1 and Day 2 (pre-dose), and on Day 4 (±1 day) and Day 7 (after the AM dose) during Period 1 and Period 2 of Study Treatment, and EOS visit. Unscheduled Phe collection may occur if at any time a patient is hypophenylalaninemic (i.e., <30 µmol/L). Phe collection should be performed with pre-fed or at least 3 hours following last meal and at approximately the same time of day at each visit.

m. Patients are to maintain a consistent diet (with respect to protein and Phe intake) during the study. The 3-day diet records will be collected during BH4 Washout and during each treatment period.

n. BH4 treatment [i.e., Kuvan® (sapropterin dihydrochloride)] will be discontinued starting with the BH4 Washout period. Patients will remain off BH4 treatment until the EOS visit.

o. Blood samples for CNSA-001 (sepiapterin), BH4, Phe, and Tyr will be collected and analyzed by the bioanalytical laboratory at the following timepoints during Period 1 and Period 2: Day 1 (pre-dose, within 30 min of dosing), +0.5 hr (±3 min), +1 hr (±5 min), +2 hr (±6 min), +4 hr (±20 min), +6 hr (±30 min), and +8 hr (±60 min, prior to Day 1 evening dose), and +24 hours (± 2 hr, prior to Day 2 AM dose) after the first dose of study drug; +72 hr (Day 4, ±1 day; Phe/Tyr only); on Day 7 (Phe/Tyr only); and EOS (Phe/Tyr only) (see Table 2). Phe concentrations for preliminary efficacy will be obtained from the same sample collected for Phe/Tyr concentrations on Day 1 and Day 2 (pre-dose), Day 4 (±1 day) and Day 7 (after the AM dose), and EOS.

p. Exploratory biomarkers in urine include sepiapterin, BH4, and neopterin. These samples will be collected at Screening, pre-dose on Day 1 and Day 2, and post-dose on Day 4 (±1 day) and Day 7. Urine samples should be the first void of the day. Samples will be sent to the bioanalytical laboratory (see Table 3).

q. CANTAB testing will include RTI, SSP, SWM, and RVP tests. These will be administered at the Screening visit and on Day 1 (pre-dose) and Day 7 of each treatment period.

r. Study drug will be administered twice daily (with breakfast and with supper) on Days 1 to 7 of each treatment period. Doses on Day 1 and Day 2 (AM only) will be administered by research staff, while all remaining doses will be self-administered.

s. Study drug will be dispensed at each Day 2 Study visit and will include enough study drug for dosing until the Day 7 study visit. CNSA-001 treatment will be discontinued if criteria related to safety or lack of efficacy are met (see Section 6.13.1).

t. Patient will receive a dosing diary and instructions for recording all doses of study drug taken and times they were taken; if a patient vomits after taking a dose of study drug, this should also be recorded in the diary and the patient should wait until the next scheduled time point to administer a dose.

u. Patients will be asked to wear a GENEActiv accelerometer device continuously for up to two 14-day periods. The initial device will be placed on the patient's wrist, ankle or other suitable location and secured with the appropriate band no earlier than Day -7 during Screening. The initial device will be removed on Day 7 of Treatment Period 1 and replaced with a second device to be worn until the End of Study visit. All devices will be collected at the End of Study visit.

v. Patients ages 3-17 will be administered the NIH Toolbox Cognitive Domain test battery on either Day -1 or Day 1 predose for Treatment Period 1 at the clinical site's option. Only one assessment will be performed and will be used as the baseline assessment for Treatment Period 1.

Abbreviations: AE = adverse event; AM = morning; AP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase; BUN = blood urea nitrogen; CO2 = carbon dioxide; HEENT=hear, eyes, ears, nose, throat; ECG = electrocardiogram; EOS = end of study; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; Phe = phenylalanine; PK = pharmacokinetic; RBC = red blood cell; RVP = Rapid Visual Information Processing; SAE = serious adverse event; RTI = Reaction Time; SSP = Spatial Span; SWM = Spatial Working Memory; WBC = white blood cell.

Appendix 2 Cockcroft-Gault Formula (Adults, ≥ 18) and Schwartz-Lyon Formula (Children < 18 Years) for Creatinine Clearance

COCKCROFT-GAULT FORMULA:

FOR SERUM CREATININE CONCENTRATION (SCr) IN MG/DL[a]

Cl_{cr} for males (mL/min) $$\frac{(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$$

CL_{cr} for females (mL/min) $$\frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(72)(SCr)}$$

FOR SERUM CREATININE CONCENTRATION (SCr) IN µMOL/L[a]

Cl_{cr} for males (mL/min) $$\frac{(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$$

CL_{cr} for females (mL/min) $$\frac{(0.85)(140\text{-age})(\text{weight}^{b})}{(0.81)(SCr)}$$

a Age in years and weight in kilograms.

b If the subject is obese (>30% over ideal body weight), use ideal body weight in calculation of estimated CL_{cr}.

D.W. Cockcroft, M.H. Gault. Prediction of creatinine clearance from serum creatinine. Nephron, 16 (1976), pp. 31-41

SCHWARTZ-LYON FORMULA:

CrCl (ml/min/1.73m^2) = k * height (cm) /PCr (plasma creatinine expressed in µmol/L)

k = 36.5 for males >13 years old
k = 32.5 for all others

De Souza VC, Rabilloud M, Cochat P, Selistre L, Hadj-Aissa A, et al. (2012) Schwartz Formula: Is One k-Coefficient Adequate for All Children? PLoS ONE 7(12): e53439. doi:10.1371/journal.pone.0053439.

Appendix 3 Pharmacokinetic, Efficacy and Exploratory Biomarker Samples

Table 3 PK, Preliminary Efficacy Biomarker, and Exploratory Biomarker Sampling Times for Plasma/Whole Blood and Urine Samples

			Day 1							Day 2	Day 4 (±1)	Day 7	EOS
Analyte	**Tube**	**Screen**	**Pre**	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**6 hr**	**8 hr**	**24 hr**	**72 hr**	**186 hr**	
Plasma or Whole Blood Samples Collection													
SEP /BH_4[a]	A/B		X	X	X	X	X	X	X	X			
Phe / Tyr	C/D		X	X	X	X	X	X	X	X	X	X	X
5HT (WB)	I/J	X	X							X	X	X	
Urine Sample Collection[b]													
SEP	E/F	X	X							X	X	X	
BH_4	E/F	X	X							X	X	X	
Neop	E/F	X	X							X	X	X	
Creatinine	G/H	X	X							X	X	X	

Abbreviations: 5HT = serotonin, BH_4 = tetrahydrobiopterin; EOS = End of Study; Neop = neopterin; Phe = phenylalanine; SEP = sepiapterin, Tyr = tyrosine, WB= whole blood

[a] Pharmacokinetic sampling timepoints/duration may be adjusted once the PK data become available from the Treatment Period 1.

[b] Urine samples will not be collected from toddlers unless they are toilet trained and a sample can be obtained.

The chemical name and structure of sepiapterin, or PTC923 (formerly known as CNSA-001), has been presented in various ways in the published literature. One such chemical name and structure was included in the Protocols included in PBD-001 CSR Section 16.1.1. However, the preferred representation of the active agent is as follows:

Chemical name: (S)-2-amino-6-(2-hydroxypropanoyl)-7,8-dihydropteridin-4(3H)-one

Chemical structure: