NCT03817684

Clinical Trial Protocol: BPN14770-CNS-201

Title	A Randomized, Double-blind, Placebo-controlled, 3-Arm Parallel Design Study to Evaluate the Effects of BPN14770 in Patients with Early Stage Alzheimer's Disease
Substance Identifier	BPN14770
IND Number	127905
Indication	Treatment of Alzheimer's Disease
Phase	Phase 2
Sponsor	Tetra Discovery Partners, Inc.
Sponsor Contact	[redacted] Tetra Discovery Partners, Inc. 38 Fulton Street West Suite 303 Grand Rapids, MI 49503-2684
Principal Investigator	TBD

Amendment	Revision Date	Reason
N/A	21 December 2018	Original submission
2.0	25 February 2019	Incorporation of clarifications; update to eligibility criteria
3.0	24 September 2019	Incorporation of additional clarifications, including eligibility criteria

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1 SIGNATURES

1.1 Sponsor Signatures

Protocol Number: BPN14770-CNS-201

Sponsor: Tetra Discovery Partners, Inc.

Sponsor Contact: [redacted] Tetra Discovery Partners, Inc.
38 Fulton Street West, Suite 303
Grand Rapids, MI 4953-2684
Phone: [redacted]

[redacted] 9/27/2019
(Signature) (Date)

Study Director & Medical Monitor [redacted] Tetra Discovery Partners, Inc.
38 Fulton Street West, Suite 303
Grand Rapids, MI 4953-2684
Phone: [redacted]

[redacted] 25Sept2019
(Signature) (Date)

1.2 Investigator Signature

I confirm that I have read and that I understand this protocol, the Investigator Brochure, and other product information provided by the Sponsor. I will provide copies of this protocol and access to all information furnished by Tetra Discovery Partners, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know that this information is confidential and proprietary to Tetra Discovery Partners, Inc. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Tetra Discovery Partners, Inc. with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.[1]
- International Conference on Harmonization Guidance for Industry, Good Clinical Practice E6.[2]
- All applicable laws and regulations (21 CFR § 11, 50, 54, 56, and 312 Subpart D), including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in this protocol.
- Terms outlined in the Clinical Study Site Agreement.

Investigator:

_____

(Signature) (Date)

SYNOPSIS

Name of Sponsor/Company:	Tetra Discovery Partners, Inc.
Name of Investigational Product:	BPN14770
Study Title:	A Randomized, Double-blind, Placebo-controlled, 3-Arm Parallel Design Study to Evaluate the Effects of BPN14770 in Patients with Early Stage Alzheimer's Disease
Study Number:	BPN14770-CNS-201
Study Phase:	Phase 2

Study Objectives:

In subjects with a clinical diagnosis of early stage Alzheimer's disease (AD) receiving cholinesterase inhibitor therapy:

- To evaluate the efficacy of two dose levels (10 mg bid and 25 mg bid) of BPN14770
- To evaluate the safety and tolerability of BPN14770 10 and 25 mg bid
- To obtain pharmacokinetic data on BPN14770 in this subject population

Overview of Endpoints

Primary Efficacy Endpoint:

- Repeatable Battery for the Assessment of Neurological Status - Delayed Memory Index (RBANS DMI) – change from baseline assessed at Week 13

Secondary Efficacy Endpoints

- RBANS total score
- Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) total score
- Mini-Mental State Exam (MMSE) score
- Clinical Dementia Rating sum of boxes score (CDR-SB)
- Clinical Global Impression – Improvement (CGI-I)
- Composite endpoint based on AD Composite Score (ADCOMS)

Safety and Tolerability: The safety variables to be assessed include adverse events; clinical laboratory parameters (chemistry, hematology, lipids, urinalysis); 12-lead electrocardiograms (ECGs); physical examinations; and vital signs (including blood pressure, heart rate, and respiratory rate).

Pharmacokinetics: Plasma BPN14770 concentrations will be obtained during the Weeks 1, 4, 8 and 13 clinic visits. Samples will be drawn according to the time of the clinic visit, with documentation of time of day testing was performed, and time of day of most recent dose of study medication. Pharmacokinetic (PK) samples will be retained and may also be utilized subsequently for biomarker assessment.

Biomarkers: Blood samples will also be obtained for biomarker testing, at Baseline (Day 1) and at Weeks 1, 4, 8 and 13. Samples will be frozen and retained with the PK plasma samples and may be utilized subsequently for biomarker assessment.

Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled, 3-arm, parallel-design study to evaluate the effects of BPN14770 in subjects with a clinical diagnosis of early stage AD. The study will consist of a Screening period of up to 28 days prior to initial study drug administration, a 13-week double-blind treatment, and a final follow-up visit for safety one week after treatment is concluded.

Randomization will be stratified based on presence or absence of an ApoE4 allele in the patient's genetic profile. Within each stratum, subjects will be randomized in a blinded, balanced fashion to receive either BPN14770 10mg bid, BPN14770 25 mg bid, or matching placebo.

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Subjects will have a total of eight clinic visits: Screening; Baseline (Day 1); Weeks 1, 2, 4, 8, 13, and the final Follow-up Visit. Cognitive testing will be performed during each clinic visit except the final Follow-up Visit. Safety and tolerability assessments throughout the study will include adverse event monitoring, ECGs, vital signs, blood chemistry, hematology; urinalysis will be performed at Screening, Baseline, and Weeks 1, 4, and 13, and lipid evaluations at Baseline and Week 13. Should gastrointestinal (GI) side effects occur, nausea may be treated with 5-HT3 antagonists, and diarrhea may be treated with loperamide. Anticholinergic drugs may not be used to treat GI side effects.

Pharmacokinetic samples will be collected during the treatment period to confirm that study drug is present, and to estimate plasma exposure at Weeks 1, 4, 8 and 13.

An independent data and safety monitoring board (DSMB) will provide safety oversight for this study. The DSMB will consist of two qualified MDs and one statistician. The DSMB will review standard safety data approximately every four (4) months, based on enrollment rate. A DSMB charter will be developed to further outline the DSMB responsibilities and the desired listings, summaries and analyses.

Planned Numbers of Subjects:
A target of 80 evaluable subjects per group (240 total) is planned. Approximately 85 subjects per group will be enrolled (255 total) in order to account for potential dropouts.

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Study Procedures:
The Screening Visit will occur up to 28 days prior to the first study drug administration on Day 1. During screening, subjects will sign the informed consent form prior to any study procedures being performed. Following a positive clinical diagnosis for early stage AD, subjects will have information collected regarding their neurological and medical/surgical history, race/ethnicity, social history (tobacco, alcohol, and/or drug use), and use of prescription and over-the-counter medications. Either a blood sample or buccal swab will be obtained for genetic testing for the ApoE4 allele if testing was not previously performed and documented for the subject. [Note: previous ApoE4 genetic testing results must be reviewed by study personnel]. Subjects will undergo a full physical exam and have vital signs and 12-lead ECG measured. Height, weight, and BMI will also be collected (or calculated in the case of BMI). Blood samples will be obtained for chemistry and hematology. Urine will be collected for urinalysis. Other eligibility criteria assessed during the screening period include serology (HbsAg, HCV); Columbia-Suicide Severity Rating Scale (C-SSRS) assessment; screening, diagnostic assessment of early stage AD, and MMSE for eligibility.

At the Baseline visit (Day 1), prior to drug administration, subjects will receive an abbreviated physical examination and ECG. Fasting blood samples for blood chemistry, hematology, lipid testing and biomarkers will be obtained. A serum pregnancy test will be conducted for females of childbearing potential. Randomization will be stratified based on presence or absence of an ApoE4 allele following the baseline assessments.

During the Double-Blind period, subjects will receive twice-daily treatment with blinded study medication. Doses of study medication should be taken in the morning and at night, approximately 12 hours apart, and at least 30 minutes prior to or 1 hour after meals.

Subjects will return to the clinic at the end of Weeks 1, 2, 4, 8, and 13, and for a follow-up safety visit approximately one week after completing the Double-Blind period. Fasting blood samples will be collected at the Week 13 visit. During clinic visits, adverse effects will be assessed, and laboratory measures, vital signs, and ECG will be repeated according to the Schedule of Assessments. Efficacy measures will be obtained to measure the effects of BPN14770 on cognition as well as functional status at Weeks 1, 2, 4, 8, and 13. Every effort will be made to retain each subject throughout the entire study period; however, if a subject must be withdrawn prior to Week 13, all Week 13 safety assessments should be completed, if possible.

Subject Inclusion/Exclusion Criteria:
Individuals are eligible for the study if they meet all of the Inclusion and none of the Exclusion criteria. The criteria below will be assessed during Screening, which will be up to 28 days prior to first study drug administration. Continued subject eligibility will be verified on Baseline Day 1.

Subject Inclusion Criteria
1. Males or females between the ages of 55 and 85 years (inclusive) with a clinical diagnosis of early stage AD, defined according to the following criteria assessed prior to randomization:
    a) Clinical Dementia Rating (CDR) score of 0.5 or 1, with Memory Box score of 0.5 or greater
    b) MMSE score of 20 or greater
    c) RBANS DMI score ≤ 85

    Note: PET imaging for amyloid is not required for diagnosis, which will be made on clinical grounds.
2. Currently receiving a stable dose regimen of donepezil or another cholinesterase inhibitor for treatment of

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Alzheimer's disease. Subjects must be receiving a stable dose of a cholinesterase inhibitor for at least 56 days prior to their baseline visit. Doses of these drugs may not be changed during the trial.

Note: Memantine is <u>not</u> permitted during the trial and must be discontinued at least 3 weeks prior to Baseline.

3. Modified Hachinski Ischemia score $\leq$ 4.
4. Body mass index (BMI) $\leq$ 38 kg/m^2, inclusive, and body weight of >48 kg (105 pounds) at screening.
5. Female subjects must be at least two years post-menopausal (subjected reported menopausal status), surgically sterile (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 6 months prior to first study drug administration), or willing to either (1) utilize hormonal contraception plus one barrier method or (2) use two barrier methods of contraception (e.g. diaphragm and spermicide) from initial screening until one month after taking the final dose. An intrauterine device (IUD) is considered a barrier method of contraception in this study. Male subjects must be willing to inform female partners of their participation in the study and must agree to use adequate contraceptive methods (vasectomy performed at least 6 months prior to first study drug administration, or use at least one barrier method of birth control) from initial screening until one month after taking the final dose.
6. Able to understand and comply with the study procedures, voluntarily agree to participate in this study, read the informed consent document, and provide written informed consent prior to start of any study-specific procedures. If the subject is unable to read the consent form and provide written consent, a legally authorized representative of the subject may read and sign the informed consent and the subject must verbally assent to participation.
7. All subjects must have a caregiver who is willing and able to ensure compliance with study medications, visits, and study procedures.

Subject Exclusion Criteria

The following Exclusions apply to findings during Screening or at Baseline (Day 1)

1. Any medical or neurological condition (other than early stage AD) that might be a contributing cause to the subject's cognitive impairment, including prominent features of Lewy body dementia, behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia.
2. No substantial concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden on imaging.
3. No evidence for another concurrent, active neurological disease, or a non-neurologic medical co-morbidity or use of medication that could have a substantial effect on cognition.
4. Clinically significant major psychiatric illness during the past 6 months, as determined by the Investigator.
5. History of unstable angina, myocardial infarction, chronic heart failure, or clinically significant conduction abnormalities during the past year.
6. Clinically significant liver or renal disease, defined as creatinine clearance <30 mL/min at screening.
7. Clinically significant abnormality, in the Investigator's judgment, in hematology, chemistry, or urinalysis.
8. Positive serology results for hepatitis B surface antigen (HbsAg) or hepatitis C virus (HCV). HCV subjects who have been treated and are now RNA negative are eligible to participate.
9. Abnormal liver function test at the Screening Visit (aspartate aminotransferase or alanine aminotransferase >2 × the upper limit of normal [ULN], or total bilirubin >1.7 × ULN, based on appropriate age and gender normal values). Subjects with Gilbert's syndrome are eligible to participate despite elevated bilirubin. Subjects may be re-screened for these tests once.
10. Marked hypotension (systolic blood pressure [BP] <90 mmHg or diastolic BP <50 mmHg) or hypertension

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(systolic BP >160 mmHg or diastolic BP >100 mmHg) based on sitting values. Out-of-range results may be repeated once at Screening and Baseline, if needed. Eligibility must be confirmed at Baseline.

11. Marked bradycardia (heart rate <45 beats per minute [bpm]) or tachycardia (heart rate >115 bpm) based on supine ECG values. Out-of-range results may be repeated once at Screening and at Baseline, if needed. Eligibility must be confirmed at Baseline.
12. Presence of any clinically important conduction abnormality(ies) as assessed by Investigator on ECG, or evidence of long QT syndrome based on supine ECG values obtained at Screening, or history of long QT syndrome based on supine ECG values. Clinically important out-of-range results may be repeated once. Eligibility must be confirmed at Baseline.
13. Active gastric or duodenal ulcers or other diseases of the gastrointestinal tract that could interfere with absorption of study drug. Note: Subjects with a history of appendectomy or cholecystectomy may be enrolled, as may subjects with gastric bypass, gastric sleeve, of controlled inflammatory bowel.
14. Active acute or chronic infectious diseases that would interfere with subject's participation in the study.
15. Patients who cannot discontinue the following centrally active medications that might interfere with cognitive assessments <u>are excluded</u>. These include:
    a. Anticonvulsants
    b. Memantine
    c. Antipsychotic drugs, tricyclic antidepressants, gabapentin, and pregabalin
    d. Stimulants including modafinil
    e. Daytime use of benzodiazepines (bedtime use of benzodiazepines is permitted)

    Note: The following medications <u>are permitted</u> provided the dosage and dose regimen have been stable for 2 months and remain stable throughout the study:
    a. Cholinesterase inhibitors as per protocol
    b. SSRIs, SNRIs, and bupropion
    c. Beta-blockers
    d. Hypnotics for <u>sleep</u>, including benzodiazepines, non-benzodiazapines (Ambien, Lunesta), antihistamines, hydroxyzine and trazodone. Other medications that are often used for sleep such as mirtazapine and quetiapine are <u>not</u> permitted.
    e. Benadryl (diphenhydramine) and other sedating antihistamines are permitted <u>only at bedtime</u> for night time sleep management.
16. Patients who cannot discontinue strong CYP450 2D6 and 3A4/3A5/3A7 enzyme inducers at least 14 days prior to the first dose of study drug are <u>excluded</u>. Specifically, this includes rifampin, barbituates, and carbamazepine. CYP450 2D6 and 3A4/3A5/3A7 inhibitors are permitted.
17. Note: Other prescription or non-prescription drugs necessary for the patient's welfare, such as antihypertensive or cholesterol lowering agents are allowed, if, in the Investigator's judgement, they would not interfere with the study medication or the cognitive testing.A suicidal ideation intensity score of 3 or higher per screening Columbia Suicide Severity Rating Scale (C-SSRS) assessment on Day 1 (Baseline) and/or any suicidal behavior within the past 3 months.
18. History of chronic alcohol or other substance abuse, including marijuana, within the previous year prior to the Screening visit (per the current edition of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5), or regular (daily) consumption of alcohol exceeding two bottles of beer, or the equivalent amount of other forms of alcohol (1 serving = 12 oz beer, 5.0 oz wine, or 1.5 oz distilled spirits).
19. Inability or unwillingness to comply with the protocol, including performing the cognitive function tests, or likely inability to complete the study.

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20. Participation in other clinical studies involving investigational drug within the previous 30 days prior to the Screening Visit. Participation in other clinical trials of monoclonal antibody products requires a 90-day wash out period prior to the screening visit.
21. Donation of blood within 4 weeks, or blood products within 2 weeks, prior to first study drug administration.
22. History of clinically significant drug allergy that includes symptoms such as shortness of breath, rash, or edema.
23. Clinically significant B12 deficiency within 12 months prior to Visit 1 (Screening), based on clinical diagnosis. Participants on stable replacement therapy for a minimum of 3 consecutive months immediately prior to screening may be included.

Investigational Product, Dosage, and Mode of Administration:
In this randomized double-blind, placebo-controlled 3-arm parallel study, 255 subjects will be randomized (1:1:1) to receive one of the following three treatments (85 per group), in addition to receiving their ongoing treatment with a cholinesterase inhibitor:

- BPN14770 10 mg bid
- BPN14770 25 mg bid
- Matching Placebo

All study medications will be provided as identical-appearing HPMC capsules in HPE bottles. Study drug will be taken by mouth (PO) with water (at least 120 mL = 4 ounces) in the morning and at night, approximately 12 hours apart, and at least 30 minutes prior to or 1 hour after meals.

Statistical Analyses:
Efficacy Analyses
The primary efficacy population will be the intent to treat (ITT) efficacy population, which will include all randomized subjects who received at least one dose of treatment and returned for at least one follow-up visit. The per protocol (PP) population (randomized subjects who received at least one dose of treatment and returned for at least one follow-up visit with no significant protocol violations) and the completers (CP) population (randomized subjects who completed all 13 weeks of treatment with no significant protocol violations) will be used to evaluate the robustness of the ITT results.

Change from baseline will be calculated for the primary and secondary efficacy parameters at each time point and descriptive statistics provided for each time point. Summary plots of these data will also be provided. For RBANS DMI and total score, MMSE score, and ADCS-ADL total score, pairwise differences in change from baseline between the treatment groups (10 mg vs 25 mg BPN14770, 10 mg BPN14770 vs Placebo, 25 mg BPN14770 vs Placebo) will be assessed using an analysis of covariance (ANCOVA) model that includes baseline as a covariate and factors for week, site and treatment and the interaction term for week and treatment; the pairwise differences will be assessed at each time point. CDR sum of boxes will be analyzed in the same manner.

Change from baseline in the other RBANS index scores (immediate memory, visuospatial/constructional, attention, language) will be summarized by time point, with descriptive statistics provided.

The composite endpoint will be based on the AD Composite Score (ADCOMS), a composite clinical outcome for prodromal Alzheimer's disease trials.[20] The composite endpoint and analysis model will be fully specified in the statistical analysis plan.

The efficacy analyses will be performed on the ITT, PP and CP analysis populations.

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Supplemental analyses assessing treatment effect relative to severity of disease based on baseline MMSE score may also be performed.

Safety Analyses

The Safety population will include all randomized subjects who received at least one dose of study treatment. Adverse Events (AEs), including clinically meaningful laboratory abnormalities as assessed by the Investigator, will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) and AE severity and relatedness to treatment will be assessed. AEs will be tabulated for each of the treatment groups separately, as well as for all BPN14770 recipients combined. Summaries will also be provided by severity and relationship to treatment. Serious Adverse Events (SAEs) will be summarized separately, in a manner similar to that used for Adverse Events.

For each AE, the difference in incidence rates between the each BPN14770 dose group will be compared to the placebo group using a Fisher's exact test.

Sample Size Determination:

This study will enroll 255 subjects (85 per treatment arm), in anticipation of evaluating at least 240 subjects (80 per treatment). Based on 80 subjects per group completing the study, the probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between BPN14770 25 mg and placebo is 7.15 units. Using the standardized mean difference (SMD) to estimate effect size, a change of 7.15 units on the DMI score is an effect size of 0.45.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AD	Alzheimer's disease
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory -
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
API	Active pharmaceutical ingredient
ApoE4	Apolipoprotein E4
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BUN	Blood urea nitrogen
°C	Degrees centigrade
cAMP	3'-5'- cyclic adenosine monophosphate
CFR	Code of Federal Regulations
C_{max}	Maximum plasma concentration
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum of Boxes
CGI-I	Clinical Global Impression - Improvement
CNS	Central nervous system
CREB	cAMP response element binding
CRF	Case report form
eCRF	Electronic case report form
CRO	Clinical research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EH	hepatic extraction ratio
FDA	Food and Drug Administration
gm	Gram
GCP	Good Clinical Practice

GI	gastrointestinal
hERG	human Ether-à-go-go-Related Gene
HDPE	High density polyethylene
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPMC	Hydroxypropyl methylcellulose
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
kg	kilogram
MAD	Multiple ascending dose
MED	Minimum effective dose
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
MHIS-NACC	Modified Hachinski Ischemic Scale - NACC Version
mL	Milliliter
MMSE	Mini Mental State Exam
msec	Millisecond
MTD	Maximum tolerated dose
NAM	Negative allosteric modulator
ng	nanogram
NOAEL	No observed adverse effect level
NOR	Novel Object Recognition
oz	ounce
PDE4	phosphodiesterase type-4
PDE4D	phosphodiesterase type-4 subtype D
PDE4D-NAM	phosphodiesterase type-4D-negative allosteric modulator
PK	Pharmacokinetic

PO	By mouth (per os)
QTc	Corrected QT interval
RBANS (DMI)	Repeatable Battery for the Assessment of Neurological Status (Delayed Memory Index)
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
sc	Subcutaneous
SD	Standard deviation
SOP	Standard operating procedure
T_{max}	Time to maximum concentration
µ	Micro
ULN	Upper limit of normal
USP-NF	The United States Pharmacopeia and The National Formulary

4 INTRODUCTION

4.1 Background

Tetra Discovery Partners, Inc. is a central nervous system (CNS) biotechnology company that uses structure-based drug design to discover negative allosteric modulators (NAMs) of phosphodiesterase-4 (PDE4) subtypes for neurological and psychiatric diseases.

Since the introduction of cholinesterase inhibitors to address the depletion of acetylcholine in the Alzheimer's brain (1995) and memantine to improve glutamatergic signaling (2003), there have been no new drugs to treat the condition. Attempts to develop disease-modifying therapies have focused mainly on the amyloid pathway.[3,4] This pathway has medical and genetic support but so far has proved challenging for therapeutic development. Also of concern is that successful disease modifying therapeutics, if they slow Alzheimer's disease (AD) progression, are unlikely to reverse the cognitive impairment caused by the disease. Thus there is a need for new drugs to address cognitive impairment in AD and other dementias, as well as a need to find drugs that may help restore cognitive function and improve brain resilience to the damage caused by AD.

Tetra has developed a mechanistically novel class of drugs to address cognitive impairment across multiple psychiatric and neurological indications. These new drugs selectively target subtypes of phosphodiesterase type-4D (PDE4D).[5,6] The PDE4D enzyme subtype is a highly validated CNS target for improving cognition.[7]

BPN14770 is a novel, selective small molecule inhibitor of the PDE4D enzyme, which is considered to play a role in modulating the 3'- 5'- cyclic adenosine monophosphate pathway (cAMP) in the brain important for learning and memory. BPN14770 is in clinical development for treating alzheimer's disease. This is the fourth clinical study evaluating its effects in humans; the first study was the single dose escalation study (BPN14770-CNS-101; clinicaltrials.gov NCT02648672), the second was a multiple dose escalation study in healthy volunteers (BPN14770-CNS-102; clinicaltrials.gov NCT02840279), and the third study was single-dose, 6-period crossover study in healthy volunteers to evaluate the effects of BPN14770 on scopolamine-induced cognitive impairment (BPN14770-CNS-103; NCT03030105).

4.2 Rationale

As of February 27, 2017, a total of 136 subjects have received BPN14770 either as a single dose or as a multiple dose regimen. Of these subjects, 106 (78%) were ≤ 55 years of age and 30 (22%) were ≥60 years of age.

The single dose escalation study (-101) in 24 subjects ≤ 55years of age determined that a single 100mg dose was the maximum tolerated dose of BPN14770, based on the occurrence of nausea and vomiting in the majority of subjects at this dose. There were no notable adverse events in other body systems, no observed changes in vital signs or electrocardiogram, no adverse laboratory findings, and no serious adverse events were recorded. The multiple dose escalation study assessed 15 mg, 30 mg, and 50 mg doses given BID to 18 subjects ≤45 years of age and doses of 10 mg, 20 mg, and 40 mg given BID to 30 subjects ≥ 60 years of age. All of these doses were well tolerated. An additional cohort of 6 subjects ≤45 years of age received 75mg

once daily in order to compare the safety and PK profiles to the 100mg MTD determined in the single dose study. The 75 mg dose was associated with GI adverse experiences, confirming the findings at 100 mg in the single ascending dose study. The BPN14770 doses assessed in the scopolamine challenge study were 10 mg and 50 mg QD. Of the 38 subjects enrolled, 37 received at least one of the two doses of BPN14770; one subject withdrew from the crossover study prior to a dosing cohort containing BPN14770.

In the dose escalation study (-102), there was evidence of greater than proportional increases in BPN14770 exposure after a single dose or repeated dosing. Drug accumulation was approximately 2-fold after QD dosing. After BID dosing, moderate drug accumulation of approximately 3- to 5-fold was observed. Steady state appeared to be reached within 2 to 4 days of BID or QD dosing. When adjusted for differences in dose, mean BPN14770 exposure appeared to be similar between healthy young and healthy elderly subjects.

In the multiple ascending dose study (-102), BPN14770 administered twice daily to healthy elderly subjects was associated with improvement in complex attention/working memory, delayed recall of verbal information, and delayed recall of visual information (10 and 20 mg doses). No beneficial or detrimental effects were observed on other cognitive tasks studied. The 40-mg BID dose was not associated with improvement in any cognitive domain, possibly because of a higher frequency of adverse events, primarily headaches, at this dose level.

In this initial Phase 2, randomized double-blind, placebo-controlled 3-arm parallel study, 255 subjects will be randomized (1:1:1) to receive one of the following three treatments (85 per group): BPN14770 10 mg bid, BPN14770 25 mg bid, matching placebo bid. Steady state exposure at the 25 mg dose is estimated to be at least 3-fold higher than at the 10 mg dose. The objectives of the study are to evaluate the efficacy and safety of the two doses of BPN 14770, as well as to obtain PK data to correlate with cognitive and safety outcomes. This study will assess two doses of BPN14770, 10 mg and 25 mg, both administered twice daily. These doses are well below the maximum tolerated single dose of 100 mg determined in the initial single dose study (-101), and also are below the maximum twice daily dose of 50 mg that was well tolerated in the multiple dose study (-102), and are therefore expected to be safe and well-tolerated in this trial in subjects with AD. Based on accumulation data from the multiple-dose study, the exposure difference between the 10 and 25 mg doses should be 4-fold.

4.3 Risk/Benefit

4.3.1 Preclinical Pharmacology

BPN14770 is a first-in-class, subtype selective, phosphodiesterase type-4D (PDE4D)-allosteric inhibitor. The unique mechanism of action and subtype selectivity distinguishes BPN14770 from the two approved PDE4 inhibitors, roflumilast (Daliresp™) and apremilast (Otezla™). Roflumilast and apremilast are competitive inhibitors that inhibit the PDE4 enzymes by binding in the active site competitively with 3'- 5'- cyclic adenosine monophosphate (cAMP). As the amino acid sequence of the PDE4 active site is conserved between the four subtypes, roflumilast and apremilast inhibit all subtypes of PDE4 equally strongly. Both compounds cause emesis in humans and other species, and as a class, PDE4 competitive inhibitors have been found to cause mesenteric vasculopathy in rats, dogs and primates, although this toxicity has not been observed in humans. In contrast, BPN14770 does not bind to the active site of the PDE4 enzyme and does

not cause emesis in ferrets, cynomolgous monkeys or marmosets; furthermore, it has not been found to cause mesenteric vasculopathy in rats or dogs in toxicological studies of 3 months duration. Thus, BPN14770 presents a unique procognitive and preclinical safety profile.

Clearance of BPN14770 by hepatocytes from human, rat, dog and monkey, expressed as hepatic extraction ratio (EH), was 16%, 8.2%, 17%, and 12%, respectively. Qualitative metabolite profiling in human, rat, dog, and monkey hepatocytes showed a single metabolite in human (<1% parent). BPN14770 was highly bound to plasma proteins in all species tested. The fraction unbound (free) was 0.5, 0.4, 0.2, and 0.5%, for mouse, rat, dog, and human, respectively.

BPN14770 is highly bioavailable in rats, mice and dogs (F% = 100), distributes to brain (B/P = 0.32-0.48), and has a plasma $t_{½}$ of 4.8 hours in rats, 10.9 hours in mice, and 11 hours in dogs. The multi-species pharmacokinetic data suggest that BPN14770 will have adequate half-life for once daily oral administration in humans. In bile duct cannulated rats, BPN14770 was eliminated as a conjugate through the bile. Only the unchanged drug was detected in plasma, and no BPN14770 was detected in urine.

BPN14770 has cognitive benefit in the mouse Novel Object Recognition (NOR) test at $\geq$0.3 mg/kg by PO, as shown by an increase in the Discrimination Index. BPN14770 maximum plasma concentration (C_{max}) at the minimum effective dose (MED) was 160 ng/mL (in plasma) and 40 ng/gm (in brain). Cognitive benefit is maintained after chronic dosing for 7 days. BPN14770 also has benefit in a mouse model of cholinergic impairment, the scopolamine-impaired Y-maze (male C57Bl6 mice MED = 1 mg/kg).

BPN14770 did not affect cardiovascular function in beagle dogs at doses up to 100 mg/kg, nor did the compound affect respiratory function or exert neuropharmacologic effects in rats at doses up to 60 mg/kg. In the in vitro human Ether-à-go-go-Related Gene (hERG) assay, an increase in current of 12% and 33% was seen at concentrations of 10 and 30 μM, respectively. No IC_{50} could be calculated due to this minor increase in current.

In rat toxicology studies of 28-days and 13-weeks, BPN14770 was well tolerated up to 60 mg/kg with no deaths on study, and no adverse hematology, clinical chemistry, liver weight or gross necropsy findings. There were no microscopic findings. Unlike the PDE4 inhibitors roflumilast and apremilast, BPN14770 did not cause mesenteric vasculopathy at the doses studied.

In dog toxicology studies of 28-days and 13-weeks, the no observed adverse effect level (NOAEL) for BPN14770 was 30 mg/kg. At 100 mg/kg in the 28-day study, BPN14770 caused inappetance and weight loss and in female dogs an approximately 30 msec increase in QTc with a concomitant increase in heart rate of 10 bpm. There were no changes in hematology or ophthalmology. Macroscopic observations included pale livers in two of eight animals at 100 mg/kg which correlated with mild alanine transaminase (ALT) elevation only in those two animals. Microscopic changes of periportal hepatocellular cytoplasmic vacuolation were observed in the livers of one male and two female dogs at 100 mg/kg. No liver changes were observed in recovery dogs suggesting that these changes, if present, were reversible.

4.3.2 Clinical Experience

4.3.2.1 BPN14770-CNS-101

A first-in-human (FIH), single ascending dose (SAD) trial (BPN14770-CNS-101) in 24 healthy subjects at doses ranging from 5 mg to 100 mg has been completed. The results from this study indicate single doses of BPN14770, in the range of 5 mg to 100 mg, were safe and generally well tolerated. The maximum tolerated dose (MTD) was determined to be 100 mg, after 4 of 6 subjects in this dose group experienced nausea and, of those, two experienced vomiting.

The most commonly reported treatment-emergent, drug-related adverse events were nausea and vomiting. No safety signals were noted in the results of the other safety analyses. No deaths or other serious adverse events were reported. No subjects withdrew from the study due to adverse events.

In the SAD trial, detectable plasma BPN14770 concentrations were measured after dosing (at all 4 dose levels) starting between 0.5 hour and 1 hour after dosing, continuing through at least 48 hours after dosing. Drug absorption was variable but moderately rapid with median time to maximum concentration (T_{max}) values ranging from 1.5 to 3 hours. The plasma pharmacokinetics of BPN14770 after oral administration appeared to be linear for single doses ranging from 5 to 100 mg; although a slight trend for a greater than proportional increase in exposure was observed in the 100-mg group as compared to the lower dose groups. The apparent terminal elimination half-life of BPN14770 was consistent among dose groups and averaged between 11 and 13 hours. Based on the preclinical models, the concentrations associated with doses as low as 15 mg were potentially adequate to produce cognitive improvement after once- or twice- per day dosing.

4.3.2.2 BPN14770-CNS-102

In the multiple ascending dose (MAD) trial (BPN14770-CNS-102), 76 healthy young and elderly subjects were administered multiple doses of BPN14770 twice daily (every 12 hours) for 8 days. Young subjects (≤45 years; n=18 treated, 7 placebo) received twice-daily doses of 15 mg, 30 mg, 50 mg or placebo for 8 days. Elderly subjects (≥60 years; n=30 treated, 15 placebo) received twice-daily doses of 10 mg, 20 mg, and 40 mg for 8 days. Twice-daily dosing was selected to ensure adequate BPN14770 levels in the brain and plasma throughout the day and night. An additional cohort of 6 young subjects received a once-daily dose of 75 mg for 8 days to obtain additional safety and pharmacokinetic (PK) data at a dose level close to the MTD determined in the SAD study.

No deaths or serious adverse events were reported, and no subjects in either the young or elderly cohorts withdrew from the study due to adverse events. All treatment-emergent adverse events resolved without sequelae by the follow-up visit.

All study-drug related adverse events that occurred in more than 1 young subject were in the 75-mg QD dose group and consisted of nausea (reported by 4 of 6 subjects, vomiting (reported by 2 of 6 subjects who also experienced nausea), and decreased appetite (reported by 3 of 6 subjects). Across the young subject cohorts, all but 2 of the reported adverse events were mild in severity; moderate nausea and vomiting were reported in 1 of 6 subjects (16.7%) in the 75-mg QD dose

group on Day 2 of multiple dosing. These events were considered by the Investigator as probably related to study treatment, resolved without sequelae within 13 hours of onset, and did not recur upon subsequent dosing. Among the young subject dose groups, no clinically significant effects of multiple oral doses of BPN14770 (15 mg, 30 mg, 50 mg, or 75 mg) were observed on biochemistry, hematology, or urinalysis; vital signs; or ECGs.

Among the elderly subject cohorts, the percentage of subjects who experienced at least one treatment-emergent adverse event was similar between the 10-mg BID, 20-mg BID, and placebo groups (ranging from 30% to 50%) and was higher for the 40-mg BID dose group (90%). Likewise, the percentage of subjects with at least one drug-related adverse event was also higher for the 40-mg BID dose group (70%) compared with the 10-mg BID dose group (40%), the 20-mg BID dose group (20%), and the placebo group (26.7%). Adverse events reported in 2 or more elderly subjects within a dose group were all reported by subjects in the 40-mg dose group and consisted of diarrhea, increased alanine and aspartate aminotransferase, hot flush (each reported at a frequency rate of 20%) and headache (reported at a frequency rate of 40%). Across the elderly subject cohorts, 2 adverse events (dizziness and hypotension) of moderate severity were reported in 1 of the 10 subjects (10.0%) in the 10 mg BID dose group, and 1 headache of moderate severity was reported in 1 of 10 subjects (10.0%) in the 40-mg BID dose group. Among the elderly subject dose groups, no clinically significant effects of multiple oral doses of BPN14770 (10 mg, 20 mg, or 40 mg) were observed on biochemistry, hematology, or urinalysis; vital signs; or ECGs.

With respect to cognitive testing, BPN14770 10 mg given twice daily was associated with improvement in complex attention/working memory and delayed recall of both visual and verbal information. Treatment with BPN14770 20 mg twice daily was associated with similar benefits as the 10 mg twice daily regimen, excluding improvement in delayed recall of visual information. Neither the 10- or 20-mg BID regimens was associated with improvement in psychomotor function, visual, or verbal learning, or executive function. The 40-mg BID regimen was not associated with improvement in any cognitive domain.

Pharmacokinetic analyses found that steady-state appeared to be reached after 3 to 4 days of BID or QD dosing in both young and elderly subjects. After a single oral dose of BPN14770 in healthy young subjects, C_{max} and AUC_{12} appeared to increase in a dose-proportional fashion over the dose range of 15 to 50 mg, with a greater than proportional increase in exposure observed after a 75-mg dose. Following BID dosing of BPN14770 in healthy young subjects, C_{max} and AUC_{12} appeared to increase in a greater than dose-proportional fashion from 15 mg to either 30 mg or 50 mg. A moderate degree of accumulation (up to approximately 5-fold) was observed after BID dosing in healthy young subjects, with less accumulation (approximately 2-fold) after QD dosing.

After a single oral dose of BPN14770 in healthy elderly subjects, C_{max} appeared to increase in a greater than dose-proportional fashion over the dose range of 10 to 40 mg, whereas AUC_{12} appeared to increase in a greater than dose-proportional fashion from 10 mg or 20 mg to 40 mg. Following BID dosing of BPN14770 in healthy elderly subjects, C_{max} and AUC_{12} appeared to increase in a greater than dose-proportional fashion over the dose range of 10 to 40 mg. A moderate degree of accumulation (up to approximately 4-fold) was observed after BID dosing in healthy elderly subjects.

In healthy young subjects, mean peak to trough fluctuation was similar among BID regimens, ranging from 171% to 179%, and was 337% for the QD regimen. In healthy elderly subjects, mean peak to trough fluctuation was similar among BID regimens, ranging from 156% to 249%.

4.3.2.3 BPN14770-CNS-103

The third Phase 1 trial of BPN14770 (BPN14770-CNS-103) was a randomized, double-blind, placebo-controlled, 6-period crossover study to evaluate the effects of BPN14770 10 and 50 mg in reversing scopolamine-induced cognitive impairment in healthy volunteers. A positive control, donepezil 10 mg, was included, and additivity of BPN14770 50 mg to donepezil 10 mg in reversing scopolamine effects was also evaluated. A total of 38 subjects were enrolled into the study. The study duration was up to 12 weeks with 6 weeks of single-dose treatment visits. The study consisted of a screening visit (up to 28 days prior to first study drug administration), 6 inpatient treatment visits (Periods 1 through 6), and a follow-up/early termination visit (7 to 10 days after the last dose of study drug). An additional study visit may have been necessary to complete the required cognitive test familiarization if not completed during the screening visit. Each treatment visit occurred approximately 1 week apart, allowing a 6 to 8 day washout period. Subjects were randomized to 1 of 6 treatment sequences, each containing the 6 following treatments:

A. Scopolamine placebo + BPN14770 placebo + donepezil placebo
B. Scopolamine 0.5 mg + BPN14770 placebo + donepezil placebo
C. Scopolamine 0.5 mg + BPN14770 10 mg + donepezil placebo
D. Scopolamine 0.5 mg + BPN14770 50 mg + donepezil placebo
E. Scopolamine 0.5 mg + BPN14770 placebo + donepezil 10 mg
F. Scopolamine 0.5 mg + BPN14770 50 mg + donepezil 10 mg

The Cogstate Computerized Battery Test results suggest that, as expected, a 0.5 mg dose of scopolamine induced a decline in cognitive function, while a 10-mg dose of donepezil ameliorated this decline. Doses of 10 or 50 mg of BPN14770 did not produce a systematic reversal of the scopolamine-induced cognitive decline, administered alone or with a 10-mg dose of donepezil.

BPN14770 10 mg was safe and generally well tolerated when administered with scopolamine in healthy subjects. BPN14770 50 mg was generally safe when administered with scopolamine, or with scopolamine and donepezil in healthy subjects. The incidence of nausea and vomiting increased several fold when either BPN14770 50 mg or donepezil was administered with scopolamine, or when both BPN14770 and donepezil were administered with scopolamine, compared to BPN14770 10 mg, placebo, or scopolamine alone. None of the TEAEs that were reported in this study were out of the ordinary or unexpected in clinical nature or character for this population of healthy subjects. The administration of BPN14770 with donepezil did not appreciably increase the incidence of adverse GI side effects associated with donepezil alone.

4.4 Study Objectives and Endpoints

4.4.1 Study Objectives

In subjects with a clinical diagnosis of early stage Alzheimer's disease receiving cholinesterase inhibitor therapy:

- To evaluate the efficacy of two dose levels (10 mg bid and 25 mg bid) of BPN14770

- To evaluate the safety and tolerability of BPN14770 10 and 25 mg bid
- To obtain pharmacokinetic data on BPN14770 in this subject population

4.4.2 Efficacy Endpoints

4.4.2.1 Primary Efficacy Outcome Measure

The primary efficacy outcome measure is the change from baseline to Week 13 in Repeatable Battery for the Assessment of Neurological Status - Delayed Memory Index (RBANS DMI)

4.4.2.2 Secondary Efficacy Outcome Measures

There are six secondary efficacy outcomes of interest. Change from baseline will be evaluated for each of the outcome measures below.

- RBANS total score
- Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory - Mild Cognitive Impairment version (ADCS-ADL) total score
- Mini-Mental State Evaluation (MMSE) score
- Clinical Dementia Rating sum of boxes (CDR-SB) score
- Clinical Global Impression- Improvement (CGI-I) score
- Composite endpoint based on AD Composite Score (ADCOMS)

4.4.3 Safety and Tolerability Endpoints

The following safety assessments will be conducted during the study.

- Treatment-emergent adverse events
- Changes in vital signs
- Clinical laboratory evaluations (chemistry, hematology, lipids, urinalysis)
- Electrocardiogram (ECG) measurements

4.4.4 Pharmacokinetic Endpoints

Plasma BPN14770 concentrations at Weeks 1, 4, 8, and 13, to verify that study drug is present and to estimate plasma exposure at these time points.

5 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, 3-arm, parallel-design study to evaluate the effects of BPN14770 in 255 subjects with a clinical diagnosis of early stage AD. The study will consist of a Screening period of 28 days or less, unless additional time is required for washout of concomitant medications. The Screening period will be followed by a 13-week double-blind treatment period, and a final follow-up visit for safety one week after treatment is concluded.

Randomization will be stratified based on presence or absence of an ApoE4 allele in the subject's genetic profile. Within each stratum, subjects will be randomized in a blinded, balanced fashion to receive either BPN14770 10mg bid, BPN14770 25 mg bid, or matching placebo. In total 255 subjects will be randomized (i.e., 85 subjects per treatment arm).

Subjects will have a total of eight clinic visits: Screening; Baseline (Day 1); Weeks 1, 2, 4, 8, 13, and the final Follow-up Visit. The screening visit will consist of consenting the subject, obtaining a medical history, full physical exam, height, weight, BMI, ECG, serology testing, chemistry, hematology, urinalysis, ApoE4 testing, pregnancy testing, and cognitive assessments. If the subject fully qualifies for the study, randomization will occur at the Baseline visit when the subject will receive study medication.

Cognitive testing will occur at each visit except the final Follow-up Visit. Safety assessments will also be performed at each visit, to include adverse event monitoring, vital signs, ECG, and chemistry and hematology. Urinalysis will also be performed at Screening and Baseline and Weeks 1, 4 and 13. Lipid testing will be performed at Baseline and Week 13. Risk of suicidality will be assessed at Screening, Baseline and Weeks 1, 4, and 13.

Pharmacokinetic testing will occur at the clinic visits at Weeks 1, 4, 8 and 13.

5.2 Dose Selection

Doses of 10 and 25 mg BPN14770 to be taken twice daily were chosen for testing in this study.

Based on pharmacokinetic data from study BPN14770-CNS-102 (MAD), steady state average plasma concentrations of BPN14770 10 mg are projected to be approximately 60 ng/ml. Therefore, the lower dose of 10 mg has the potential to demonstrate efficacy in this study, although given the uncertainties of translation from preclinical models, it may be below the effective range. On the other hand, the 25 mg dose should be above that needed for efficacy, and is estimated to produce steady state with projected average plasma levels of concentrations over 200 ng/ml. The twice-daily doses of 10 mg and 25mg selected for this study both fall well within the tolerance limits defined by the SAD and MAD studies.

5.3 Study Duration

The total duration of the study for each subject will be up to 127 days (18 weeks), including a maximum of a 28-day screening period, 13 weeks of dosing, and a follow-up period (7 days after last dose).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Study Population

Individuals are eligible for the study if they meet all of the inclusion and none of the exclusion criteria. The criteria below will be assessed at the Screening visit which should within 28 days prior to first study drug administration. Continued subject eligibility will be verified at Baseline, prior to randomization.

6.2 Subject Inclusion Criteria

1. Males or females between the ages of 55 and 85 years with a clinical diagnosis of early stage AD, defined according to the following criteria assessed prior to randomization:
    - Clinical Dementia Rating (CDR) score of 0.5 or 1, with Memory Box score of 0.5 or greater
    - MMSE score of 20 or greater
    - RBANS DMI score $\leq$ 85

    Note: PET imaging for amyloid is not required for diagnosis, which will be made on clinical grounds

2. Currently receiving a stable dose regimen of donepezil or another cholinesterase inhibitor for treatment of AD. Subjects must be receiving a stable dose of a cholinesterase inhibitor for at least 56 days prior to their baseline visit. Doses of these drugs may not be changed during the trial.
    Note: Memantine is <u>not</u> permitted during the trial and must be discontinued at least 3 weeks prior to Baseline

3. Modified Hachinski Ischemia score $\leq$ 4.
4. Body mass index (BMI) $\leq$38 kg/m^2, inclusive, and body weight of >48 kg (105 pounds) at screening.
5. Female subjects must be at least two years post-menopausal (subjected reported menopausal status), surgically sterile (bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 6 months prior to first study drug administration), or willing to either (1) utilize hormonal contraception plus one barrier method or (2) use two barrier methods of contraception (e.g. diaphragm and spermicide) from initial screening until one month after taking the final dose. An intrauterine device (IUD) is considered a barrier method of contraception in this study. Male subjects must be willing to inform female partners of their participation in the study and must agree to use adequate contraceptive methods (vasectomy performed at least 6 months prior to first study drug administration, or use at least one barrier method of birth control) from initial screening until 1 month after taking the final dose.
6. Able to understand and comply with the study procedures, voluntarily agree to participate in this study, read the informed consent document, and provide written informed consent prior to start of any study-specific procedures If the subject is unable to read the consent form and provide written consent, a legally authorized representative of the subject may read and sign the informed consent and the subject must verbally assent to participation.
7. All subjects must have a caregiver who is willing and able to ensure compliance with study medications, visits, and study procedures.

6.3 Subject Exclusion Criteria

The following Exclusions apply to findings during Screening or at Baseline (Day 1):

1. Any medical or neurological condition (other than early stage AD) that might be a contributing cause to the subject's cognitive impairment, including prominent features of

Lewy body dementia, behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia.

2. No substantial concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden on imaging.
3. No evidence for another concurrent, active neurological disease, or a non-neurologic medical co-morbidity or use of medication that could have a substantial effect on cognition.
4. Clinically significant major psychiatric illness during the past 6 months, as determined by the Investigator.
5. History of unstable angina, myocardial infarction, chronic heart failure, or clinically significant conduction abnormalities during the past year.
6. Clinically significant liver or renal disease, defined as creatinine clearance <30 mL/min at screening.
7. Clinically significant abnormality, in the Investigator's judgment, in hematology, chemistry, or urinalysis.
8. Positive serology results for hepatitis B surface antigen (HbsAg) or hepatitis C virus (HCV). HCV subjects who have been treated and are now RNA negative are eligible to participate.
9. Abnormal liver function test at the Screening Visit (aspartate aminotransferase or alanine aminotransferase >2 × the upper limit of normal [ULN], or total bilirubin >1.7 × ULN, based on appropriate age and gender normal values). Subjects with Gilbert's syndrome are eligible to participate despite elevated bilirubin. . Subjects may be re-screened for these tests once.
10. Marked hypotension (systolic blood pressure [BP] <90 mmHg or diastolic BP <50 mmHg) or hypertension (systolic BP >160 mmHg or diastolic BP >100 mmHg) based on sitting values. Out-of-range results may be repeated once at Screening and at Baseline, if needed. Eligibility must be confirmed at Baseline.
11. Marked bradycardia (heart rate <45 beats per minute [bpm]) or tachycardia (heart rate >115 bpm) based on supine ECG values. Out-of-range results may be repeated once at Screening. Eligibility must be confirmed at Baseline.
12. Presence of any clinically important conduction abnormality(ies) as assessed by Investigator on ECG, or evidence of long QT syndrome based on supine ECG values obtained at Screening, or history of long QT syndrome based on supine ECG values. Clinically important out-of-range results may be repeated once. Eligibility must be confirmed at Baseline.
13. Active gastric or duodenal ulcers or other diseases of the gastrointestinal tract that could interfere with absorption of study drug. Note: Subjects with a history of appendectomy or cholecystectomy may be enrolled, as may subjects with gastric bypass, gastric sleeve, of controlled inflammatory bowel.
14. Active acute or chronic infectious diseases that would interfere with subject's participation in the study.
15. Patients who cannot discontinue the following centrally active medications that might interfere with cognitive assessments <u>are excluded</u>. These include:
    a. Anticonvulsants
    b. Memantine
    c. Antipsychotic drugs, tricyclic antidepressants, gabapentin, and pregabalin
    d. Stimulants including modafinil
    e. Daytime use of benzodiazepines (bedtime use of benzodiazepines is permitted)

Note: The following medications are permitted provided the dosage and dose regimen have been stable for 2 months and remain stable throughout the study:

a. Cholinesterase inhibitors
b. Antidepressants other than tricyclics, including SSRIs, SNRIs, and bupropion
c. Beta-blockers
d. Hypnotics for sleep, including benzodiazepines, non-benzodiazapines (Ambien, Lunesta), antihistamines, hydroxyzine and trazadone. Other medications that are often used for sleep such as mirtazapine and quetiapine are not permitted.
e. Benadryl (diphenhydramine) and other sedating antihistamines are permitted only at bedtime for night time sleep management.

16. Patients who cannot discontinue strong CYP450 2D6 and 3A4/3A5/3A7 enzyme inducers at least 14 days prior to the first dose of study drug are excluded. Specifically, this includes rifampin, barbituates, and carbamazepine. CYP450 2D6 and 3A4/3A5/3A7 inhibitors are permitted.

    Note: Other prescription or non-prescription drugs necessary for the patient's welfare, such as antihypertensive or cholesterol lowering agents are allowed, if, in the Investigator's judgement, they would not interfere with the study medication or the cognitive testing.

17. A suicidal ideation intensity score of 3 or higher per screening Columbia Suicide Severity Rating Scale (C-SSRS) assessment on Day 1 (Baseline) and/or any suicidal behavior within the past 3 months.
18. History of chronic alcohol or other substance abuse, including marijuana, within the previous year prior to the Screening visit (per the current edition of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition: DSM-5), or regular (daily) consumption of alcohol exceeding two bottles of beer, or the equivalent amount of other forms of alcohol (1 serving = 12 oz beer, 5.0 oz wine, or 1.5 oz distilled spirits).
19. Inability or unwillingness to comply with the protocol, including performing the cognitive function tests, or likely inability to complete the study.
20. Participation in other clinical studies involving investigational drug within the previous 30 days prior to the Screening Visit. Participation in other clinical trials of monoclonal antibody products requires a 90-day wash out period prior to the Screening Visit.
21. Donation of blood within 4 weeks, or blood products within 2 weeks, prior to first study drug administration.
22. History of clinically significant drug allergy that includes symptoms such as shortness of breath, rash, or edema.
23. Clinically significant B12 deficiency based on clinical diagnosis within 12 months prior to Screening. Participants on stable replacement therapy for a minimum of 3 consecutive months immediately prior to Screening may be included.

6.4 Subject Withdrawal

All subjects have the right to withdraw from this study at any time. In addition, it is the right of the Investigator to remove subjects from the study as a result of adverse reactions, a protocol violation, or non-compliance, or any other reason. Subjects must be discontinued for the following reasons:

- Subject withdraws consent or requests discontinuation from the study for any reason;
- Occurrence of a medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol as determined by the Investigator;
- Any serious adverse event (SAE), clinical significant adverse event, severe laboratory abnormality, concomitant illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject;
- Pregnancy;
- Requirement for prohibited concomitant medication;
- Termination of the study by the Sponsor or the regulatory authority.

Should a subject withdraw after administration of BPN14770 (or placebo), or should the Investigator decide to withdraw the subject, all efforts will be made to complete and report the protocol-stipulated observations up to the time of withdrawal. Week 13 procedures (see Section 10.3 Week 13) and Section 16.1 Schedule of Study Assessments) will be completed at the time of the subject's withdrawal and an explanation provided as to why the subject is withdrawing or being withdrawn from the study.

In a case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's medical records.

The Investigator must document the primary reason for discontinuation of a study subject on the appropriate case report form (CRF). If the reason for withdrawal is a clinical AE, monitoring will continue until the AE resolves or the Investigator assesses the AE as chronic and stabilized.

6.5 Replacement of Subjects

Subjects who do not meet eligibility criteria at Baseline will not be randomized and will be considered a screen failure. Subjects who withdraw from the study for any reason will not be replaced.

7 TREATMENT OF SUBJECTS

7.1 Treatment Arms

In this randomized, double-blind, placebo controlled, 3-arm, parallel group study, 255 subjects will be assigned to receive one of three treatments via balanced randomization (1:1:1). Randomization will occur separately within each ApoE4 stratum (presence/absence of ApoE4 isoform) to ensure similar numbers of ApoE4 positive subjects are present in each treatment group. The three treatments are:

A. BPN14770 10mg, twice-daily

B. BPN14770 25mg, twice-daily

C. Matched placebo, twice daily

7.2 Study Medications

The 10 mg and 25 mg BPN14770 capsules and placebo capsules intended for use in this Phase 2 clinical trial are manufactured by Catalent, Inc. and will be packaged, labeled, and shipped for clinical use to sites by Sherpa Clinical Packaging (San Diego, CA).

The 10 mg and 25 mg BPN14770 capsules are manufactured using a wet granulation process. The same granulation is used to manufacture both strengths of capsules by adjusting the amount of granulation. The appropriate amount of granulation is blended with additional excipients to provide a homogeneous blend. The blend is then filled into hydroxypropyl methylcellulose (HPMC), size 1, opaque white/opaque white capsules. The capsules are packaged as 34-count in 60 cc, white, high-density polyethylene (HDPE), round bottles with 33 mm, with white polypropylene ribbed caps; 12-count bottles are similarly packaged. Over the course of the study, each subject will receive six 34-count bottles and one 12-count bottle. The container-closure system is labeled with a study-specific label and stored at controlled room temperature (20ºC – 25ºC) in a secured location (locked) with access restricted to authorized personnel only. Storage temperature will be monitored and recorded.

BPN14770 placebo capsules are manufactured, packaged, labeled and stored similarly to the active capsules.

7.3 Drug Accountability

The Investigator or designated study personnel is responsible for keeping accurate records of the study drugs (and other components) used in this study. These records should include documentation of receipt, inventory, and disposition to subject. The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and any unique code numbers assigned (if applicable).

The study monitor will review study drug records periodically during the conduct of the study.

At the end of the study, all partial and empty containers must be returned to the Sponsor or, if requested by the Sponsor, destroyed at the site according to standard operating procedure (SOP). Records of destruction of study drug at the site must include bottle identifying information and number of capsules in each bottle. All documentation is to be filed in the Pharmacy Manual.

In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel when handling study drug.

7.4 Blinding

This is a randomized, double-blind study, meaning that neither site staff nor subject will know what the subject is receiving.

Randomization codes for a specific subject will be available to the Investigator or designee for use in case of an emergency code break requirement. Confirmation of release of the unblinded treatment designation will be required by the Sponsor. The PI or designee will be responsible for maintaining the blind, consistent with protocol design, throughout the study, except in the case of an emergency code break.

The Investigator will be required to notify the Sponsor in the event of any breaking of the blind for any reason. Blinding is not to be broken during the study unless considered necessary by the Investigator for emergency situations for reasons of subject safety. The Investigator should contact the Medical Monitor before breaking the blind. When the blind is broken, the reason must be fully documented.

The subjects, Investigator, and all other study personnel involved with subject assessments will remain blinded to the actual treatment assignments of the subjects. The Investigator will be ultimately responsible for ensuring that the integrity of the blind is maintained throughout the study.

7.5 Assignment of Subjects to Treatment Arms

A randomization schedule will be generated by a statistician unassociated with the study execution prior to the start of the study. Subjects will be randomized on Day 1and receive their bottle of medication that same day.

7.6 Study Drug Administration

Study drug will be taken by mouth (PO) with water (at least 120 mL = 4 ounces) in the morning and before bed, approximately 12 hours apart, and at least 30 minutes prior to or 1 hour after meals. The first dose should be taken one hour after dinner on Day 1.

7.7 Prior and Concomitant Medications

All concomitant medication taken 14-days prior to the first dose of study drug (Day 1) and during the study through the Week 14 Follow-up Visit should be recorded with indication, daily dose, and start and stop dates of administration.

Subjects are required to be on a stable dosing regimen of donepezil or another cholinesterase inhibitor for at least 2 months, i.e., 56 days prior, to their Baseline visit. Doses of these medications may not change during the study.

Memantine is not permitted during the trial and must be discontinued at least 3 weeks (21 days) prior to Baseline. Subjects are required to discontinue all other centrally active medication, other than cholinesterase inhibitors, including psychotropic drugs, or other centrally active medications [e.g., CNS- penetrant beta blockers], and moderate to strong inhibitors or inducers of CYP3A4, CYP2D6, or other cytochromes) at least 14 days prior to the first dose of study drug (Treatment Period 1, Day 1) and during the study (Follow-Up Visit). For specific medications, refer to Subject Exclusion Criteria, Exclusions # 15 and #16.

Benadryl (diphenhydramine) and other sedating antihistamines are permitted only at bedtime for night time sleep management. Hypnotics for sleep, including benzodiazepines, non-benzodiazapines (Ambien, Lunesta), antihistamines, hydroxyzine and trazadone are permitted.

Other medications that are often used for sleep such as mirtazapine and quetiapine are not permitted.

Other prescription or non-prescription drugs such as antihypertensive or cholesterol lowering drugs are allowed, if, in the Investigator's judgement, they would not interfere with the study medication or the cognitive testing.

Subjects using over-the-counter herbal preparations, dietary supplements, or nutraceuticals including vitamins, minerals and calcium supplements at screening may continue with these treatments, but must not change dosages during the study. NSAIDs and acetaminophen are permissible.

7.8 Dietary Guidelines

There are no dietary restrictions. Subjects should follow their usual eating behaviors.

7.9 Lifestyle Guidelines

There no lifestyle restrictions or guidelines associated with this study.

8 STUDY PROCEDURES AND ASSESSMENTS

8.1 Informed Consent

Informed consent must be obtained prior to the subject entering into the study and before any protocol-directed procedures are performed.

8.2 Medical /Surgical History

Medical/Surgical history will be recorded at the Screening Visit as specified in Section 10.2. Subject eligibility will be evaluated to determine all inclusion and none of the exclusion criteria are met. The Investigator will inquire with the subject on Day 1 (Baseline, prior to randomization) to determine if there have been any changes in the subjects's health affecting eligibility or requiring an update to their medical and surgical history.

8.3 Demographics and Social History

Demographics (sex, ethnicity, race) and social history (tobacco, alcohol, and/or drug use) will be recorded at the Screening Visit as specified in the Schedule of Assessments.

8.4 Physical Examination (Full and Abbreviated)

The full physical examination will be conducting at the Screening and Week 13 (or Early Termination) Visits as specified in the Schedule of Assessments and will include:

- General appearance
- Skin
- Eyes, ears, nose, and throat (EENT)
- Head/neck

- Extremities
- Musculoskeletal examination
- Respiratory examination
- Cardiovascular assessment including rhythm and presence of cardiac abnormalities
- Abdominal examination
- Neurologic examination to record the presence of abnormalities in mental status, motor, and sensory function, and
- Any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences

An abbreviated physical examination will be conducted at on Day 1 (Baseline) and Week 14 Follow-Up and will include:

- General appearance
- Skin
- Extremities
- Respiratory examination
- Cardiovascular assessment including rhythm and presence of cardiac abnormalities
- Abdominal examination

Significant findings prior to the start of dosing will be recorded on the Medical History page of the eCRF. Only changes from baseline physical examination findings that meet the definition of a treatment-emergent AE will be recorded as an AE; any changes occurring between Screening and Baseline require an update to medical history.

8.5 Height, Weight, Body Mass Index

Body weight and height are to be measured at Screening, and body weight will be repeated at Baseline and the Week 13 visit as specified in the Schedule of Assessments. Subjects will wear indoor clothing and remove their shoes prior to the measurements. Body Mass Index (BMI) will be calculated and recorded.

8.6 Vital Signs

Vital signs (pulse rate, blood pressure, respiration rate, and temperature) will be measured at Screening, during the Treatment Visits, and Follow-Up as specified in the Schedule of Assessments.

Blood pressure and heart rate will be measured using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, blood pressure may be measured manually. Blood pressure at the Screening Visit should be obtained in both arms and the arm with the higher value should be used for ongoing monitoring throughout the rest of the study. For each subject, measurement on the same arm (right or left) using the same method (either automated or manual) should occur throughout the study. All blood pressure measurements should be obtained with the subject in the sitting position, after the subject is at rest for 5 minutes.

For purposes of qualifying any given subject for study participation based on Inclusion/Exclusion Criteria, out-of-range results may be repeated once at Screening and once at

Baseline. Eligibility must be confirmed at Baseline. Additional vital signs measurements may be performed as deemed medically necessary by the Investigator.

8.7 Electrocardiograms

Single 12-lead ECGs will be performed at every clinic visit except the Week 14 Follow-up Visit, as Visit as specified in the Schedule of Assessments.

ECGs should be obtained after the subject has been resting comfortably in a supine position for approximately 5 minutes. ECGs will be collected prior to blood collection whenever possible.

ECGs will be assessed locally for eligibility determinations and safety, and electronic tracings will also be sent to a central reader for review. All ECG traces will be kept as source data.

For purposes of qualifying any given subject for study participation based on Inclusion/Exclusion Criteria, the ECG may be repeated once in the case of clinically significant out-of-range results. The ECG may be repeated immediately or later within the visit.

8.8 Laboratory Assessments

Appendix 16.2 Clinical Laboratory Analytes provides a list of the clinical laboratory tests that will be performed according to the collection schedule provided in the Schedule of Assessments.

Blood samples for chemistry, hematology and lipid testing and urine samples will be collected in accordance with acceptable laboratory procedures. Blood samples for chemistry, hematology and lipid testing performed on Day 1 and Week 13 require an 8 hour fast and will include glucose testing; samples obtained at all other visits do not require fasting and will not include glucose or lipid testing.

A central laboratory will be used to analyze the clinical laboratory samples.

8.9 Management of Abnormal Clinical Laboratory Tests

It is the Investigator's responsibility to review the results of all lab tests as they become available and to document their review by signing and dating the lab report. For each lab test outside of the laboratory normal range, the Investigator must ascertain if this is a clinically significant change from baseline for the individual subject. This determination does not necessarily need to be made the first time an abnormal lab is observed. The Investigator may repeat the lab test or request additional tests to verify the results of the original lab test.

All clinically significant laboratory abnormalities occurring during the study that were not present at baseline should be reported as AEs, and followed and evaluated with additional tests if necessary until determination of the underlying cause or adverse event resolution.

8.10 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a prospective assessment instrument that directly classifies suicidal ideation and behavior into 11 preferred categories.[8] The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

The C-SSRS will be conducted Screening, Baseline, Week 1 and Week 4, as specified in the Schedule of Assessments.

At Screening, a subject is ineligible for the study if the subject scores a suicidal ideation intensity of 3 or higher (per the C-SSRS) or has exhibited any suicidal behavior within the past three months.

If a subject scores an intensity of 3 or higher for suicidal ideation (per the C-SSRS) during the Treatment and Follow-Up Visits a suicide risk assessment must be completed by the investigator. If a subject scores an intensity of 3 or higher for suicidal ideation and has any suicidal behavior, the subject will be discontinued from the study and referred for psychiatric evaluation.

8.11 Additional Safety Measures

Subjects and caregivers will be instructed to inform the study physician and/or research personnel of any AEs that occur at any time during the study.

Procedures will be completed as specified in this protocol unless contraindicated due to a reported AE.

If, in the judgement of the Investigator, additional testing is required to assess an adverse event or otherwise clinically significant event, this testing should be discussed first with the sponsor unless needed urgently.

8.12 Cognitive Battery

At Screening, the Repeatable Battery for the Assessment of Neurological Status-Delayed Memory Index (RBANS DMI), Mini Mental State Exam (MMSE), Clinical Dementia Rating (CDR), and the Modified Hachinski Ischemia Scale (MHIS) will be used to assess the cognitive status of the subject.

During the Baseline Visit, the subjects will be reassessed on RBANS and MMSE. Caregivers will also complete the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL).

The subjects will be assessed with the RBANS and MMSE instruments at Weeks 1, 2, 4, 8, and 13 during the treatment period. The investigator will also assess subjects using the CGI-I scale at Weeks 1, 2, 4, 8, and 13. Caregivers will be asked to complete the ADCS-ADL at Weeks 8 and 13.

Section 16.3 Cognitive Test Scales provides a summary description for each of the test in the cognitive battery to be assessed in this study.

8.13 Clinical Global Impression- Improvement

At the clinic visits during Weeks 1, 2, 4, 8, and 13, the Investigator will assess the degree of improvement in the subject with respect to their AD on a 1-7 point scale, where:

- 1=Very much improved
- 2= Much Improved
- 3= Minimally improved
- 4= No Change
- 5=Minimally worse
- 6= Much worse
- 7=Very much worse

8.14 Pharmacokinetic Assessment

8.14.1 Plasma Pharmacokinetic Samples

Blood samples for BPN14770 concentrations will be drawn during the clinic visits at Weeks 1, 4, 8 and 13. Samples will be drawn at the time of the clinic visit, with documentation of time of day testing was performed, and time of day of most recent dose of study medication.

Pharmacokinetic samples will be retained and may also be utilized subsequently for biomarker assessment. Blood samples (1 × 4 mL) will be collected in Vacutainer tubes containing K_2-EDTA as a preservative.

8.14.2 Processing and Shipment of Pharmacokinetic Samples

Blood samples will be kept on wet ice from the time of collection and throughout processing until frozen.

8.14.2.1 Pharmacokinetic Sampling

Blood samples will be centrifuged at approximately 3000 rpm for 10 minutes at 4°C. If a chilled centrifuge is not available, it is acceptable to keep sample on wet ice prior to centrifugation and use an ambient centrifuge to process the sample. The resulting plasma samples will be harvested and transferred into appropriately labeled polypropylene screw-cap tubes. Pharmacokinetic samples will be placed in a freezer at -70°C within 60 minutes of the blood draw. If a clinical site does not have a -70°C or -80°C freezer, it is acceptable to use a -20°C freezer, but samples stored must be shipped for storage with the laboratory vendor within 2 weeks of collection. Samples will remain frozen until assayed. A more detailed description of plasma sample preparation requirements may be provided by the analytical laboratory and will supersede those provided in this protocol. Appropriate documentation will be placed in the study master file at the Clinical Site.

The samples will be transferred to the central laboratory for storage after completion of the study or at mutually agreed upon time points during the clinical conduct of the study. Prior to shipment, the samples will be appropriately packed in a Styrofoam cooler containing dry ice. Sufficient dry ice will be added to ensure that the samples will remain frozen for at least 72 hours for remote shipments. The shipment will be accompanied by documentation containing the following information: name of the study drug product, protocol number, number of subjects, and number of samples included in the shipment.

All frozen pharmacokinetic samples will be shipped with accompanying documentation (Study ID BPN14770-CNS-201 / 38019XX045; Site Number: XXX) to:

Eurofins Central Laboratory Lancaster
Eurofins Central Laboratory, LLC.
2430 New Holland Pike
Building D, Suite 100
Lancaster PA 17601
United States of America
Tel: +1 717 556 3886

The central lab will ship the PK samples to the analytical lab (CMIC, Inc., Hoffman Estates, IL) at mutually agreed upon time points during the study. PK samples will be stored in a freezer at -80°C both the central and analytical lab.

8.14.2.2 Metabolite Sampling at Week 13 (select sites)

At approximately 5-6 study sites, an additional sample of plasma spun for PK analysis will be aliquoted for assessment of BPN14770 metabolites at Week 13. Instructions for storing and shipping the plasma vials for metabolite assessment will be provided to the select participating sites.

8.14.3 Analytical Methods

Plasma samples for standard PK and metabolites will be analyzed for BPN14770 using validated assays.

Samples will only be analyzed for subjects whose treatment included administration of BPN14770. Samples will not be analyzed when matching placebo for BPN14770 was administered.

8.14.4 Plasma Pharmacokinetic Parameters

BPN14770 plasma concentration levels will be presented in tabular form by dose level and week, and a listing of all subjects' data will be provided. Metabolite data will be analyzed and reported separately from the clinical study data.

8.15 Biomarker Assessments

Blood samples for future biomarker assessments will be drawn during the clinic visits at Baseline and Weeks 1, 4, 8 and 13. Samples will be drawn at the time of the clinic visit, with documentation of the date and time the samples were obtained.

Blood samples will be collected in Vacutainer tubes (2 x 4 mL) containing K2 EDTA as a preservative. Blood samples will be kept on wet ice from the time of collection and throughout processing until frozen.

One tube will be centrifuged at approximately 3000 rpm for 10 minutes at 4°C. If a chilled centrifuge is not available, it is acceptable to keep sample on wet ice prior to centrifugation and use an ambient centrifuge to process the sample. The resulting plasma sample will be harvested

and transferred evenly into two appropriately labeled polypropylene screw-cap tubes. The other tube will be retained as whole blood. The plasma and whole blood tubes for biomarker use will be placed in a freezer at -70°C within 60 minutes of the blood draw. If a clinical site does not have a -70°C or -80°C freezer, it is acceptable to use a -20°C freezer, but samples stored must be shipped for storage with the laboratory vendor within 2 weeks of collection. These biomarker samples will be retained and may be utilized subsequently for biomarker assessment.

9 EVALUATION AND REPORTING OF ADVERSE EVENTS

9.1 Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

Adverse events, which include abnormal and clinically significant clinical laboratory test variables, will be monitored and documented from the time Informed Consent until study participation is complete (the Follow-up Visit). Subjects should be instructed to report any adverse event that they experience to the Investigator. Any medical condition present prior to consent should be recorded in medical history. Beginning with the signing of the informed consent until the time of the first dose of study drug, investigators should make updates to source records to document any pre-existing medical condition or signs or symptoms that change in severity, frequency, or seriousness in the medical history; if the subject is subsequently randomized, these occurrences will be reported as adverse events that began prior to dosing. Serious adverse events that occur prior to the first dose of study drug should be reported similarly, except that an SAE report will be completed regardless of whether the subject is randomized..

Beginning with the first dose of study drug, investigators should make an assessment for adverse events at each visit and record all adverse events, non-serious and serious, on the appropriate adverse event eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate adverse event on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an adverse event, not the procedure. Concomitant procedures should be recorded as such on the appropriate eCRF.

Clinically significant abnormal laboratory values or other examinations (e.g., ECG) that are detected after the first dose of study drug and worsen during the study should be reported as adverse events. An abnormal laboratory result that is not verified by repeat testing does not necessitate reporting as an adverse event. The Investigator will exercise his or her medical,

scientific, and clinical judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an adverse event.

Treatment of any adverse reactions will be evaluated and managed by a physician.

9.2 Definitions

9.2.1 Adverse Drug Reaction

For adverse events with a causal relationship to study drug, follow-up by the Investigator will be required until the event or its sequelae resolve or stabilize to a level acceptable to the Investigator.

9.2.2 Unexpected Adverse Event/ Unexpected Adverse Drug Reaction

An unexpected AE/unexpected suspected adverse reaction is an AE or suspected adverse reaction that is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

9.2.3 Serious Adverse Events

An adverse event or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- NOTE: An adverse event or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;
  NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.
  NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical

judgment, they may jeopardize the subject 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 hospitalizations, or the development of drug dependency or drug abuse.

9.3 Assessment of Adverse Events by the Investigator

9.3.1 Causality/Relatedness

The relationship of an adverse event to the administration of the study drug is to be assessed by the Investigator according to the following definitions:

Not Related (unlikely related, unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and/or another cause (e.g., medical history, concomitant drugs, therapies, and complications) is suspected.

Related (possibly related, related) – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (e.g., medical history, concomitant drugs, therapies, and complications) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drug. This means that there are facts (evidence) or arguments to suggest a causal relationship. The following factors should also be considered:

- The temporal sequence from study drug administration - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant diseases (medical history) - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

- Concomitant drug - The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drug - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.3.2 Severity

The Investigator is responsible for assessing the severity (intensity) of each adverse event as mild, moderate, or severe according to the following definitions:

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

It should be noted that a severe AE need not be serious and that a serious adverse event (SAE) need not, by definition, be severe.

9.3.3 Adverse Event Monitoring and Follow-up

Subjects who experience AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. In accordance with good medical practice, all AEs must be followed to satisfactory resolution or stabilization of the event(s), or, if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor. Any actions taken and follow-up results must be recorded either on the appropriate page of the CRF or in a follow-up letter to the Sponsor, as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution or stabilization of the event(s).

Subjects who have non-serious AEs that are ongoing at study completion or study withdrawal must be followed until resolution of the AEs or for 30 days after the last dose of study drug, whichever comes first. Subjects who have an ongoing SAE at study completion or study withdrawal must be followed until the event resolves or the event or sequela stabilizes.

9.3.4 Reporting Serious Adverse Events

From the time of informed consent until 30 days following the last administration of study drug The Investigator or designee will notify the sponsor contact and clinical research organization (CRO) within 24 hours after the SAE detection, observation, or report of occurrence (regardless of the relationship to study treatment). The Sponsor and the CRO medical monitor contact information for SAE reporting is provided below.

[redacted]
Tetra Discovery Partners, Inc.
Email: [redacted]
Office: [redacted]
24-hour contact number (cell): [redacted]

and

[redacted]
Syneos Health
Email: [redacted]
24-hour contact number (cell): [redacted]

The final SAE report must contain the following information, but the event may be initially reported without complete data, if necessary:

- Study name/number
- Study drug
- Investigator details (name, phone, fax, e-mail)
- Subject number (randomization number)
- Subject initials
- Subject demographics (age, date of birth, sex, weight)
- Clinical event
  - Description
  - Date of onset
  - Treatment (drug, dose, dosage form)
  - AE relationship to study drug
  - Action taken regarding study drug in direct relationship to the AE
- If the AE was fatal or life-threatening
- Cause of death (whether or not the death was related to study drug)
- Autopsy findings (if available)

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must update the Sponsor and submit any supporting documentation (e.g., subject discharge summary or autopsy reports).

Any new SAE that occurs within one month after the study period and is considered to be possibly related to the investigational product should be recorded and reported immediately to the Sponsor.

All serious event reporting will adhere to Code of Federal Regulations (CFR), specifically 21 CFR 312.32 (7- and 15-day alerts) for Investigational New Drugs (IND). The clinical research site will be responsible for reporting SAEs to the Institutional Review Board (IRB) per FDA regulations. The Sponsor will be responsible for reporting and processing any SAEs to the FDA or other applicable regulatory agency.

9.4 Data Safety and Monitoring Committee

An independent data and safety monitoring board (DSMB) will provide safety oversight for this study. The DSMB will consist of two qualified MDs and one statistician. The DSMB will review standard safety data approximately every four (4) months, based on enrollment rate. A

DSMB charter will be developed to further outline the DSMB responsibilities and the desired listings, summaries and analyses.

9.5 Reports of Pregnancy

If a subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days of discontinuing study drug, the Investigator should report the pregnancy to the Sponsor within 24 hours of being notified. Investigator will complete then forward the Exposure In Utero form to the Sponsor.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and early termination study procedures will be performed.

The subject should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

10 STUDY PROCEDURES AND ASSESSMENTS BY VISIT

10.1 Schedule of Assessments

The study timetable in the Schedule of Assessments shows the schedule of planned study procedures. Every effort should be made to adhere to this procedure schedule.

10.2 Screening (Day -28 to Day -1)

The study will consist of a Screening period of 28 days or less, unless additional time is required for washout of concomitant medications.

Each potential study participant will have the following assessments completed by the Investigator or designee up to 28 days prior to the first dose of study medication:

- Obtain informed consent;
- Obtain medical/surgical history;
- Obtain demographics and social history (tobacco, alcohol, and/or drug use);
- Obtain prior/concomitant medication use;
- Obtain vital signs;
- Obtain height and weight;
- Conduct full physical exam;
- Conduct single ECG;
- Serology (HbsAg, HCV)
- Serum pregnancy (females of childbearing potential , even if using birth control)
- Draw blood samples for Chemistry and Hematology (fasting or nonfasting);
- Collect urine for safety urinalysis;
- ApoE4 testing, if not in medical history;

- Conduct C-SSRS assessment;
- Conduct RBANS, MMSE, CDR and MHIS evaluations
- Evaluate inclusion and exclusion criteria.

10.3 Baseline (Day 1)

Subjects will return to the clinic for the Baseline Visit following successful screening.

Prior to Randomization

The following assessments will be completed:

- Complete urine pregnancy test (females of childbearing potential , even if using birth control)
- Conduct abbreviated physical exam;
- Obtain vital signs;
- Obtain weight;
- Draw blood samples for Chemistry, Hematology and Lipids (following a minimum 8-hour fast);
- Draw blood sample for biomarkers (no PK sample drawn);
- Collect urine for safety urinalysis;
- Conduct ECG (single);
- Conduct C-SSRS assessment;
- Conduct RBANS and MMSE evaluations;
- Conduct ADCS-ADL assessment;
- Record any updates to medical/surgical history;
- Record any updates to prior/concomitant medication use;
- Assess and record and adverse events;
- Re-evaluate inclusion and exclusion criteria based on preceding activities; and
- Verify continued eligibility.

If subject remains eligible for the study:

- Randomize subject;
- Dispense study medication

10.4 Week 1 (Day 7 ± 2)

The following assessments will be completed at the Week 1 visit:

- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for Chemistry and Hematology (fasting or nonfasting);
- Draw blood samples for pharmacokinetic analysis and biomarkers;
- Collect urine for safety urinalysis;
- Conduct C-SSRS assessment;
- Conduct RBANS, MMSE, and CGI-I evaluations;
- Record pill count remaining in bottle to assess dosing compliance;

- Record any updates to concomitant medication use; and
- Assess and record and adverse events.

10.5 Week 2 (Day 14 ± 2)

The following assessments will be completed at the Week 2 visit:

- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for Chemistry and Hematology (fasting or nonfasting);
- Conduct RBANS and MMSE evaluations;
- Assess CGI-I;
- Collect study medication and record pill count remaining in bottle to assess dosing compliance;
- Dispense study medication;
- Record any updates to concomitant medication use; and
- Assess and record and adverse events.

10.6 Week 4 (Day 28 ± 2)

The following assessments will be completed at the Week 4 visit:

- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for Chemistry and Hematology (fasting or nonfasting);
- Draw blood samples for pharmacokinetic analysis and biomarkers;
- Collect urine for safety urinalysis;
- Conduct C-SSRS assessment;
- Conduct RBANS and MMSE evaluations;
- Assess CGI-I;
- Collect study medication and record pill count remaining in bottle to assess dosing compliance;
- Dispense study medication;
- Record any updates to concomitant medication use; and
- Assess and record and adverse events.

10.7 Week 8 (Day 56 ± 3)

The following assessments will be completed at the Week 8 visit:

- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for Chemistry and Hematology (fasting or nonfasting);
- Draw blood samples for pharmacokinetic analysis and biomarkers;
- Conduct RBANS and MMSE evaluations;
- Conduct ADCS-ADL assessment;

- Assess CGI-I;
- Collect study medication and record pill count remaining in bottle to assess dosing compliance;
- Dispense study medication;
- Record any updates to concomitant medication use; and
- Assess and record and adverse events.

10.8 Week 13 (Day 91 ± 3)

The following assessments will be completed at the Week 13 visit:

- Conduct full physical exam;
- Collect weight;
- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for:
    - Chemistry, Hematology and Lipids (following a minimum 8-hour fast);
    - Pharmacokinetic analysis and biomarkers;
    - Serum pregnancy test (females of childbearing potential , even if using birth control);
- Collect urine for safety urinalysis;
- Conduct RBANS, MMSE and CDR evaluations;
- Conduct ADCS-ADL assessment;
- Assess CGI-I;
- Conduct C-SSRS assessment;
- Collect study medication and record pill count remaining in bottle to assess dosing compliance;
- Record any updates to concomitant medication use; and
- Assess and record and adverse events.

10.9 Week 14 Follow-up Visit (Day 98 ± 3)

The following assessments will be completed at the final follow up visit at Week 14:

- Obtain vital signs;
- Conduct abbreviated physical exam;
- Assess and record AEs;
- Record any updates to concomitant medication use; and
- Record final subject disposition.

10.10 Early Termination

It is hoped that all subjects can be followed through to the conclusion of the study at Week 14. However, if an early termination occurs, the Week 13 procedures should be completed at the time of the subject's withdrawal (if possible) and an explanation provided as to why the subject

is withdrawing or being withdrawn from the study. Procedures to be completed early termination:

- Conduct a full physical exam;
- Collect weight;
- Collect vital signs;
- Conduct ECG (single);
- Draw blood samples for:
  - Chemistry, Hematology and Lipids (following a minimum 8-hour fast);
  - Pharmacokinetic analysis;
  - Serum pregnancy test (females of childbearing potential, even if using birth control);
- Collect urine for safety urinalysis;
- Conduct RBANS, MMSE, and CDR evaluations;
- Conduct ADCS-ADL assessment;
- Conduct C-SSRS assessment;
- Collect study medication and record pill count remaining in bottle to assess dosing compliance;
- Record any updates to concomitant medication use;
- Assess and record and adverse events; and
- Record final subject disposition.

11 PLANNED STATISTICAL METHODS

11.1 Sample Size

The BPN14770-CNS-201 study will enroll 255 subjects (85 per treatment arm), in anticipation of evaluating at least 240 subjects (80 per treatment). The Primary Efficacy Outcome measure will be change from baseline at Week 13 for the Repeatable Battery for the Assessment of Neurological Status - Delayed Memory Index (RBANS DMI).

The normalized mean of the RBANS DMI is 100, with an SD of 15, and the test-retest reliability is 0.80 with no practice effects using alternate versions of the test.[9] RBANS DMI was used in a recent natural history study of Mild Cognitive Impairment (MCI) due to probable AD.[16] In the large amnestic MCI sample (81 subjects), the mean was 73.4 with a SD of 16.5 in a normal distribution. Performance of healthy, age-matched controls was a mean of 101.4 with a SD of 14.4 (81 subjects) yielding estimates of the standard deviation for the DMI from 14.4-16.5. Therefore, the power analysis is based on the assumption that the standard deviation of the response variable is 16.

The power of the proposed study is driven by the assumed difference between BPN14770 25mg (higher dose) and placebo. Based on randomization of 80 patients per group into the parallel-design study, the probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between BPN14770 25 mg and placebo is

7.15 units. Using the standardized mean difference (SMD) to estimate effect size,[17] a change of 7.15 units on the DMI score is an effect size of 0.45.

Table 1 provides sample size estimates for 80 percent and 90 percent probability that the study will detect a treatment difference at a two-sided 0.05 significance level assuming the standard deviation of the DMI is 16.

Table 1 Clinical Sample Size (1:1 Active + Placebo) Based on Effect Size (Change From Baseline) And Desired Power

	Number of Subjects Per Group Based on Desired Effect Size (SMD)					
Standardized Mean Difference (SMD)	0.3	0.35	0.4	0.45	0.5	0.75
RBANS DMI change (M1-M2)	4.8	5.6	6.4	7.2	8	12
Number of Subjects (Power 0.8)	176	130	100	79	64	29
Number of Subjects (Power 0.9)	235	173	133	105	86	39

For comparison, a donepezil study reported by Seltzer et al., 2004, randomized a total of 153 subjects (2:1 active vs placebo) and reported treatment benefit at a significance level of 0.03 after 12 weeks of treatment.[18] In a larger study of mild-to-moderate AD patients, the effect size of donepezil reported by Rogers et al. 1998 was 0.4,[19] so the assumption of an effect size of 0.45 for BPN14770 in a milder, early AD population, using a sensitive outcome measure, is reasonable.

Therefore, based on clinical trials of donepezil in a similar population, the proposed sample size will provide adequate power to detect a clinically and statistically significant difference of BPN14770 treatment in early AD.

11.2 Demographics

Summary statistics [number (n), mean, standard deviation (SD), minimum, median, and maximum] will be tabulated for the observed values for all continuous demographic parameters. Frequencies and percentages will be tabulated for categorical data.

11.3 Analysis Populations

The primary efficacy population will be the intent to treat (ITT) efficacy population, which will include all randomized subjects who received at least one dose of treatment and returned for at least one follow-up visit. The per protocol (PP) population (randomized subjects who received at least one dose of treatment and returned for at least one follow-up visit with no significant protocol violations) and the completers (CP) population (randomized subjects who completed all 13 weeks of treatment with no significant protocol violations) will be used to evaluate the robustness of the ITT results.

The Safety population will include all randomized subjects who received at least one dose of study treatment.

11.4 Efficacy: Cognitive Testing Analysis

Change from baseline will be calculated for the primary and secondary efficacy parameters at each time point and descriptive statistics provided for each time point. Summary plots of these data will also be provided. For RBANS DMI and total score, MMSE score, and ADCS-ADL total score, pairwise differences in change from baseline between the treatment groups (10 mg vs 25 mg BPN14770, 10 mg BPN14770 vs Placebo, 25 mg BPN14770 vs Placebo) will be assessed using an analysis of covariance (ANCOVA) model that includes baseline as a covariate and factors for week, site and treatment and the interaction term for week and treatment ; the pairwise differences will be assessed at each time point. CDR sum of boxes will be analyzed in the same manner.

Change from baseline in the other RBANS index scores (immediate memory, visuospatial/constructional, attention, language) will be summarized by time point, with descriptive statistics provided.

The composite endpoint will be based on the AD Composite Score (ADCOMS), a composite clinical outcome for prodromal Alzheimer's disease trials.[20] The composite endpoint and analysis model will be fully specified in the statistical analysis plan.

The efficacy analyses will be performed on the ITT, PP and CP analysis populations.

Supplemental analyses assessing treatment effect relative to severity of disease based on baseline MMSE score may also be performed.

11.5 Safety Analysis

Safety analysis will be based on all subjects receiving at least one dose of study medication. Treatment emergent AEs will be summarized based on the frequency of AEs and their severity for all dosed subjects. All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment group and for the combined BPN14770 groups using preferred term and primary system organ class. Overall safety and tolerability will be assessed by clinical and/or statistical review of all safety parameters including adverse experiences, laboratory values, vital signs, physical exams, C-SSRS, and ECG data. General clinical and laboratory adverse events will be presented in frequency tables. Summary statistics (n, mean, SD, median, and range (minimum, maximum) will be tabulated for the observed values and the change (or percent change) from baseline for all continuous parameters for vital signs, ECG, and laboratory tests.

For each AE, the difference in incidence rates between each BPN14770 dose group will be compared to the placebo group using a Fisher’s exact test.

11.6 Pharmacokinetic Analysis

BPN14770 plasma levels will be presented in tabular form by study arm, dose level and subject.

12 DATA MANAGEMENT

12.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the CRA during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

12.2 Computer Systems

Data will be collected and processed using a validated EDC system. The system and procedures are designed in compliance with Title 21 of the Code of Federal Regulations (21 CFR Part 11).

12.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms.

12.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA for medical history and adverse events, and
- World Health Organization Drug Dictionary for prior and concomitant medications.

12.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

13 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

13.1 Ethical Conduct of the Study

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures that are described in the protocol and to conduct the study in accordance with the CFRs (21 CFR

§ 11, 50, 54, 56, and 312 Subpart D), which originate from the ethical principles laid down in the current revision of the Declaration of Helsinki, Good Clinical Practice (GCP), and the policies and procedures as outlined by the ethical requirements for IRB review and informed consent form.

The Investigator agrees to allow monitoring and auditing of all essential clinical study documents by the Sponsor or its authorized representatives and inspection by the FDA or other appropriate regulatory authorities. Monitoring and auditing visits by the Sponsor will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The Investigator will ensure proper implementation and conduct of the trial, including those study-related duties that are delegated to other appropriately qualified individuals. The Investigator will ensure that study staff cooperates with monitoring and audits and will demonstrate due diligence in recruiting and screening study subjects.

For this study and all studies conducted under an IND, the Investigator must sign and return a completed Form FDA 1572, "Statement of Investigator," to the Sponsor.

13.2 Institutional Review Board (IRB)

Before initiation of the study, the Investigator must obtain approval or favorable opinion of the research protocol, informed consent form, and any advertisement for subject recruitment from an IRB complying with the provisions specified in 21 CFR §56 and applicable pertinent state and federal requirements of each participating location including International Conference on Harmonization (ICH) and GCP guidelines.

Institutional review boards must be constituted according to the applicable laws. It is the responsibility of each investigational site to submit the protocol, Investigators' Brochure, subject informed consent, subject recruitment materials (if applicable), and other documentation as required by the IRB to their IRB for review and approval. A copy of the written approval must be provided to the Sponsor.

Sites must adhere to all requirements stipulated by their respective IRB. This includes notification to the IRB regarding: protocol amendments, updates to the subject informed consent, recruitment materials intended for viewing by subjects, IND Safety Reports, serious and unexpected AEs, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB, and submission of final summaries to IRB.

The Investigator must promptly inform his/her IRB of all SAEs or other safety information reported by the clinical site or the Sponsor.

13.3 Informed Consent

The informed consent form (ICF) and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, provisions specified in 21 CFR §50, and applicable pertinent state and federal requirements.

The Investigator, or a person delegated the responsibility by the Investigator, must ensure that each study subject (or legally acceptable representative) is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the subject has been informed of his/her rights to privacy. The Investigator or delegate will allow the subject (or legally acceptable representative) adequate opportunity to read the written informed consent and ask any questions. The Investigator will obtain written informed consent from each subject (or legally acceptable representative) before any study-specific activity is performed and should document in the source documentation that consent was obtained prior to any study-specific activity. If consent is signed by a legally authorized representative, the subject must provide verbal assent, which will be documented on the consent form. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB/EC and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

13.4 Study Monitoring

The role of the study monitor is to verify the rights and well-being of the subjects are protected, the data is accurate, complete, and verifiable from source documents, and the conduct of the study is in compliance with the protocol, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements.

To achieve this objective, the monitor's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: Clinical Protocol, Investigator's Brochure, eCRFs and procedures for their completion, informed consent process, management of investigational product, and the procedure for reporting adverse events such as SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-specific monitoring log and findings documented in a follow-up letter.

It is important that the Investigator and their relevant personnel are available during the monitoring visits and that sufficient time is devoted to the process.

13.5 Disclosure of Information

It is understood by the Investigator that the information and data included in this protocol is confidential and proprietary to the Sponsor, Tetra Discovery Partners, Inc. This information may

be disclosed to study personnel under the Investigator's supervision and the Institutional Review Board for the purpose of evaluating or conducting the study under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical trial, disclosed to any other person or entity, and/or published without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, the Investigator will give prompt notice to the Sponsor of any such disclosure.

The medical information and completed original CRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

13.6 Record Storage and Retention

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study product, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. **The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.**

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

13.7 Protocol Amendments and Deviations

Any amendments to the study protocol will be communicated to the Investigator by the Sponsor or authorized representative. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented only after it has been approved by the IRB, unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the Sponsor immediately and to the IRB within 5 working days.

13.8 Access to Source Documentation

The Sponsor (or the Sponsor's authorized representative) must have access to inspect all documents and records that are to be maintained by the Investigator, including, but not limited to, medical records (office, clinic, or hospital) for the subjects in this trial. These regulations also allow the Sponsor's records to be inspected by authorized representatives of the FDA or other regulatory authorities. The names and identities of all research subjects will be kept in strict confidence and will not appear on CRFs or other records that are provided to or retained by the Sponsor (or the Sponsor's authorized representative).

13.9 Financial Disclosure

Clinical Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

For this study, any personnel listed on the FDA 1572 will be required to provide financial disclosure information.

13.10 Publication Policy

Manuscript(s) and abstract(s) may only be prepared through cooperation between the Sponsor (or designee) and the study Investigator(s). The Investigator agrees not to publish or publicly present any results of the study without prior written consent of the Sponsor.

14 ADMINISTRATIVE INFORMATION

14.1 Sponsor

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301 Michigan Ave NE
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Phone: [redacted]

14.2 Clinical Research Organization

Syneos Health
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16 APPENDICES

16.1 Schedule of Assessments

	Screening	Baseline	Treatment					Follow-Up
	Days -28 thru Day 0	Day 1	Week 1	Week 2	Week 4	Week 8	Week 13[e]	Week 14
Visit Number	1	2	3	4	5	6	7	8
Target Study Day	---	1	7	14	28	56	91	98
Visit Window			±2	±2	±2	±3	±3	±3
Informed Consent	X							
Eligibility Criteria Confirmed	X	X						
Medical/Surgical History	X	X						
Demographics and Social History	X							
Full Physical Exam	X						X	
Abbreviated Physical Exam		X						X
Height, Weight, BMI	X	X[a]					X[a]	
Vital Signs [b]	X	X	X	X	X	X	X	X
ECGs (single)	X	X	X	X	X	X	X	
Serology (HbsAg, HCV)	X							
Chemistry and Hematology	X	X[c]	X	X	X	X	X[c]	
Lipids		X[c]					X[c]	
ApoE4 testing	X							
Serum Pregnancy [d]	X						X	
Urine Pregnancy [d]		X						
Urinalysis	X	X	X		X		X	
C-SSRS	X	X	X		X		X	
RBANS	X	X	X	X	X	X	X	
MMSE	X	X	X	X	X	X	X	
CGI-I			X	X	X	X	X	
ADCS-ADL		X				X	X	
CDR	X						X	
Hachinski (MHIS-NACC)	X							
PK and Biomarker Sampling		X (biomarkers only)	X		X	X	X	
Randomization		X						
Dispense Medication		X		X	X	X		
First Dose of Medication		X (PM dose following dinner)						
Daily Medication Administration BID			X----------X					
Medication accountability			X	X	X	X	X	
Prior/Concomitant Medication Recording	X	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X	X

Final Disposition								**X**

[a] Weight only
[b] Vital signs include pulse rate, blood pressure, respiration rate, and temperature
[c] Fasting for a minimum of 8 hours prior to blood draw is required at Baseline (Day 1) and End of Treatment (Week 13)
[d] All females of childbearing potential, even if using birth control)
[e] If a subject terminates from the study prior to Week 13, evaluations intended for Week 13 should be completed at discontinuation, if possible.

16.2 Clinical Laboratory Analytes

Standard Chemistry

Alanine aminotransferase (ALT)	Albumin
Alkaline phosphatase	Aspartate aminotransferase (AST)
Bicarbonate	Blood urea nitrogen (BUN)
Calcium	Chloride
Creatinine	Glucose[a]
Potassium	Sodium
Total bilirubin	Total protein

Hematology

Hematocrit	Hemoglobin
Platelet count	Red blood cell (RBC)
Mean corpuscular hemoglobin concentration (MCHC)	Mean corpuscular hemoglobin (MCH)
White blood cell count and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils)	Mean corpuscular volume (MCV)

Lipids[b]

High Density Lipoprotein (HDL)	Low Density Lipoprotein (LDL)
Total Cholesterol	

Urinalysis[c]

Bilirubin	Blood
Glucose	Ketones
Nitrite	pH
Protein	Specific Gravity
Urobilinogen	Leukocyte esterase

[a] Glucose will only be tested in fasting blood samples obtained at Baseline (Day 1) and End of Treatment (Week 13 or early termination)

[b] Lipids will only be tested in fasting blood samples obtained at Baseline (Day 1) and End of Treatment (Week 13 or early termination)

[c] If protein, urine occult blood, nitrite, or leukocyte esterase values are out of range, the microscopic examination will be reported.

Pregnancy Test

Serum pregnancy test at Screening and urine pregnancy tests at each Day-1 Treatment Visit will be administered to all females of childbearing potential, even if using birth control.

Serology

Hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV)

16.3 Cognitive Test Scales

16.3.1 RBANS

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a brief, individually administered test measuring attention, language, visuospatial/constructional abilities, and immediate and delayed memory.[9] It consists of 12 subtests, which yield five Index scores and a Total Scale score.

16.3.2 MMSE

The Mini–Mental State Examination (MMSE) is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used to screen for dementia.[10] It consists of a series of questions and tests, each of which scores points if answered correctly. The MMSE tests a number of different mental abilities, including a person's memory, attention and language.

16.3.3 ADCS-ADL

The Alzheimer's Disease Cooperative Study scale for ADL (ADCS- ADL)[10,11] is administered by an independent rater. The interview was developed to assess impairment of everyday tasks in non-demented individuals with high sensitivity.

16.3.4 CDR

The Washington University Clinical Dementia Rating scale[12,13] is a structured, clinician-rated interview that collects information on cognitive capacity from both the collateral source and patient for the evaluation of staging severity of dementia. The CDR was developed primarily to assess severity level in persons with dementia but it can be used to stage dementia in other illnesses as well (e.g., Parkinson's disease). Six domains are assessed and then synthesized to assign a Global CDR score. The domains are memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Impairment is defined only when caused by cognitive loss rather than by physical disability or other non-cognitive factors. Severity ratings range along a 5-point scale (except for the personal care domain):

- CDR-0: no cognitive impairment
- CDR-0.5: questionable or very mild dementia
- CDR-1: mild
- CDR-2: moderate
- CDR-3: severe

The CDR is frequently utilized in clinical and research settings to describe stage-dependent features of dementia and for use as a clinically-meaningful outcome measure in clinical drug trials.

16.3.5 Modified Hachinski Ischemia Score (MHIS)

A modified version of the Ischemic Score of Hachinski uses 4 items of Hachinski's Ischemic Score plus CT findings (if available in subject's history) as a suitable tool for the diagnosis of vascular

dementia.[14,15] Such a modified ischemic score could comprise 5 items, that is, 4 relevant items of Ischemic Score and the CT features (if available).

1. Abrupt onset (2 points)
2. History of stroke (1 point)
3. Focal neurological symptoms (2 points)
4. Focal neurological signs (2 points)
5. CT-Low density areas isolated (2 points) or multiple (3 points)

Maximum Total Score = 10

A 9-10 point total score points to the existence of old or recent cerebrovascular lesions, simple or multiple.