Protocol Title:

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Effects of Posiphen® in Subjects with Early Alzheimer's Disease (AD) or Early Parkinson's Disease (PD)

Protocol Short Title:

Posiphen® Dose-Finding, Biomarker Study in Early Alzheimer's and Parkinson's Patients

CONTRACT RESEARCH ORGANIZATION	**SPONSOR**
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SPONSOR SIGNATURE

Maria Maccecchini, PhD

Aug 25, 2020

Date

CAUTION: Investigational New Drug

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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I, the undersigned, have reviewed this protocol and I agree to conduct this protocol in accordance with the ethical principles set forth in the Declaration of Helsinki, the Guideline for Good Clinical Practice (ICH E6), the U.S. Code of Federal Regulations (CFR) governing the protection of human subjects (21CFR§50), Institutional Review Boards (21CFR§56) and the requirements for conducting clinical investigations (21CFR§312), and all applicable local, state and federal government regulations and laws.

SIGNATURE

_____ _____

Name: Date

Institution:_____

LIST OF ABBREVIATIONS

5'UTR	5' untranslated region
αSYN	Alpha-synuclein
Aβ	Beta-amyloid
Aβ38	Beta Amyloid 38
Aβ40	Beta Amyloid 40
Aβ42	Beta Amyloid 42
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive
ADL	Activities of Daily Living
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
APOE/APOE4	Apolipoprotein E /Apolipoprotein epsilon 4
APP	Amyloid Precursor Protein
ANOVA	Analysis of variance
AUC	Area under the curve
BACE	β-secretase
BChE	Butyrylcholinesterase
BDNF	Brain-derived neurotrophic factor
BID	Twice a Day
BP	Blood pressure
CDR	Clinical Dementia Rating
CFR	Code of Federal Regulations
CTCAE	Common Terminology Criteria for Adverse Events
CLBP	Chronic low back pain
Cmax	Maximum plasma and CSF concentration
ChE	Cholinesterase
CJD	Creutzfeldt-Jakob Disease
C-SSRS	Columbia Suicide Severity Rating Scale
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CV	Coefficients of variation
CVD	Cerebrovascular Dementia
DNA	Deoxyribonucleic Acid
DS	Down Syndrome
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic Case Report Form

FCR	Fractional clearance rate
FDA	Food and Drug Administration
FSR	Fractional Synthesis Rate
FWA	Federal wide Assurance
GCP	Good Clinical Practice
GI	Gastrointestinal
GRAS	Generally recognized as safe
GWAS	Genome Wide Association Studies
HEK 293	Human embryonic kidney cells
HEENT	Head/ears/eyes/nose/throat
hERG	Human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxypropyl methylcellulose
H&Y	Hoehn and Yahr
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRE	Iron-responsible element
IRP1	Iron Regulatory Protein 1
LBD	Lewy Bodies Dementia
LP	Lumbar Puncture
MAD	Multiple Ascending Dose
MCI	Mild Cognitive Impairment
MDS-UPDRS	MDS-United Parkinson's Disease Rating Scale
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
NPH	Normal Pressure Hydrocephalus
OHRP	Office for Human Research Protections
p-tau	Phosphorylated tau
PD	Parkinson's disease
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetic
PSP	Progressive Supranuclear Palsy
QD	Once a Day
QID	4 Times a Day
QT	Interval seen in electrocardiogram (ECG) test
QTc	Interval seen in QT (ECG) test
sAPP	Soluble Amyloid Precursor Protein
sAPPα	Soluble Amyloid Precursor Protein alpha
sAPPβ	Soluble Amyloid Precursor Protein beta
SAD	Single Ascending Dose

SAE	Serious Adverse Event
SH-SY-5Y	Human Derived Cell Line
SILK™	Stable Isotope Labeling and Kinetics
SD	Standard Deviation
$t_{1/2}$	Half-life
tau	Tau protein
TID	Three Times a Day
TPN	Total Parenteral Nutrition
WAIS-IV	Weschler Adult Intelligence Scales, 4th edition

Table of Contents

1 PROTOCOL SYNOPSIS

PROTOCOL TITLE	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Effects of Posiphen® in Subjects with Early Alzheimer's Disease (AD) or Early Parkinson's Disease (PD)
STUDY DESIGN	This study will be conducted in two parts. **Part 1** will evaluate the safety, tolerability, and pharmacokinetics of Posiphen in 14 Early AD and 14 Early PD patients at the following dose: • 80 mg QD Each group will include 14 Early AD patients, randomly assigned, 10 to Posiphen and 4 to placebo and 14 Early PD patients randomly assigned, 10 to Posiphen and 4 to placebo. Part 1 of the study will also include exploratory measures of pharmacodynamics and efficacy of Posiphen with target engagement, pathway engagement and functional/cognitive measures, including the degree of memory loss and cognitive function in AD patients as well as the degree of motor impairment and non-motor symptoms and quality of life in PD patients. Subjects who drop out during the initial 3-week at-home treatment period will be discontinued and replaced by new subjects. If 4 subjects are discontinued due to adverse events, no additional subjects will be recruited until a safety review has been conducted. After Part 1 has been completed study data will be locked to allow a full analysis of biomarker data to sensitize analysis plans in Part 2. **Part 2** will evaluate the safety, tolerability, and pharmacokinetics of Posiphen in 40 patients with early PD, randomly assigned to the following dose levels, 10 patients per dose level: • 5 mg QD • 10 mg QD • 20 mg QD • 40 mg QD Part 2 of the study will also include exploratory measures of pharmacodynamics and efficacy of Posiphen in Early PD patients with target engagement, pathway engagement and functional/cognitive measures, including the degree of motor impairment as well as other non-motor symptoms and quality of life in PD patients.

	Subjects who drop out during the initial 3-week at-home treatment period will be discontinued and replaced by new subjects. If 4 subjects are discontinued due to adverse events, no additional subjects will be recruited until a safety review has been conducted.
DURATION OF STUDY PARTICIPATION	Each subject will have up to a 42-day screening period, a baseline visit including a lumbar puncture (LP), followed by 25±2 days of treatment at home, followed by an in clinic visit that includes treatment and a 6-hour LP procedure.
SUMMARY OF INVESTIGATIONAL PRODUCT	Part 1: Posiphen/placebo 80 mg QD, taken orally for 25±2 days by Early AD and PD patients. Part 2: Posiphen at 5, 10, 20, or 40 mg QD, taken orally for 25±2 days by Early PD patients.
SUMMARY OF KEY ELIGIBILITY CRITERIA: FOR **AD**	• Diagnosis of early AD • Age 45 or older • MMSE 18-28 • Clinical Dementia Rating (CDR) of 0.5 or 1.0
SUMMARY OF KEY ELIGIBILITY CRITERIA: FOR **PD**	• Diagnosis of early PD • Age 45 or older • MMSE 18-30 • Hoehn & Yahr ≤ 4
PRIMARY OUTCOME MEASURES	Aim 1. Safety and Tolerability Aim 2. PK of Posiphen in Plasma
EXPLORATORY MEASURES	TARGET ENGAGEMENT Levels of neurotoxic proteins in blood, plasma and CSF: • aSYN and Aβ monomers and dimers, and infective oligomers • Aβ38, Aβ40, Aβ42 • soluble Amyloid Precursor Proteins: sAPPα and sAPPβ • T-Tau and P-Tau proteins PATHWAY ENGAGEMENT Levels of proteins involved in the toxic cascade leading to nerve cell death in blood, plasma and CSF

	• Neurotransmitters • Neurotrophic factors • Inflammatory factors • Synaptic factors • Control proteins that should not change FUNCTIONAL/COGNITIVE MEASURES PD: MMSE, WAIS-IV, MDS-UPDRS AD: MMSE, WAIS-IV, ADAS-Cog 14, CDR

2 INTRODUCTION

Currently, there is no treatment available to stop or reverse the progression of Alzheimer's (AD) and Parkinson's disease (PD). Neurodegenerative diseases such as AD and PD share many common characteristics, including the central role of neurotoxic aggregating proteins in their pathogenesis. Amyloid β (Aβ) and tau aggregates (senile plaques and neurofibrillary tangles, respectively) have been traditionally associated with AD, while α-synuclein (αSYN) aggregates (Lewy bodies) have been associated with PD. However, it is becoming increasingly clear that all these proteins are involved in both diseases and that aggregation of one can lead to accumulation of another. Furthermore, in several studies of brains from older patients, a high percentage of all AD brains present mixed pathologies, such as Lewy body disease. Several clinical trials targeting just one (often Aβ) of the neurotoxic aggregating proteins have failed. Finally, other fragments of Amyloid β Precursor Protein (APP) have been implicated in AD pathology. Collectively, these facts point to the need for development of combination therapies that target multiple neurotoxic aggregating proteins simultaneously, if we are to have a good chance of at least halting disease progression.

Posiphen has a unique mechanism of action, in that it inhibits the translation and, therefore, reduces the levels of several neurotoxic aggregating proteins both *in vitro* and *in vivo*, including α-Synuclein (αSYN), Amyloid Precursor Protein (APP), its fragments, and tau. All three proteins have been implicated in the pathogenesis of PD. Furthermore, at older ages, there is a high incidence of patients with mixed pathologies, such as PD dementia. Therefore, it is reasonable to hypothesize that inhibiting expression of all three proteins should lead to a better efficacy outcome in PD patients than inhibiting just one.

Posiphen's safety has been established in three Phase I clinical studies by Maccecchini et al. Importantly, Posiphen normalized levels of αSYN, APP, and tau in the cerebrospinal fluid (CSF) of mildly cognitively impaired (MCI) patients at a dose of 4x60 mg/day (Protocol QR12001). Preclinical data proves Posiphen's efficacy in restoring colonic motility in a human *SNCA*^{A53T} tg mouse model of early PD, in restoring memory and learning in an *APP/PS1* transgenic (tg) mouse model of AD, restoring axonal transport in DS trisomic mice, preserving memory and learning in traumatic brain injury rats and preserving the retina in acute glaucoma.

αSYN, APP, and tau contribute to the progression of AD and PD in similar ways: they impair axonal transport and lower neurotransmitter and neurotrophic factor release, they cause inflammation, they form aggregates, and, finally, they lead to nerve cell death. In our *in vitro* and *in vivo* preclinical studies, Posiphen has normalized all those actions.

We have conducted a proof-of-concept study in mildly cognitive impaired patients at 4x60 mg/day (Protocol QR12001) and found that Posiphen lowers levels of neurotoxic proteins and of inflammatory markers. Presently, we are testing Posiphen in the DISCOVER study at 1x60, 2x60 and 3x60 mg/day for up to 25 days to see if it changes the synthesis and degradation

kinetics of Aβ in a stable isotope labelling kinetic (SILK) study. The DISCOVER study is on-going through the ADCS and is planned for 24 patients to be enrolled; currently, approximately half of the study has been enrolled, and there have been no severe AEs or SAEs attributed to Posiphen reported.

From our animal data, we found that Posiphen works in more than Alzheimer animals, because it inhibits more than one neurotoxic protein. We found that in transgenic AD and PD animals it lowers levels of neurotoxic proteins and restores the affected function. Therefore, we want to test Posiphen in a comparison study of AD and PD patients and measure not just target engagement, but also pathway engagement.

From our animal data, we also found that the doses used to show an effect on neurotoxic proteins are very high and that we can see an effect of Posiphen at much lower doses. Therefore, we are testing Posiphen in a randomized dose de-escalation study to see what the lowest effective dose is in humans.

In this study, we want to find out if the animal Posiphen data can be replicated in humans and show target and pathway engagement in CSF. Target engagement means that Posiphen would lower and normalize the levels of neurotoxic proteins in CSF. Pathway engagement means that Posiphen would increase levels of neurotransmitters, neurotrophic factors, and lower levels of inflammatory and neurodegeneration markers in both AD and PD patients. By examining all these factors in early AD and PD patients, we will specify the biomarkers that change with Posiphen treatment, which will be used in later phase studies. Additionally, we will assess function and cognition, so we can make sure that Posiphen has no deleterious effect and potentially identify any improvement. Collectively, these endpoints will help assess the efficacy of Posiphen and drive it to late phase clinical studies.

2.1 Objectives

Study objectives include assessing safety, tolerability, and pharmacokinetics of Posiphen as well as exploring pharmacodynamics and efficacy in Early AD and Early PD patients with target engagement, pathway engagement and functional/cognitive measures being the focus of the exploratory analyses. This study will be conducted in two parts as follows.

Part 1

Primary objectives are to assess the safety, tolerability, and pharmacokinetics of Posiphen in 14 Early AD and 14 Early PD patients at a dose of 80 mg QD for 25±2 days.

Each group will include 14 Early AD patients, randomly assigned, 10 to Posiphen and 4 to placebo and 14 Early PD patients randomly assigned, 10 to Posiphen and 4 to placebo.

Exploratory objectives will include investigating the pharmacodynamics and efficacy of Posiphen as well as the relationship between them. Efficacy assessments will focus on the following:

- degree of memory loss and cognitive function in AD patients
- degree of motor impairment and non-motor symptoms and quality of life in PD patients.

Part 2

Primary objectives are to assess the safety tolerability, and pharmacokinetics of Posiphen in 40 patients with early PD, 10 patients randomly assigned to each of the following dose levels, given for 25±2 days:

- 5 mg QD
- 10 mg QD
- 20 mg QD
- 40 mg QD

Exploratory objectives will include investigating the pharmacodynamics and efficacy of Posiphen as well as the relationship between them. Efficacy assessments will focus on the degree of motor impairment in PD as well as other non-motor symptoms and quality of life.

2.2 Endpoints

SAFETY AND TOLERABILITY

- adverse events
- physical examinations
- vital signs
- 12-lead ECGs
- clinical laboratory values

PHARMACOKINETICS

PK parameters will minimally be determined, as data permit: Area under the curve (AUC), Cmax, Tmax, t½, and CL.

Additionally, the following Exploratory Objectives will be evaluated:

TARGET ENGAGEMENT

Levels of neurotoxic proteins in blood, plasma and CSF

- aSYN and Aβ monomers and dimers, and infective oligomers
- Aβ38,40,42
- soluble Amyloid Precursor Proteins: sAPPα and sAPPβ
- T-tau and P-tau protein

PATHWAY ENGAGEMENT

Levels of proteins involved in the toxic cascade leading to nerve cell death in blood, plasma and CSF

- neurotransmitters
- neurotrophic factors
- Inflammatory factors
- Synaptic factors
- Control proteins that should not change

FUNCTIONAL/COGNITIVE MEASURES

PD: MMSE, WAIS-IV, MDS-UPDRS

AD: MMSE, WAIS-IV, ADAS-Cog 14, CDR

3 PRELIMINARY STUDIES

The following is a brief summary of the available information on Posiphen. Detailed information can be found in the current Posiphen Clinical Investigational Brochure.

3.1 Summary of Non-Clinical Findings

In wild type mice, Posiphen lowered brain APP and Aβ levels by up to 60% (Lahiri 2007, Cullen 2006). In APP transgenic AD mice, Posiphen led to a decrease in APP levels, improved neuronal stem cell survival and increased levels of brain-derived neurotrophic factor (BDNF) (Marutle 2007; Kadir 2008, Lilja 2013). Chronic administration of Posiphen to APP transgenic mice totally prevented decline in memory and learning as well as in long-term potentiation at brain and plasma concentrations that are 10 times lower than originally published. These plasma levels are attainable with low oral dosing in humans (Teich 2018). In alpha-synuclein (αSYN) transgenic PD mice, Posiphen restored gut motility to normal and lowered aSYN in the brain and gut of the tg PD mice. Again, the efficacious levels were 10 times lower than originally published (Kuo 2019). In DS trisomic mice Posiphen fully restored axonal transport *in vitro* and *in vivo* (Mobley Lab, UCSD, 2019; manuscript submitted for publication). In summary, Posiphen is a translational inhibitor of APP and aSYN and fully restores function at doses that are very low and very safe.

Posiphen was not mutagenic or clastogenic as assessed by *in vitro* assays.

The cardiac electrophysiological properties of Posiphen tartrate were negative *in vitro* using human ether-a-go-go related gene (hERG) transfected human embryonic kidney cells (HEK 293). Posiphen did not adversely affect the interval seen in an electrocardiogram (ECG) test (QT (or QTc)) interval.

Toxicity studies in dogs showed brain toxicity (ataxia and tremors/twitching) and gastrointestinal (GI) toxicity at 30 mg/kg/day, which was dose-dependent and reversible. The no observed adverse effect level (NOAEL) was 20 mg/kg/day in dogs. Posiphen readily crosses the blood-brain barrier. The signs/symptoms noted at high doses of Posiphen may be related to cholinergic manifestations. In in vitro assays, Posiphen showed minimal inhibition of AChE or BChE (Butyrylcholinesterase) activity, however, a metabolic product of Posiphen, N1-norposiphen demonstrated acetyl cholinesterase inhibitory activity (Yu 2013). There were no effects on the reproductive organs associated with 4-week exposure to Posiphen in male or female rats or dogs.

3.2 Summary of Clinical Findings

Three Phase 1 studies have been conducted with Posiphen (IB 2019). The first was a single ascending dose (SAD) study in healthy volunteers; the second was a multiple ascending dose (MAD) study in healthy volunteers, and the third one was a pharmacokinetic

(PK)/pharmacodynamic study of CSF obtained from mild cognitively impaired participants (Protocol QR12001).

In the MAD trial, Posiphen was administered orally in doses of 20, 40, and 60 mg 4 times a day (QID). The first two treatments were administered for 7 days, and the third, for 10 days. Single doses were given on the first and last day to determine the pharmacokinetics of the drug. In general, the drug was well tolerated, resulting in no serious or severe adverse events and only one premature discontinuation, a subject in the 60 mg group discharged because of nausea, vomiting, dizziness and "feeling warm." The incidence of adverse events, all either mild or moderate severity, also occurred with similar frequency in the placebo group. The most common AEs were dizziness, headache, and nausea/vomiting.

Posiphen was absorbed rapidly after oral administration, achieving maximum plasma and CSF concentration (C_{max}) within 1.2 - 1.5 hours. For the 40 and 60 mg doses, with fully defined plasma profiles, the mean terminal $t_{½}$'s were 3.80 ± 0.88 and 5.23 ± 1.24 hours, respectively after a single dose and 3.53 ± 1.03 and 4.104 ± 0.91 hours, respectively, after repeat dosing. The half-life ($t_{½}$) of the plasma concentrations at the lower doses could not be calculated accurately. The C_{max} increased disproportionally with dose (24, 144, and 2310 ng.h/mL after a single dose of 20, 40, and 60 mg, respectively and 110, 134, and 2101 ng.h/mL after multiple doses of 20, 40, and 60 mg, respectively).

In the proof of mechanism of action study (Protocol QR12001), the PK of Posiphen was measured after 10 days of administration (4x60 mg) over 6 hours in CSF and plasma of the AD participants. The pharmacodynamics of a number of biomarkers was compared for 6 hours before the first dose at day 0 and after the last dose at day 11 of Posiphen administration. We found that the plasma concentrations of Posiphen overlapped with the plasma concentrations found in the MAD study. In this study, the N1 metabolite reached about 10 to 15%, while the level of the N8 metabolite reached about 20 to 25% of the Posiphen levels measured in plasma.

Because a substantial proportion of the adverse events observed in AD patients treated with cholinesterase inhibitors appear to reflect the cholinomimetic properties of molecules in this class, Posiphen's highest tolerated dose is determined by the levels of the N1-norposiphen in blood and brain.

While the $t_{1/2}$ of Posiphen in plasma was 5 hours as seen in the SAD and MAD studies, the $t_{1/2}$ in CSF/brain was longer than 12 hours. Concentrations of Posiphen in the brain, extrapolated from blood and CSF, were 8 times higher than in plasma. 10 days of treatment with Posiphen normalized CSF levels of sAPP, tau, αSYN and a series of inflammatory markers. The concentration and persistence of Posiphen in the brain suggest that much lower doses of drug administered once daily could achieve the desired pharmacological effect.

4 BACKGROUND AND STUDY OVERVIEW

4.1 Background

A major pathological hallmark of AD is the appearance of plaques and tangles in the brain and of PD the appearance in the gut and in the brain of aSYN aggregates that form Lewy bodies. In both diseases these aggregates are thought to occur one or two decades prior to overt symptom development. Recent research has shown that soluble forms of phosphorylated tau (p-tau) and Aβ may also contribute to neuronal loss and that PD as well as AD carry a high load of inflammation and microglia activating factors that contribute to neurodegeneration.

For small molecules that target biomarker levels, studies using CSF and plasma sampling in humans can provide data to demonstrate that a drug crosses the blood-brain barrier and engages the relevant target, and to describe the relationship between blood levels and CNS effects. Repeated sampling through a lumbar CSF catheter for 6 hours can mirror image, what happens in the brain as to the levels of aSYN monomers and dimers, Aβ monomers and dimers as well as other biomarkers and help guide the development of drugs targeting neurotoxic aggregating proteins.

Posiphen is the (+) enantiomer of phenserine, an AChE inhibitor which had been tested in several AD studies without significant evidence of efficacy. While phenserine inhibits AChE, Posiphen has no AChE activity itself and develops some activity in vivo with the metabolism to N1-bisnorposiphen. In vivo phenserine has about 200 times more AChEI activity than Posiphen's metabolite N1-bisnorposiphen. Posiphen absorption is affected by food; however, at steady state there is no effect on the PK analyses results.

Posiphen has been found to significantly reduce soluble APP and Aβ as well as tau, p-tau and αSYN in the rodent brain and in human CSF. In preliminary studies in animals and humans, inhibition of APP, Aβ, tau, p-tau and αSYN occurs at levels 6 to 10 times lower than the levels causing cholinomimetic effects.

Posiphen acts at the 5'UTR of the aSYN and APP mRNA and lowers their protein expression levels in animal models; it also decreased aSYN and sAPP levels in human CSF. Our data suggests that these effects are achieved via the same mechanism: the 5'UTRs of these mRNAs form a complex with iron regulatory protein 1 and Posiphen stabilizes the complex, thereby inhibiting the translation of these mRNAs.

As Posiphen inhibits the synthesis of aSYN and APP, as well as other neurotoxic aggregating proteins, it might have a broader spectrum of activity than PD and AD. By protecting neurons from dying it has a disease-modifying effect in PD, AD as well as other neurodegenerative disorders.

4.2 Study Overview

Study population: The study will be conducted in patients with early AD or early PD.

Dose selection: In Part 1 Posiphen will be tested at 80 mg QD and in Part 2, Posiphen will be tested at 5, 10, 20, 40 mg QD, for 25±2 days.

Whereas, the plasma t½ of Posiphen has been determined to be 5 hours, the CNS t½ has been measured to be over 12 hours, allowing that once daily dosing is feasible. Previous studies indicated that likely cholinergic adverse events are mostly driven by Cmax and occur at 160mg QD. Since our maximum dose is 80 mg QD, we do not expect any cholinomimetic effects.

Study Design: Part 1 is a study with 14 Early AD and 14 Early PD patients who are randomized to 80 mg of Posiphen or placebo. They will undergo a Screening Visit, and if they provide informed consent and are considered eligible per the inclusion and exclusion criteria, will proceed to participate in the treatment period. Period 1 consists of first-time dosing in clinic with administration of 80 mg of Posiphen or Placebo. Period 2 consists of an at home dosing period of 25±2 days, with daily administration of 80 mg of Posiphen or Placebo. Period 3 will be comprised of a stay at the clinical research unit where the subject will undergo study procedures that include safety assessments (AE and concomitant medication monitoring, 12-lead ECGs, clinical laboratory testing, vital signs assessments, and physical examinations), the last dose of Posiphen or Placebo, and 6 hours of PK blood and CSF sampling. At the end of blood/CSF sampling, the subjects will need to stay for a minimum of 1 hour of observation but may stay if necessary for observation until the following day (e.g., if the subject has blood/CSF sampling on Day 25, he/she may stay for observation until Day 26). After all end-of-study procedures are complete, the subject will be discharged to home. A 24-hour follow-up call will occur to assess the participants current condition and if there are any additional adverse events to report.

After completion of Part 1 of the study, the plasma and CSF samples will be analyzed for the biomarkers to determine if changes are needed to the biomarkers to be measured in Part 2. Since the conduct of the study in Part 2 will be identical to the conduct of the study in Part 1, recruitment will continue uninterrupted. The only potential change between Part 1 and Part 2 are the biomarkers to be measured.

Part 2 is a study with 40 Early PD patients, 10 patients each who are randomized to one of 4 treatment conditions of Posiphen (5 mg, 10 mg, 20 mg, or 40 mg). They will undergo a Screening Visit, and if they provide informed consent and are considered eligible per the inclusion and exclusion criteria, will proceed to participate in the treatment period. Period 1 consists of first-time dosing in clinic with administration of 5, 10, 20, or 40mg of Posiphen. Period 2 consists of an at home dosing period of 25±2 days, with daily administration of 5, 10, 20, or 40mg of Posiphen. Period 3 will be comprised of a stay at the clinical research unit where the subject will undergo study procedures that include safety assessments (AE and concomitant medication monitoring, 12-lead ECGs, clinical laboratory testing, vital signs assessments, and physical examinations), the last dose of Posiphen or Placebo, and 6 hours of PK blood and CSF

sampling. At the end of blood/CSF sampling, the subject will need to stay for a minimum of 1 hour of observation but may stay if necessary for observation until the following day (e.g., if the subject has blood/CSF sampling on Day 25, he/she may stay for observation until Day 26). After all end-of-study procedures are complete, the subject will be discharged to home. A 24-hour follow-up call will occur to assess the participant's current condition and if there are any additional adverse events to report.

For both parts, subjects who drop out during the initial 3-week at home treatment period will be discontinued and replaced by new subjects. If 4 subjects are discontinued due to adverse events a safety review will be conducted.

Outcome measures to assess pharmacodynamics: Translational inhibition of the aSYN mRNA will result in decreased production of aSYN, which may be reflected by decreased secretion of the aSYN monomers and oligomers into the spinal fluid. Similarly, translational inhibition of the APP mRNA will result in decreased production of APP and its fragments, which may be reflected by decreased secretion of the Aβ monomers and oligomers into the spinal fluid. We also will measure secreted sAPPα and sAPPβ and levels of tau and p-tau in CSF. sAPP reflects processing of APP by α-secretase to produce sAPPα and β-secretase (BACE) to produce sAPPβ. Tau levels are being measured since we found that tau translation may be under the regulation of a similar iron-responsible element (IRE) that may also be affected by Posiphen treatment. In fact, we have measured in human CSF and in mouse brain that tau and p-tau levels are lowered by Posiphen treatment.

Safety outcome measures: Reports of adverse events (AEs) and serious adverse events (SAEs) during exposure to Posiphen will be collected to evaluate if there are any significant clinical safety issues for the study population. All SAEs occurring up to 30 days after last study drug administration that are considered drug-related must also be reported. Extensive clinical and laboratory safety data already exist for Posiphen; therefore, this approach will be sufficient in the proposed study.

Clinical, functional and cognitive assessment measures: Although clinical benefit is unlikely due to the short duration of this study, AD and PD specific tests will be performed. It is predicted that cognition and function will remain stable over the course of drug exposure; however, this will be assessed formally in the clinic. For both populations, the MMSE (Folstein 1975) will be administered as a global measure of cognition and the Coding subtest from the Weschler Adult Intelligence Scales, 4th edition (WAIS-IV) will serve as a sensitive measure of CNS dysfunction. The subjects with AD will also be administered the ADAS-Cog 14 (Schafer 2012). The subjects with PD will be administered the Hoehn & Yahr (1967) for determination of inclusion into the study. Functional impairment will be evaluated using the Clinical Dementia Rating (CDR) scale (Berg1988) for AD and the MDS-UPDRS (Goetz 2008) for those with PD.

5 POTENTIAL RISKS AND BENEFITS OF INVESTIGATIONAL PRODUCT AND STUDY PROCEDURES

5.1 Risks and Benefits Associated with Posiphen or Placebo

There are no benefits to the subjects other than receiving medical and selective functional and cognitive evaluations.

The clinical investigator must advise all potential subjects of the possibility of unexpected side effects and carefully evaluate each person exposed to Investigational Product for possible AEs.

Side effects to the Placebo are not uncommon but are obviously not due to a pharmacological agent as an industry standard placebo (non-lactose compound) will be provided. The placebo used for the study consists of microcrystalline cellulose which is generally recognized as safe (GRAS), with no known side effects anticipated.

In clinical studies to date, Posiphen has been well tolerated with single doses of 80 mg or less and QID doses of 60 mg up to 25 days. A higher single dose of 160 mg was associated with an increased incidence of nausea and vomiting, potentially cholinergic based side effects, which resulted in the decision not to test higher single doses. Aside from nausea and vomiting, which are well-known responses to treatment with ChE inhibitors, the only consistent pattern of AEs entailed dizziness/fainting, headache, and reduction in total serum protein. These effects were seen to varying degrees at all doses of Posiphen and also in the Placebo group. There was a tendency, but no definitive pattern of increased incidence of AEs with increasing dose of Posiphen. There have been no SAEs in prior clinical studies with Posiphen.

Definitive reproductive and developmental toxicity studies have not been conducted with Posiphen. As a result, women of childbearing potential will be excluded from participating in this study.

5.2 Risk/Benefit Associated with Blood Collections

Phlebotomy is associated with mild to moderate discomfort due to piercing of the skin. This can be minimized with the use of a well-trained phlebotomist/nurse. Sometimes the blood draw site may become discolored with a “bruised” appearance that is transient and not painful. Rarely, the blood draw site may become infected and require antibiotic treatment.

5.3 Risk/Benefit Associated with CSF Sampling

The most frequent adverse event associated with these studies was post-lumbar puncture headache. This was successfully managed by blood patching if a participant is unresponsive to orally administered fluids and/or caffeine.

Other potential risks include meningitis, pain or tingling sensation in the lower extremities, temporary eye weakness or double vision, infection or bleeding at the site of catheter insertion,

pain at the site of insertion, backache, epidural or subdural bleeding, infection, paralysis and potential injury to the nerve root.

6 SAMPLE SIZE AND STATISTICAL PLAN

For Part 1: A sample size of up to 2x14 subjects (10 randomized to Posiphen and 4 to Placebo for AD and PD respectively) is planned.

For Part 2: A sample size of up to 40 Early PD patients is planned to be randomized to Posiphen, 10 patients each dosed at 5 mg, 10 mg, 20 mg, or 40 mg.

Definitions of the analysis populations and a detailed description of the analysis rules will be presented in a separate Statistical Analysis Plan (SAP).

6.1 Randomization

Subjects who have signed an informed consent and meet screening eligibility requirements will be randomly assigned to the active and placebo treatment groups (10 randomized to Posiphen and 4 to Placebo for AD and PD, respectively) in Part 1. In Part 2, 40 Early PD patients will be randomly assigned, 10 patients each to one of the 4 different dose levels of Posiphen (5, 10, 20 or 40mg).

6.2 Power and Sample Size Determination

This is an exploratory study to assess safety, tolerability and pharmacokinetics for Early AD and Early PD patients in addition to investigating pharmacodynamics and efficacy focusing on target engagement, pathway engagement and functional/cognitive measures. 10 patients per dose group provides enough data to characterize the PK of Posiphen as well as adequately supporting potential dose proportionality analyses.

Due to the sample size computation below, we will state that sAPPα, sAPPβ and aSYN were given specific consideration in deciding the need to have 10 Posiphen patients in each treatment group given their specific importance in the emergence and progression of AD and PD. The statistical background and rational for having 10 Posiphen patients in each treatment group to have a meaningful interpretation of sAPPα, sAPPβ and aSYN data are outlined below.

The statistical evaluation of our previous study in MCI patients with soluble APPα and β levels measured in spinal fluid before and after Posiphen administration (Protocol QR12001) can be used to power this study (Maccecchini 2012). All assay data collected were analyzed using a repeated measure mixed model analysis of variance. The model included Day (Day 11/Day0) as a fixed effect, Time (9 time points per person between 0 and 6 hours) as a repeat measure effect

and Patient (18 samples per person total) as a random effect. Data are presented as means ±SEs. The statistical evaluations were undertaken by Data Magik (Salisbury, UK).

Human biomarker	CSF % of time 0	SE	p Value
(A) AD biomarkers			
sAPPα	−59.9%	0.231	0.0006
	−34.1%	0.659	0.0661
sAPPβ	−57.7%	0.361	0.0001
	−34.0%	1.516	0.0901

Analysis of sAPPα and β using type, day and id as variables shows:

	type	time	N	delta_MN	delta_SE	delta_SD	%chng_MN	%chng_SE	z	pv
1	alpha	1.5h	4.0000	0.0603	0.0960	0.1921	0.0561	0.2167	0.6273	0.5304
2	alpha	2h	4.0000	0.1245	0.0423	0.0846	0.3020	0.0690	2.9445	0.0032
3	alpha	6h	3.0000	0.2660	0.0558	0.0967	0.4542	0.1367	4.7650	0.0000
4	alpha	8h	4.0000	0.3135	0.0847	0.1695	0.5248	0.0653	3.6995	0.0002
5	alpha	0h	4.0000	0.0948	0.0928	0.1856	0.1691	0.2493	1.0213	0.3071
6	alpha	12h	4.0000	0.2960	0.0623	0.1245	0.4966	0.0862	4.7549	0.0000
7	alpha	1h	4.0000	-0.0683	0.1660	0.3320	-0.4285	0.6604	-0.4111	0.6810
8	alpha	3h	4.0000	0.4858	0.3922	0.7844	0.3579	0.1981	1.2385	0.2155
9	alpha	4h	4.0000	0.3030	0.2753	0.5505	0.3200	0.2905	1.1008	0.2710
10	beta	1.5h	4.0000	-0.1160	0.2670	0.5339	-0.7568	0.9151	-0.4345	0.6639
11	beta	2h	4.0000	0.1975	0.0876	0.1752	0.3639	0.1315	2.2550	0.0241
12	beta	6h	3.0000	0.4717	0.0572	0.0991	0.5910	0.0519	8.2431	0.0000
13	beta	8h	4.0000	0.5715	0.1271	0.2542	0.6648	0.0550	4.4960	0.0000
14	beta	0h	4.0000	0.1092	0.1134	0.2268	0.1425	0.2227	0.9632	0.3354
15	beta	12h	4.0000	0.4620	0.0581	0.1161	0.6040	0.0604	7.9570	0.0000
16	beta	1h	4.0000	-0.4895	0.1652	0.3304	-1.4024	0.6361	-2.9635	0.0030
17	beta	3h	4.0000	2.2147	1.9988	3.9977	0.5025	0.1616	1.1080	0.2679
18	beta	4h	4.0000	0.0277	0.3313	0.6626	-0.2181	0.2404	0.0838	0.9332

The results of the 10 days at 8 hours on sAPPα and β is SD = 0.1695.

Assuming type one error, α=0.05 and type two error, β=0.2, or a power of 0.8, the calculated sample range of delta effect sizes was 0.3 to 2 SD.

	delta	standardized_delta	N
1	0.08	0.30	175.00
2	0.10	0.40	99.00
3	0.13	0.50	64.00
4	0.15	0.60	45.00
5	0.18	0.70	33.00
6	0.20	0.80	26.00
7	0.23	0.90	20.00
8	0.25	1.00	17.00
9	0.28	1.10	14.00
10	0.31	1.20	12.00
11	0.33	1.30	10.00
12	0.36	1.40	9.00
13	0.38	1.50	8.00
14	0.41	1.60	7.00
15	0.43	1.70	7.00
16	0.46	1.80	6.00
17	0.48	1.90	5.00
18	0.51	2.00	5.00

sAPPα

Using the above data, we can calculate that a power analysis of APPα shows the requirement of 9 people to see a 36% change in sAPPα levels at a statistical significance level of >0.05

	delta	standardized_delta	N
1	0.05	0.30	175.00
2	0.07	0.40	99.00
3	0.08	0.50	64.00
4	0.10	0.60	45.00
5	0.12	0.70	33.00
6	0.14	0.80	26.00
7	0.15	0.90	20.00
8	0.17	1.00	17.00
9	0.19	1.10	14.00
10	0.20	1.20	12.00
11	0.22	1.30	10.00
12	0.24	1.40	9.00
13	0.25	1.50	8.00
14	0.27	1.60	7.00
15	0.29	1.70	7.00
16	0.31	1.80	6.00
17	0.32	1.90	5.00
18	0.34	2.00	5.00

sAPPβ

Using the above data, we can calculate that a power analysis of APPβ shows the requirement of 9 people to see a 24% change in sAPPβ levels at a statistical significance level of >0.05. We are expecting changes in sAPPα and β levels to be between 20 and 50% and for the higher doses an n<5 would be adequate to detect those changes.

aSYN

However, we do not expect the changes in alpha-synuclein and in neurotransmitters to be that pronounced. Therefore, we chose an n=10. If dropouts are to occur, they will be replaced to allow the full sample size of 5 x 10 participants to be achieved.

6.3 Safety and Tolerability Analysis

Safety and tolerability will be assessed with physical examinations, vital signs, clinical laboratory values, 12-lead ECG, use of concomitant medications, and AE reports. The frequencies of adverse events, serious adverse events and laboratory abnormalities between the participants across the treatment groups will be compared. The severity of cholinergic adverse events will be carefully evaluated taking the criteria in Appendix 2 into consideration (modified from the latest version of the Common Terminology Criteria for Adverse Events (CTCAE)) as there is potential for an interaction between Posiphen and Donepezil through the inhibition of AChE, thereby resulting in increased cholinergic activity.

Subjects who dropout during the initial 3-week at-home treatment period will be discontinued and replaced by new subjects. If 4 subjects are discontinued due to adverse events a safety review will be conducted.

6.4 PK Analysis

Plasma concentration-time data will be analyzed by non-compartmental methods using SAS version 9.4 or greater. Calculations will be based on the actual sampling times recorded during the study. Since the study is blinded, all subjects' plasma will be included in the PK analysis. From the plasma concentration-time data, the following PK parameters will minimally be determined, as data permit: Area under the curve (AUC), Cmax, Tmax, t½, and CL. Dose-proportionality may be assessed on Cmax and AUC as appropriate. Serial pre-dose trough concentrations Cmax will be assessed for the attainment of steady state.

Plasma concentration-time data for Posiphen will be listed and summarized descriptively (number of subjects (N), mean, median, standard deviation (SD), minimum (min), and maximum (max)) and graphically presented. PK parameters will be listed and summarized descriptively (N, mean, median, SD, min, max, and 95% CI) by each dose regimen. In addition, geometric means and between-subject coefficients of variation (CV) will be calculated.

6.5 Exploratory Pharmacodynamic and Efficacy Analysis

Pharmacodynamics and efficacy analyses will focus on exploratory endpoints outlining target engagement, pathway engagement and functional/cognitive measures being the reference stones of the exploratory analyses both for Part 1 and Part 2.

Analysis will include descriptive summary tables, listings and figures for Part 1 and Part 2 as well as combined analyses of dose/treatment groups from Part 1 and Part 2. Statistical comparisons will be descriptively performed for PD and efficacy parameters as well as the relationships between them using mixed models.

6.6 Criteria for the termination of the trial

The trial may be terminated by the Project Directors and/or the Sponsor based on issues of safety, feasibility, and Data Safety Monitoring Board (DSMB) recommendations.

6.7 Interim Analysis

No interim analysis is planned. However, after completion of Part 1 of the study, the plasma and CSF samples will be analyzed unblinded for the biomarkers to determine if changes are needed to the biomarkers to be measured in Part 2. Since the conduct of the study in Part 2 will be identical to the conduct of the study in Part 1, recruitment will continue uninterrupted. The only potential change between Part 1 and Part 2 are the biomarkers to be measured. Due to COVID-19 potentially causing recruitment challenges, at the time of intended analysis, Part 1 data may be analyzed should only 1 of the 2 cohorts in Part 1 be complete (e.g., 14 PD Patients, 5 AD

Patients). Only the full cohort would be unblinded, any patients not analyzed as part of the Part 1 analysis will be analyzed when that cohort is fully completed. Full details of all analyses will be detailed in the SAP.

7 STUDY DRUG AND CONCOMITANT MEDICATIONS

7.1 Name and Description of IP and Comparator

Posiphen will be prepared in 5 mg, 10 mg, 20 mg, 40mg, and 80 mg HPMC hard capsule shells. Matching Placebo capsules (non-lactose compound) will be prepared with an inert inactive excipient generally recognized as safe for human pharmaceutical use.

7.2 Dosage

The study drug is to be taken orally; one capsule, once a day in the morning, with or without food, for 25 days ± 2 days at home (depending on when the confinement visit is scheduled).

Participants must take 80% of all doses (across 25±2 days). Bottles will be examined in clinic at the pre-confinement visit to assess compliance overall and in the last week.

7.3 Packaging/Dispensing/Labeling

The study drug (Posiphen capsules and placebo capsules) will be manufactured under cGMP, in a manner to preserve the blind, i.e., identical color and shape opaque HPMC hard capsule shells and packaged 30 capsules per bottle.

The investigational drug supply will be shipped directly to the clinical sites to dispense to participants.

The dosing schedule and storage requirements will be clearly explained to the participants and caregiver before dispensing the study drug, and it will be printed on the labels.

All clinical trial material dispensed under this protocol will bear the requisite cautionary statement “CAUTION: Limited by Federal (United States) Law to Investigational Use Only”.

7.4 Storage

Both Posiphen capsules and the matching placebo capsules must be stored at room temperature (15-30 °C; 59-86 °F), protected from moisture, in a locked, temperature-controlled area with restricted staff access.

7.5 Drug Accountability

The investigator is responsible for investigational product reconciliation and records maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff must maintain investigational product accountability records throughout the course of the study. The responsible person(s) will document the amount of investigational product dispensed to and returned by subjects. All used and unused study drug containers must be returned to the site for accountability. Once authorized by a clinical monitor, unused study

drug (including partially used bottles) may be destroyed on site per appropriate site SOPS or should be shipped back to the Sponsor for destruction.

7.6 Compliance

Site personnel will assess compliance based on the amount of study drug dispensed to and returned by the participants, together with any related information, including the administration of study drug by study staff during the confinement visit. Participants must take 80% of all doses at home (25±2 days) depending on the confinement visit date. Site personnel will count capsules and evaluate compliance from the bottle at the pre-confinement visit.

Prior to the pre-confinement visit, site personnel will also contact the participant and study partner to remind them of the dose regimen, to ensure that the necessary level of compliance has been achieved to continue with the confinement visit procedures.

Site personnel will assess compliance at the pre-confinement visit and again at the time of admission for the confinement visit. If participants are found to be < 80% compliant the site must consult with the Project Directors and/or Medical Monitor regarding timing and conduct of the confinement visit procedures. It is possible that subjects will be discontinued early from the study due to insufficient drug compliance.

7.7 Breaking the Blind

Only in the case of an emergency, when knowledge of whether the participant has received the investigational product is essential for the clinical management or welfare of the participant, may the investigator request to unblind a participant's treatment assignment. If the investigator needs the blind to be unmasked for a subject for any reason, the investigator must contact the Medical Monitor and/or Project Directors to obtain an approval. If the blind is broken, whether it be by accident or for the welfare of the participant, the investigator MUST contact the Medical Monitor. Refer to the study procedures manual for detailed procedures related to breaking the blind and reporting.

7.8 Overdose

No specific antidote for the overdose of Posiphen is known; however, signs or symptoms of possible overdose should be noted and treated. The Medical Monitor and Project Directors should be notified as well. Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. Although Posiphen is a weak AChE inhibitor, based upon overdose information published in prescribing information for related products, overdose with AChE inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anti-cholinergics such as atropine may be used as an antidote for overdosage. Intravenous atropine sulfate titrated to effect is recommended. Atypical responses in blood pressure (BP) and HR have been reported with other cholinomimetics when

co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) is an effective treatment for overdose.

7.9 Concomitant Medications

7.9.1 Prohibited Concomitant Medications

Current use of anti-coagulants (e.g., warfarin (Coumadin), dabigatran (Pradaxa) or anti-platelet drugs (e.g., Plavix)see section 12.1.1, other than aspirin up to a dose of 325 mg per day, is prohibited. Prospective subjects who in consultation with the prescribing physician can safely discontinue these medications for 4 weeks before screening and remain off these medications throughout the study, can be considered for inclusion in the study.

Use of the following medications is prohibited within 4 weeks of screening and throughout the study:

- tricyclic antidepressants
- antipsychotics prescribed for any reason, except ≤50 mg quetiapine daily, risperidone ≤1.5 mg/day, olanzapine ≤5 mg/day, and aripiprazole ≤10 mg/day
- psychostimulants

Investigational agents are prohibited 4 weeks prior to entry and for the duration of the trial.

Initiation of prohibited medications during the course of the study is discouraged, however, if an excluded medication is initiated after screening, the site should consult with the Project Directors and Medical Monitor for further guidance.

7.9.2 Permitted Concomitant Medications

This protocol allows concomitant treatment with anti-parkinsonian medications at stable doses for 4 weeks or greater prior to screening and with cholinesterase inhibitors and/or memantine if on a stable dose (FDA approved drug ranges) for at least 12 weeks prior to screening.

Anticonvulsant medications used for epilepsy or mood stabilization; neuropathic pain indications. Dosing must be stable for at least 4 weeks prior to Screening.

Mood-stabilizing psychotropic agents, including but not limited to lithium. Dosing must be stable for at least 4 weeks prior to Screening.

Use of short acting benzodiazepines and hypnotics for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted but should be avoided for 8 hours before administration of cognitive tests. If sedating medication is given for any short-term use, then all cognitive assessments must be administered at least 24 hours after administration of the sedative.

8 STUDY POPULATION

Participants in this study must be in accordance with the criteria specified below. Subjects who do not meet all inclusion criteria, disease diagnostic criteria, or who meet any exclusion criteria may not be randomized into the study without prior approval from the Project Directors and Medical Monitor.

8.1 Inclusion Criteria

Subjects must meet the following criteria:

1. Male or female aged 45 years and over.
2. Female participants must be of non-childbearing potential or post-menopausal for at least 2 consecutive years or surgically sterile (bilateral tubal ligation, hysterectomy or bilateral oophorectomy) for at least 6 months prior to screening.
3. Female participants will be given a urine pregnancy test at the screening visit for which they should test negative.
4. A) AD - CDR = 0.5 or 1.

   B) PD - Hoehn & Yahr ≤ 4; PD criteria by MDS-UPDRS.
5. A) AD MMSE score between the range of 18 to 28.

   B) PD MMSE score between the range of 18 to 30.
6. General cognition and functional performance sufficiently preserved that the subject can provide written informed consent.
7. No evidence of current suicidal ideation or previous suicide attempt in the past month as evaluated in the Columbia Suicide Severity Rating Scale.
8. MRI scan within the 12 months prior to screening without evidence of infection, infarction, or other focal lesions and without clinical symptoms suggestive of intervening neurological disease. Lacunes that are not believed to contribute to the subject's cognitive impairment are permissible. If there is no MRI available within a 12-month timeframe, then an MRI must be performed as part of the screening procedures for eligibility.
9. Stability of permitted medications prior to screening.
    a. Stable for at least 12 weeks: Cholinesterase inhibitors and/or memantine medication
    b. Stable for at least 4 weeks:
        i. Anti-parkinsonian medication
        ii. Anticonvulsant medications used for epilepsy or mood stabilization; neuropathic pain indications
        iii. Mood-stabilizing psychotropic agents, including, but not limited to, lithium.

10. Adequate visual and hearing ability (physical ability to perform all the study assessments).

11. Good general health with no disease expected to interfere with the study.

12. Subjects previously exposed to Posiphen may be included in the study.

8.2 Exclusion Criteria

Subjects meeting any of the following criteria must not be included in the study:

1. Has a history of a psychiatric disorder such as schizophrenia, bipolar disorder or major depression according to the criteria of the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Mild depression or history of depression that is stable on treatment with a SSRI or SNRI medication at a stable dose is acceptable.

2. History of a seizure disorder.

3. Has a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 450ms, or torsades de pointes.

4. Has bradycardia (<50 bpm) or tachycardia (>100 bpm) on the ECG at screening.

5. Has uncontrolled Type-1 or Type-2 diabetes . A Subject with HbA1c levels up to 7.5% can be enrolled if the investigator believes the subject's diabetes is under control.

6. Has clinically significant renal or hepatic impairment.

7. Has any clinically significant abnormal laboratory values. Subjects with liver function tests (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) greater than twice the upper limit of normal will be excluded.

8. Is at imminent risk of self-harm, based on clinical interview and responses on the C SSRS, or of harm to others in the opinion of the Investigators. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan or method (e.g. positive response to Items 4 or 5 in assessment of suicidal ideation on the C SSRS) in the past 2 months, or suicidal behavior in the past 6 months.

9. Has four or more signal hypointensities on T2*-weighted gradient recalled echo magnetic resonance sequences that are thought to represent hemosiderin deposits including microhemorrhages and superficial siderosis or evidence of acute or sub-acute micro or microhemorrhage as noted on the MRI scan.

10. Has cancer or has had a malignant tumor within the past year, except patients who underwent potentially curative therapy with no evidence of recurrence. (Patients with stable untreated prostate cancer or skin cancers are not excluded).

11. Alcohol / Substance use disorder, moderate to severe, in the last 5 years according to the most current version DSM.
12. Participation in another clinical trial with an investigational agent and have taken at least one dose of study medication, unless unblinded on placebo, within 60 days prior to the start of screening. (The end of a previous investigational trial is the date the last dose of an investigational agent was taken), or five half-lives of the investigational drug, whichever is greater.
13. Subjects with infection or inflammation of the skin or skin disease at or in proximity to the lumbar puncture site.
14. History of lumbar spine surgery or chronic low back pain (CLBP).
15. Subjects with learning disability or developmental delay.
16. Subjects whom the site PI deems to be otherwise ineligible.

9 DESCRIPTION OF STUDY VISITS

Each subject will have a 42-day screening period followed by 25±2 days of treatment at home. The study visits are described below and outlined in the Schedule of Events in Appendix 1.

9.1 Screening Visit

The screening visit should occur up to 42 days before the baseline visit. The screening visit procedures may be completed over multiple days.

Potential participants, or legally authorized representatives, and their study partners must sign an informed consent form prior to administration of any study-related procedures. Information regarding the subject's demographics, concurrent medications, and medical history will be collected along with cognitive assessments, physical examination, and neurological examination.

Safety assessments will include an MRI scan (up to 12 months prior) and ECG that will need to be read locally and reviewed by the site investigator to confirm eligibility. The clinical safety laboratory blood and urine tests will be sent to a central lab for analysis. The screening safety laboratory tests will be comprised of a metabolic panel, complete blood count, coagulation panel, and urinalysis as listed in Section 12.1.3. Coagulation panel results must be obtained prior to performing the lumbar puncture. Urine dipstick pregnancy test will be completed for female subjects.

Cognitive and functional assessments should not be administered when the subject is in a fasted state. Once all screening visit procedures are completed, all information related to eligibility, including screening lab results, must be reviewed by the site investigator to assess the subject's eligibility before proceeding to Baseline.

Sites should try to enroll patients who already have an MRI scan available to limit patient burden. Any patient who requires a new MRI **must** have all other screening assessments completed prior to performing the MRI.

9.2 Baseline Visit

Baseline procedures include functional, cognitive, and behavioral assessments, safety assessments, and review of concurrent medications and adverse events that occur in clinic.

Following completion of all baseline procedures, subjects who continue to meet all protocol inclusion criteria and no exclusion criteria, should be scheduled for the confinement visit. The subject should then be randomized, dispensed study drug, and instructed on proper storage and at-home dosing based on the scheduled date of the confinement visit. The subject should be instructed on 1.) to take the first dose immediately after the baseline spinal tap and venipuncture 2.) the Day 14 Contact and the Pre-Confinement Phone Contact and 3.) Study drug compliance and study drug return.

A lumbar puncture will be performed as part of the baseline visit, in the morning (before 10 am is recommended), after an overnight fast. After the collection of the baseline lumbar puncture and venipuncture, the first dose of Posiphen will be administered to the patient.

The subject will stay at the unit for a 1 hour observation period and may be safely discharged to home per investigator discretion. Subjects will have the option to stay overnight in the occurrence of adverse events associated with the LP procedure.

Subject baseline visit can be split over two (2) consecutive days should the investigator feel that the neuropsychological tests are better completed without fatigue (i.e., after LP or unfasted).

9.3 Day 14 Telephone Contact

A telephone call will be conducted at 14 ± 4 days from the baseline visit to assess for any changes in status, adverse events, or concomitant medications. Study medication compliance will be discussed, and reminders given about the upcoming confinement visit. If there is an insufficient level of drug compliance (less than 80% overall), the site must consult with the Project Directors and Medical Monitor regarding timing and conduct of the remaining confinement visit procedures. It is possible that subjects will be discontinued early from the study due to insufficient drug compliance.

9.4 Confinement Visit

Admission for the confinement visit should occur 25 ± 2 days following the first dose of study medication. A pre-confinement phone call will be conducted 1-3 days prior to admission and a post-confinement phone follow-up will be conducted approximately 24 hours following discharge. Confinement procedures include functional, cognitive, and behavioral assessments, safety assessments, and review of concurrent medications and adverse events that occur in clinic, blood and CSF collection.

9.4.1 Pre-Confinement Telephone Contact

A telephone call will be conducted at 1-3 days prior to confinement to assess for any changes in status, adverse events, or concomitant medications. Study medication compliance will be discussed, and reminders given about the upcoming confinement visit. If there is an insufficient level of drug compliance (less than 80% overall), the site must consult with the Project Directors and/or Medical Monitor regarding timing and conduct of the Confinement Visit procedures. It is possible that subjects will be discontinued early from the study due to insufficient compliance.

9.4.2 Confinement Visit

The confinement visit will consist of the following: admission procedures, Time 0 blood and CSF sampling, administration of last dose of study drug, 6-hours of blood and CSF sampling, at least a 1-hour observation period while subject remains on bed rest with the observation period

to be extended as clinically necessary as per the Investigator's decision, and discharge procedures. Subjects will be provided with sleeping accommodations during this visit, if necessary, and maybe permitted to remain overnight per investigator discretion in the event there are adverse events associated with the study medications or study procedures.

Subject confinement visit can be split over two (2) consecutive days should the investigator feel that the neuropsychological tests are better completed one day before the lumbar puncture.

Period 1: Admission

Subjects should arrive fasted in the early morning after an overnight fast. Clinical safety labs will be drawn and sent to the central lab for analysis.

Study drug compliance over the preceding days will be assessed. If there is an insufficient level of drug compliance (less than 80% overall), the site must consult with the Project Directors and Medical Monitor) regarding timing and conduct of the remaining confinement visit procedures. It is possible that subjects will be discontinued early from the study due to insufficient study drug compliance.

Admission visit procedures include conducting a Physical and Neurological Exam, administering functional and cognitive evaluations and C-SSRS, collecting vital signs, ECG, clinical labs, reviewing and recording adverse events and concurrent medications.

Period 2: 6-Hour Sampling

If no medical or compliance concerns are identified during the admission procedures, the subject will move on to the 6-Hour Sampling Phase, which entails the following procedures:

1. Place an intravenous line for blood sampling. Alternatively, blood may be sampled by direct venipuncture if deemed appropriate by the PI.
2. Place the CSF catheter.
3. Collect initial samples of blood and CSF (Hour 0).
4. Administer last dose of assigned study drug after the 0 hour sampling.
    a. Collect CSF (6 mL) and blood (10mL) every hour at the following time points: 1, 2, 3, 4, 5, 6 hours.
        i. CSF and blood should be taken within ± 10 mins of hourly times.
        ii. If unable to obtain a total of 6 mL CSF at any given collection time (e.g. due to participant headache or participant's CSF production level), reduce

the collection volume to a tolerated amount (minimum 2mL). If there is poor flow at any of the time points, then the next collection could be skipped to allow for better flow at the subsequent collection time. For example, if less than 2mL of CSF is collected at the 1-hour time point, then the 2-hour CSF collection could be skipped, and CSF collection would resume at the 3-hour time point.

b. Perform periodic safety monitoring during the collection period. This includes questions about any symptoms in relation to the CSF catheter (including potential adverse events such as leg or back pain, dizziness or headaches) and vital sign monitoring. Participants also should be asked about pain, redness or swelling at the blood collection site in the arm.

c. Subjects remain on bed rest throughout the CSF sampling period of 6 hours. They are allowed to use a bedside commode for toileting.

5. After the final 6-hour blood and CSF samples have been collected, remove the blood collection line and LP catheter.

6. Perform final safety monitoring, a physical, and a neurological exam.

The site should complete the LP catheter via their local practice/procedures; however, sites can refer to the LP catheter supporting documentation which will be provided.

If the subject experiences intolerable AE(s) that require early discontinuation of the sampling procedures and removal of the LP catheter, contact the Medical Monitor and Project Directors as soon as possible to discuss the situation. If feasible, the standard 6-hour observation and discharge procedures should be followed to allow for management and follow-up on the adverse events.

Period 3: Observation

The subject should be observed for at least 1 hour following removal of the LP catheter. The subject should remain on bed rest during this 1 hour follow up.

A blood patch will be administered as required if a subject exhibits signs of a post-spinal tap headache that is not managed with bed rest, oral and intravenous fluids, caffeine, and/or mild analgesics (e.g., Ibuprofen, Naproxen or Tylenol). All unused study drug should be returned to the clinical site for final accountability.

Subjects may be permitted to stay overnight in the event there are ongoing adverse events that require monitoring per investigator discretion.

Period 4: Discharge

Prior to discharge, vital signs should be recorded, and a review of AE(s) and Concurrent Medications should be conducted. Upon determination by the investigator (or qualified designee) that the subject is stable, the participant will be discharged. If a participant experiences an unstable AE, please contact the Medical Monitor and Project Directors for guidance on the appropriate course of action to be taken.

9.4.3 Post-Confinement 24-Hour Phone Follow-up

Approximately 24 hours following discharge from the Confinement Visit the subject or a person designated to speak for them will be contacted by phone to confirm the subject's well-being and to query about any new AEs.

10 EARLY TREATMENT/STUDY DISCONTINUATION

The investigators at each site will make every reasonable effort to maximize subject retention. However, if an investigator removes a subject from treatment or study, or if a subject declines further treatment or study participation, an early discontinuation visit will be completed as soon as possible following discontinuation. The early discontinuation visit will contain the same assessments as the confinement (admission) visit. If an in-person visit is not possible, site personnel will complete as much of the early discontinuation visit as possible by telephone.

Subjects who discontinue from the study prior to completing all protocol procedures may be replaced at the discretion of the Coordinating Center, in consultation with the Sponsor.

10.1 Reasons for Early Discontinuation

Participants may withdraw from the study at any time as stated in the informed consent document given to the participant at the time of enrollment. Participants may also be discontinued from treatment/study for reasons such as the following:

- Adverse experience: The participant has experienced an adverse event that, in the opinion of the investigator, requires early termination. This may include abnormal laboratory values.
- Death.
- Safety risk: Any participant who becomes a safety risk to themselves during the trial will be withdrawn.
- Protocol violation: The participant fails to meet protocol entry criteria or does not adhere to protocol requirements.
- Non-compliance: The participant is non-compliant with completion of study-related evaluations and/ or intake of study drugs.
- Development of suicidal or homicidal ideation requiring hospitalization or confinement.
- Consent is withdrawn. The participant wishes to withdraw from the study, or the legally authorized representative wishes that the participant be withdrawn.
- The study is terminated by the Sponsor/Coordinating Center, alone or at the recommendation of the Data Safety Monitoring Board.
- Lost to follow up. Participant could not be recalled back to conduct follow up visits.

11 STUDY-SPECIFIC INSTRUMENTS

We are planning a number of tests that measure states of function, depression, dementia, memory and attention. Those measures include minimally the following:

PD: MMSE, WAIS-IV, MDS-UPDRS

AD: MMSE, WAIS-IV, ADAS-Cog 14, CDR

12 STUDY-SPECIFIC PROCEDURES

12.1 Safety Assessments

Safety will be evaluated by monitoring for changes in the parameters summarized below, including any AEs/SAEs as reported by subjects or observed by the clinical staff, or by the use of concomitant medication during the study.

12.1.1 Physical and Neurological Examination

A medically qualified professional will perform a physical examination that consists of a review of the major body systems (i.e., skin, head/ears/eyes/nose/throat (HEENT), cardiovascular, pulmonary, abdomen, musculoskeletal, and extremities) and a neurological examination which will include an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, gait and mental status. Assessments of height, weight, and vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiration) are included.

12.1.2 Electrocardiogram (ECG)

An appropriately qualified individual will conduct a standard 12-lead supine resting ECG. The ECG report must be reviewed, signed, and dated by the site PI (or a medically qualified individual delegated by the site PI). Those with clinically significant ECG findings will be referred for follow-up as deemed appropriate by the investigator and may be excluded from the study.

12.1.3 Clinical Laboratory Evaluations

Blood and urine samples will be obtained for clinical safety lab assessments as described in the Schedule of Events (Appendix 1). The following table lists the clinical safety lab tests that will be assessed by the central lab at three time points: the screening visit, the pre-confinement visit, and the end of the 6-hour sampling period. Refer to the Laboratory Manual for additional details.

CLINICAL SAFETY LAB TESTS

METABOLIC PANEL	COMPLETE BLOOD COUNT	URINALYSIS
Sodium (Na)	White Blood Cell Count (WBC)	Color
Potassium (K)	Red Blood Cell Count (RBC)	Appearance
Chloride (Cl)	Hemoglobin (Hb)	Specific Gravity
Carbon Dioxide (CO2)	Hematocrit (HCT)	pH
Blood Urea Nitrogen (BUN)	Mean Corpuscular Volume (MCV)	Blood
Glucose	Mean Corpuscular Hemoglobin (MCH)	Glucose
Calcium (Ca)	Mean Corpuscular Hemoglobin	Protein
Creatinine (Crn)	Concentration (MCHC)	Ketones
Bilirubin Total	Red Blood Cell Distribution Width (RDW)	Leukocyte Esterase
Albumin	Mean Platelet Volume (MPV)	Nitrite
Protein (NOS) Total	Platelet Count (PLT)	Urobilinogen
Glutamic-OxaloaceticTransferase (AST, SGOT)		Bilirubin
Glutamic-PyruvateTransferase (ALT, SGPT)	COAGULATION PANEL	
Alkaline Phosphatase NOS	PPT/PTT [Screening Visit ONLY]	

Lab reports will be reviewed, signed and dated by the site PI (or a medically qualified individual delegated by the PI). If a value is outside of the laboratory's normal range, the clinician will indicate if the value has clinical significance. Those results that are deemed clinically significant may need to be repeated and may require follow up with the subject's primary care physician for further evaluation.

12.2 Biofluids

12.2.1 CSF for Biomarkers

Standard Lumbar Puncture (LP):

A LP will be performed as part of the baseline visit, in the morning (before 10 am is recommended), after an overnight fast.

Participants taking an anti-platelet agent (e.g. Plavix) must be discontinued from that agent for a minimum of 5 days prior to the lumbar puncture. These participants may continue with the agent after a minimum of 24 hours post LP. Participants who are taking anticoagulants (e.g. warfarin (Coumadin) and/or dabigatran (Pradaxa) may not undergo an LP and are not suitable to participate in this study.

Each study participant or a person designated to speak for them will be contacted by phone approximately 24 hours after the LP to confirm participant well-being and any adverse events.

CSF Catheter Sampling:

CSF should be collected at each timepoint during the CSF catheter sampling. At hours 0, 1, 2, 3, 4, 5, 6 (± 10min), each 6 mL of CSF is collected.

NOTE: The final dose of study drug should be given **after** the 0 hour sample but **before** the 1 hour sample

NOTE: If unable to obtain a total of 6 mL CSF at any given collection time (e.g. due to participant headache or participant's CSF production level), reduce sampling size and obtain the maximum tolerated amount (minimum 2mL). If unable to obtain a total of 6 mL CSF at any given collection time (e.g. due to participant headache or participant's CSF production level), reduce the collection volume to a tolerated amount (minimum 2mL). If there is poor flow at any of the time points, then the next collection could be skipped to allow for better flow at the subsequent collection time. For example, if less than 2mL of CSF is collected at the 1-hour time point, then the 2-hour CSF collection could be skipped, and CSF collection would resume at the 3-hour time point.

To clear blood associated with needle insertion, the first 1-2 mL (or more if needed) of CSF will be discarded. Refer to the CSF Manual for additional details.

Each study participant or a person designated to speak for them will be contacted by phone one day after being discharged from the confinement visit. The participant will be asked about their wellbeing and the occurrence of any adverse events.

12.2.2 APOE Genotype and other DNA Markers

DNA will be extracted from participant blood samples at the baseline visit and will be analyzed for APOE genotype. This will allow secondary analyses of data on the impact of the APOE genotype on putative biomarkers of AD, clinical outcome measures, and adverse events. APOE polymorphisms are an important genetic risk factor for AD. Individuals with one or two Apolipoprotein epsilon 4 (APOE4) alleles have a higher risk of developing AD and an earlier age of onset. Furthermore, those with one or two APOE4 alleles exhibit a more rapid rate of clinical change in some, but not all studies.

Blood is collected in a uniform fashion using EDTA as anti-coagulant, as described in the Laboratory Manual. Participants will be asked to consent to optional DNA banking for future research studies.

12.2.3 Plasma for Biomarkers and Pharmacokinetics

Plasma samples will be collected at the baseline visit and during the confinement visit every hour for analysis of biomarkers, inflammatory factors, dopamine, acetylcholine and drug level analyses.

Biomarker and PK analyses sample collection will be performed on the 10 mL EDTA plastic tube whose collection is described in the Laboratory Manual.

12.2.4 Blood Samples for Exosomes

Blood will be collected in the morning, after an overnight fast, in EDTA tubes and will be subjected to two sequential centrifugations to generate platelet-poor plasma within one hour from the blood draw, as described in the Laboratory Manual. **Note -** for exosomes draws at the confinement visit after the 0-hour sample, strict fasting is no longer required. Low lipid foods (e.g., apple, banana, bread) are allowed.

13 PERSONNEL REQUIREMENTS

The site PI is responsible for the overall conduct of the study at the site. The PI is to supervise project personnel and ensure that clinical raters maintain a high level of skill and accuracy in conducting assessments. Additionally, the PI will perform or supervise clinical evaluation of all subjects and ensure protocol adherence. Additional key personnel will be required, as outlined in the procedure manual.

14 ADVERSE EVENTS (AEs)

14.1 Definition

An AE is defined as per the US Code of Federal Regulation, Title 21, Part 312.32 [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32]. An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Collection of adverse events will begin once informed consent is signed and will continue until the follow-up phone call performed on the day after discharge. Adverse events include but are not limited to: (1) worsening or change in nature, severity, or frequency of conditions or symptoms present at the start of the study; (2) Subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction. An abnormal laboratory value will only be reported as an AE if the investigator considers it clinically significant, or if it leads to the Subject being withdrawn from the study.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs or symptoms. Symptoms and conditions present at the beginning of the study will be characterized, so that AEs can be defined as any new symptom, or any increase in frequency or severity of an existing symptom. Adverse events should be described with medical terminology so that the event can be matched against a medical coding dictionary, such as MedDRA (Medical Dictionary for Regulatory Activities).

Investigators should report their assessment of the potential relatedness of each AE to the protocol procedure, and to the investigational product, and/or drug delivery system used in the protocol.

Following questioning and evaluation, all AEs, whether determined to be related or unrelated to the study drug by a medically qualified site PI or clinician must be documented in the Subject's records, in accordance with the investigator's normal clinical practice, and on the AE electronic case report form (eCRF).

14.2 Following Up on AEs

The investigator is obliged to follow subjects with AEs until the events have subsided, the conditions are considered medically stable, or the subjects are no longer available for follow up. Subjects who discontinue due to adverse experiences will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF. Adverse events will be reported to the Medical Monitor, Sponsor, and DSMB, per Coordinating Center SOPs and the DSMB Charter.

Because of the potential of additive cholinergic adverse events caused by a combination of Posiphen and cholinesterase inhibitors in some subjects, the severity of such adverse events should be carefully evaluated taking the criteria in Appendix 2 into consideration (modified from CTCAE version 4.03.)

15 SERIOUS ADVERSE EVENTS (SAE)

15.1 Definition

A SAE is defined as per the US Code of Federal Regulation, Title 21, Part 312.32 [http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32].

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the 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 hospitalization, or the development of drug dependency or drug abuse.

15.2 Reporting SAEs

Collection of serious adverse events will begin once informed consent is signed (regardless of study drug exposure) and will continue until 30 days following the last dose of study drug. All SAEs must be reported to the Medical Monitor, the Sponsor, Project Directors and the Coordinating Center within 24 hours of learning of the event. This in turn will trigger an alert to

the appropriate Coordinating Center personnel and Protocol Project Directors, which will lead to the initiation of the creation of the report. A notification will be sent to all participating sites and the DSMB once the report is available. Sites will inform their IRB of the event based on local IRB requirements. The Sponsor is the IND holder and is responsible for submitting any SAEs according to the FDA reporting requirements.

16 DATA AND SAFETY MONITORING BOARD (DSMB)

A DSMB will review the safety information from the study on an ongoing basis. The DSMB, will identify the study-specific data parameters and format of the information to be reported, as well as the timing of reports based on the enrollment status of the study. The DSMB will initially be provided with data blinded to treatment status, but they may request unblinded data if there is a safety concern.

Additionally, the DSMB will be informed of the occurrence of any serious adverse events within 7 days of being reported to the Coordinating Center. The DSMB may at any time request additional information from the Coordinating Center.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. Using the Safety Review Process (review of lab data, vitals, and adverse events) and the DSMB, there is substantial oversight and case review to alert the investigators, in a timely manner, to any safety issues that may arise. Further details will be provided in the DSMB charter.

17 RECORDING AND COLLECTION OF DATA

17.1 Electronic Case Report Form (eCRF)

The PI or designee will record all data collected (either written or electronic record of data). Written or electronic data of record must be entered into the eCRF provided for that purpose. In some instances, no prior written or electronic record of data may exist, and data recorded directly into the eCRF is considered source data. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be authorized to provide electronic signatures. The PI is responsible to verify the integrity of the data and acknowledge as such by signature.

All site entries will be made in a secured eCRF and the PI will review the record for completeness. If corrections are necessary to the eCRFs, the PI or designee will update the eCRF and provide documentation for the reason for change.

Completed eCRFs will be submitted according to provided instructions and reviewed by the Coordinating Center to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site.

17.2 Study Files and Source Documents

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the Coordinating Center and/or sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, video/audio recordings, and other records that leave the site will be identified only by a subject identification number (Subject ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the Subject, except as necessary for monitoring by the Institutional Review Board (IRB), the FDA, and the Office for Human Research Protections (OHRP).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Those regulations require a signed Subject HIPAA Authorization informing the Subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. Each site PI, under the guidance of his/her IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

18 ETHICS AND REGULATORY CONSIDERATIONS

18.1 Good Clinical Practice

This study will be conducted in compliance with the protocol and accordance with Good Clinical Practice (GCP) guidelines, as defined by the International Conference on Harmonization (ICH)

Guideline, Topic E6, the United States Code of Federal Regulations (CFR), Title 21, Part 50 – Protection of Human Subjects, and Part 56 – IRBs, HHS Regulations (45 CFR part 46, 160, 164 HHS Regulations for the Protection of Human Subjects; HIPAA; 42 CFR part 50), Subpart F HHS Regulations for Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

No study document shall be destroyed without prior written agreement between the Coordinating Center and the investigator. Should the investigator wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent of the Coordinating Center.

18.2 Institutional Review Board (IRB)

Institutional Review Boards must be constituted, and their authority delegated through the institution's normal process of governance according to applicable State and Federal requirements for each participating location. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States, only institutions holding a current US Federal wide Assurance (FWA) issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

The investigator must obtain approval from the IRB for all subsequent protocol amendments and, when warranted, changes to the informed consent document. Protocol and informed consent form amendments can be made only with the prior approval of the Coordinating Center. The investigator may not implement any protocol deviation without prior notification, review, and documented approval by the Study Director, except where necessary to eliminate an immediate hazard to study subjects, or when change(s) involve only logistical or administrative aspects of the trial. The investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

18.3 Informed Consent and Health Insurance and Portability and Accountability Act (HIPAA) Compliance

Informed consent will be obtained in accordance with 21CFR §50.25, and ICH Good Clinical Practice. Applicable HIPAA privacy notifications will be implemented, and HIPAA authorizations signed before protocol procedures are carried out. Information should be given in both oral and written form as deemed appropriate by the Site's IRB.

Prior to the beginning of the trial, the investigator must obtain the IRB's written approval of the informed consent form and any other written information to be provided to subjects and be acceptable by Regulatory Affairs. Consent forms must be in a language fully comprehensible to the prospective subjects and/or their authorized representatives and study partners. Subjects, their relatives, guardians, or authorized representatives and study partners will be given ample opportunity to inquire about the details of the study. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. Subjects will be provided a copy of the signed ICF.

The informed consent will not only cover consent for the trial itself, but for the genetic samples/data/storage and biomarker samples/data/storage as well. Consent forms will specify that DNA and biomarker samples are for research purposes only; the tests on the DNA and biomarker samples are not diagnostic in nature and subjects will never receive results.

19 STUDY MONITORING

The clinical monitor is responsible for inspecting the case report forms (CRFs) and source documentation at specific time points throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research. The monitoring visits must be conducted according to the applicable ICH and FDA guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Site Investigator will cooperate in the monitoring process by ensuring the availability of the CRFs, source documents and other necessary documents at the time of the monitoring visits. Site Investigator will promptly address any matters brought to his/her attention by the monitor. The Site Investigator may also be asked to meet in-person with the site monitor during certain visits.

20 AUDIT

In accordance with ICH E6 (Good Clinical Practices) representatives of the Coordinating Center and/or Sponsor and/or regulatory agency may select this study for audit. The investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by Regulatory Affairs that will be suitable for inspection at any time by the CRO, Sponsor, its designees, and/or regulatory agencies. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the trial conduct and compliance with the protocol may also occur.

21 RECORD RETENTION

Essential documents and study records must be retained for a minimum of seven years following primary publication of study results. The Coordinating Center will notify sites when retention of such documents is no longer required. Essential documents should be retained for at least 2 years

after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

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23 APPENDIX 1: SCHEDULE OF EVENTS

Visit Timing[a]	Day -42 to 0		Day 14 (± 4)	1-3 days prior to confinement	Days 25 (± 2)		
Procedures	**Screening**	**Baseline**	**Phone**	**Pre-Confinement Phone Contact**	**Confinement**		
					Admission	**6-Hour Sampling**	**Discharge[e]**
Informed Consent	X						
Demographics	X						
Medical and Psychiatric History	X						
Height and BMI	X						
Inclusion and Exclusion Criteria	X	X					
Urine Dipstick Pregnancy Test	X						
Physical and Neurological Examination	X	X			X		X
AD & PD: MMSE	X	X			X		
AD: CDR	X	X			X		
AD: ADAS-Cog 14		X			X		
AD & PD: WAIS-IV		X			X		
PD: MDS-UPDRS	X[g]	X			X		
C-SSRS	X	X			X		
Vital Signs [b]	X	X			X	X	X
Clinical Lab Safety Tests	X	X[i]			X[i]		
12-Lead ECG	X	X			X		X
MRI of Brain[c]	X						
Adverse Events	X	X	X	X	X	X	X
Prior/Concomitant Medication	X	X	X	X	X	X	X
Randomization		X					
Dispense Study Drug		X					

Dosing Study Drug in Clinic		X				X	
Study Drug Compliance Check			X	X	X		
APOE Genotype and DNA Markers		X					
Blood Sampling for PK		X				X	
Lumbar Puncture for baseline Pharmacodynamics		X					
LP Catheter Placement[h]					X		
Sampling for Biomarkers in Blood, Plasma and CSF		X				X[f]	
24-Hour Phone Follow-Up[d]		X					X
Lumbar Xray[h] (Optional)	X						

[a] Refer to Section 9 for more details on visit timing and windows.

[b] Vital signs will include sitting blood pressure, pulse, temperature, respiration rate, and weight, except during the 6-hour Sampling Phase of the Confinement Visit when weight will not be included.

[c] An MRI of the brain will only be conducted if there is no brain MRI available from within the window specified in Inclusion Criteria.

[d] Phone Follow-up should occur approximately 24-hours after completion of the LP procedure at Baseline and after discharge from the Confinement Visit.

[e] The Early Discontinuation Visit will contain the same assessments as the Pre-confinement Visit.

[f] Sampling Times: 0,1,2,3,4,5,6 hrs (±10 mins for collection)

[g] Hoehn & Yahr Stage only for inclusion determination

[h] X-Ray is only required if LP insertion will not be performed with fluoroscopy

[i] Safety labs at baseline and confinement (for sample 0 hour) should be taken fasted

24 APPENDIX 2: SEVERITY EVALUATION OF CHOLINERGIC ADVERSE EVENTS (ADVERSE EVENTS OF SPECIAL INTEREST)

Because of the potential of additive cholinergic adverse events caused by a combination of Posiphen and cholinesterase inhibitors in some subjects the severity of such adverse events should be carefully evaluated taking the criteria below into consideration (modified from "CTCAE version 4.03.)

Adverse Event	Mild	Moderate	Severe
nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	≥6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated
diarrhea	Increase of <4 stools per day over baseline	Increase of 4 - 6 stools per day over baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; limiting self-care ADL
anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated
fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self-care ADL