Cover Page for ClinicalTrials.gov

Sponsor name:	Annovis Bio, Inc.
NCT number:	NCT05357989
Sponsor trial ID:	ANVS-22001
Official title of study:	A 6-month prospective, randomized, double-blind, placebo-controlled clinical trial investigating the efficacy, safety, and tolerability of two different doses of buntanetap or placebo in patients with early Parkinson's disease
Document type:	Protocol
Document date:	August 21, 2023

Protocol Title:

A 6-month prospective, randomized, double-blind, placebo-controlled clinical trial investigating the efficacy, safety, and tolerability of two different doses of buntanetap or placebo in patients with early Parkinson's disease

Protocol Short Title:

A double-blind study to investigate efficacy and safety of buntanetap compared with placebo in participants with early PD

Protocol Number: ANVS-22001

Sponsor: Annovis Bio, Inc., Berwyn, Pennsylvania 19312, USA

US IND Number: 159667

NCT Number: 05357989

EudraCT Number: 2022-001542-38

IMP Identifier: Buntanetap

Confidentiality Statement

SPONSOR SIGNATURE PAGE:

Protocol Title:

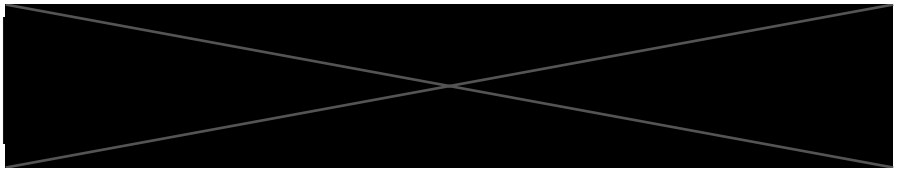
A 6-month prospective, randomized, double-blind, placebo-controlled clinical trial investigating the efficacy, safety, and tolerability of two different doses of buntanetap or placebo in patients with early Parkinson's disease

Protocol Short Title:

A double-blind study to investigate efficacy and safety of buntanetap compared with placebo in participants with early PD

CONTRACT RESEARCH ORGANIZATION	**SPONSOR**
TFS Trial Form Support International AB together with each of its subsidiaries and affiliates ("TFS") Medicon Village Scheeletorget 1 Byggnad 601 SE – 223 81 Lund, Sweden	ANNOVIS BIO, Inc. 1055 Westlakes Drive, Suite 300 Berwyn, Pennsylvania 19312 USA Maria L. Maccecchini, PhD President & CEO maccecchini@Annovisbio.com Tel: +1-(610) 727-3710

SPONSOR SIGNATURE



_____ _____

Maria Maccecchini, PhD Date

PRINCIPAL INVESTIGATOR SIGNATURE PAGE:

Protocol Title:

A 6-month prospective, randomized, double-blind, placebo-controlled clinical trial investigating the efficacy, safety, and tolerability of two different doses of buntanetap or placebo in patients with early Parkinson's disease

Protocol Short Title:

A double-blind study to investigate efficacy and safety of buntanetap compared with placebo in participants with early PD

CONTRACT RESEARCH ORGANIZATION	**SPONSOR**
TFS Trial Form Support International AB together with each of its subsidiaries and affiliates ("TFS") Medicon Village Scheeletorget 1 Byggnad 601 SE – 223 81 Lund, Sweden	ANNOVIS BIO, Inc. 1055 Westlakes Drive, Suite 300 Berwyn, Pennsylvania 19312 USA Maria L. Maccecchini, PhD President & CEO maccecchini@Annovisbio.com Tel: +1-(610)-727-3710

I, the undersigned, have carefully reviewed this clinical study protocol and I agree to conduct this study in accordance with the ethical principles set forth in the Declaration of Helsinki, the International Council for Harmonization guidelines on Good Clinical Practice (ICH E6, R2), and any applicable regulations and laws.

INVESTIGATOR SIGNATURE

_____ _____

Signature **Date**

Investigator Name: _____

Institution Name: _____

LIST OF ABBREVIATIONS

5'UTR	5' untranslated region
αSYN	Alpha-synuclein
Aβ	Amyloid Beta
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS	Alzheimer's Disease Cooperative Study
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APP	Aβ Precursor Protein
AST	Aspartate Aminotransferase
AUC	Area under the curve
BChE	Butyrylcholinesterase
BDNF	Brain Derived Neurotrophic Factor
BP	Blood pressure
BPM	Beats per minute
BSA	Body surface area
CA	Competent authority
CFR	Code of Federal Regulations
CGIS	Clinical Global Impression of Severity
cGMP	Current Good Manufacturing Practice
CTCAE	Common Terminology Criteria for Adverse Events
CLBP	Chronic low back pain
Cmax	Maximum plasma and CSF concentration
ChE	Cholinesterase
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
C-SSRS	Columbia Suicide Severity Rating Scale
CNS	Central Nervous System
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CV	Coefficients of variation
CVD	Cerebrovascular Dementia
CYP3A4	Cytochrome P450 3A4 enzyme
DNA	Deoxyribonucleic Acid
DS	Down Syndrome
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	European Community
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	European Union
FCR	Fractional clearance rate
FDA	Food and Drug Administration

FSR	Fractional Synthesis Rate
FWA	Federal wide Assurance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFAP	Glial Fibrillary Acidic Protein
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
HbA1c	Hemoglobin A1C
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxypropyl methylcellulose
H&Y	Hoehn and Yahr
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intrauterine Device
IUS	Intrauterine Hormone Releasing System
kg	kilogram
MAD	Multiple Ascending Dose
MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
MDS-UPDRS	MDS-United Parkinson’s Disease Rating Scale
MedRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
mITT	Modified Intent to Treat
mL	milliliter
MMRM	Mixed Model for Repeated Measures
MMSE	Mini-Mental State Examination
mRNA	Messenger Ribonucleic Acid
ms	milliseconds
N	Number of Subjects
NFL	Neurofilament Light
NG	Neurogranin
ng.h	Nanogram per hour
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
OHRP	Office for Human Research Protections
p-tau	Phosphorylated tau
PD	Parkinson’s disease
PGIC	Patients' Global Impression of Change
pH	Power of Hydrogen
PHI	Protected Health Information
PI	Principal Investigator

PID	Patient/Participant ID
PK	Pharmacokinetic
POC	Proof of Concept
PS1	Presenilin 1
QD	Once a Day
QID	4 Times a Day
QT	Interval seen in electrocardiogram (ECG) test
QTcf	Interval seen in QT (ECG) test
RA	Regulatory Authority
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sAPPa	soluble APP alpha
sAPPb	soluble APP beta
SARS-CoV-2	Covid 19 Virus
SAS	Statistical Analysis System
SD	Standard Deviation
SH-SY-5Y	Human Derived Cell Line
SILK™	Stable Isotope Labeling and Kinetics
SNCA	Synuclein Alpha
SOC	Standard of Care / System Organ Class
SNRI	Selective Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
sTREM	Soluble Triggering Receptor Expressed on Myeloid Cells
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
tau	Tau protein
TEAE	Treatment Emergent Adverse Event
TDP-43	TAR DNA-binding Protein 43
TG	Transgenic
Tmax	Time to peak drug concentration
TMF	Trial Master File
ULN	Upper limit of normal
US	United States
WAIS-IV	Wechsler Adult Intelligence Scales, 4th edition

TABLE OF CONTENTS

1.0 PROTOCOL SYNOPSIS

PROTOCOL TITLE	A 6-month prospective, randomized, double-blind, placebo-controlled clinical trial investigating the efficacy, safety, and tolerability of two different doses of buntanetap or placebo in patients with early Parkinson's disease
STUDY DESIGN	The study will be 6-month placebo-controlled and double-blinded: subjects, investigators and the sponsor will be blinded to the subjects' treatment. Qualified subjects will be randomly assigned at a 1:1:1 ratio to one of three treatment arms: buntanetap 10 mg, buntanetap 20 mg, and placebo, through an Interactive Randomization System, after a screening period of up to 42 days. MDS-UPDRS, PGIC, CGIS, WAIS coding, and MMSE will be assessed by clinicians who have successfully completed the requisite certifications/trainings for each assessment. All efforts will be made to ensure subjects will be assessed by the same clinician throughout the study. Participants should stop SOC Parkinson's medications 12 hrs before clinical visits to ensure clinical OFF-state during visit.
DURATION OF STUDY PARTICIPATION	Each subject will have up to a 42-day screening period, a baseline visit, followed by 6 months of treatment at home, followed by an in-clinic visit. The total duration of study participation will be 7-8 months.
SUMMARY OF INVESTIGATIONAL PRODUCT	Buntanetap 10mg, 20 mg, or placebo capsules, taken orally once a day for 6 months.
SUMMARY OF KEY ELIGIBILITY CRITERIA	• Diagnosis of idiopathic PD • Age 40 to 85 • MMSE 22-30 • Hoehn & Yahr =1,2,3 during ON-state & OFF-state < 2hrs per day
PRIMARY OUTCOME MEASURES	Aim 1. Change from baseline to Month 6 in MDS-UPDRS Part II (OFF-state) Aim 2. Safety and Tolerability
SECONDARY OUTCOME MEASURES	Aim 1. Change from baseline to Month 6 in the sum of MDS-UPDRS Part II+III (OFF-state) Aim 2. Change from baseline to Month 6 in the MDS-UPDRS Part III (OFF-state) Aim 3. Change from baseline to Month 6 in the total MDS-UPDRS score (OFF-state) Aim 4. Percentage of Responders with "Much Improved" or "Very Much Improved" on Participant Global Impression of Change (PGIC) (ON-state) Aim 5. Change from baseline to Month 6 on Clinical Global Impression of Severity of illness (CGIS) (OFF-state)
EXPLORATORY OUTCOME MEASURES	Aim 1. Change from baseline to Month 6 in the plasma biomarkers measured

	Aim 2. Change from baseline to Month 6 in WAIS Coding Test (OFF-state) Aim 3. Change from baseline to Month 6 in MMSE (OFF-state) Aim 4. Pharmacokinetics (PK)

2.0 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 AD 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.

Buntanetap 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 αSYN, 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 PD 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.

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, buntanetap has normalized all those actions.

Preclinical data proves buntanetap's efficacy in restoring colonic motility in a human $SNCA^{A53T}$ and $SNCA^{A30T}$ transgenic (tg) mice models of early PD, in restoring memory and learning in an *APP/PS1* tg mouse model of AD, restoring axonal transport in DS trisomic mice, preserving memory, and learning in traumatic brain injury rats and in stroke mice, and preserving the retina in acute glaucoma.

Buntanetap's safety has been established in three Phase 1 clinical studies by Maccecchini et al (2012). Importantly, buntanetap normalized levels of αSYN, APP, and tau as well as inflammatory markers in the cerebrospinal fluid (CSF) of mildly cognitively impaired (MCI) subjects at a dose of 4x60 mg/day (Protocol QR12001).

Recently, we also tested buntanetap 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 conducted by the ADCS and was completed with 16 treated subjects (Protocol QR15001). The study officially finished in December 2021, with 7 patients treated in cohort 1 (1x60mg/day), 6 patients in cohort 2 (2x60mg/day), and 2 patients in cohort 3 (3x60mg/day). The CSF measurements of Aβ showed in a dose-dependent fashion that buntanetap slows the synthesis and lowers the total amount of Aβ synthesized by half. It also showed improvement in cognition as measured by the ADAS-Cog11 scale.

We recently completed a double Phase 2a study (ANVS-12003) in both early AD and early PD populations. In PD, 54 subjects were recruited and randomized into 0, 5, 10, 20, 40 and 80mg QD buntanetap for 25±2 days. CSF biomarkers were collected and analyzed. MDS-UPDRS and WAIS coding were tested. CSF biomarker results show that buntanetap lowered αSYN level, reduced inflammation (shown by GFAP, YKL-40, sTREM and Complement C3), preserved axonal integrity shown by neurofilament light (NFL) and improved synaptic density shown by neurogranin (NG). Although sample size was not powered to see efficacy, buntanetap improved PD subjects WAIS coding scores at all doses including 5mg QD. Buntanetap also improved PD subjects MDS-UPDRS Part II, III, IV and Total score.

In this study, we want to confirm buntanetap's efficacy in early PD subjects. During the dose-finding Phase 2a study, we saw a dose-response curve between 0 and 10/20 mg QD. Therefore, we decided to dose subjects with 10 and 20 mg QD.

2.1. OBJECTIVES

Study objectives include assessing buntanetap' s efficacy and safety in early PD subjects.

Study drugs will be 10 mg, 20mg of buntanetap, or matching placebo capsules, taken once per day in the morning before food. Eligible subjects will be randomly assigned at a 1:1:1 ratio to one of the three treatment arms: buntanetap 10 mg, buntanetap 20 mg, and placebo, through an Interactive Randomization System, after a screening period of up to 42 days. The total duration of the study will be 7-8 months. MDS-UPDRS, PGIC, CGIS and WAIS coding will be assessed by clinicians who have successfully completed the requisite certifications/trainings for each assessment. All efforts will be made to ensure subjects will be assessed by the same clinician throughout the study. Participants should stop SOC Parkinson's medications 12 hrs before clinical visit to ensure clinical OFF-state during visit.

2.2. ENDPOINTS

Primary Endpoints:

1. **Change From Baseline to Month 6 in MDS-UPDRS Part II (OFF-state)**

Change in the Score from the MDS- Unified Parkinson's Disease Rating Scale (UPDRS) Parts II from Baseline to the End of Trial. MDS-UPDRS Part II (Motor experiences of daily living) has 13 items and the score ranges from 0–52, with higher score reflecting greater severity.

2. **Safety and Tolerability**

    - Adverse Events (AE)
    - Severity of AEs
    - Drug related AEs
    - AEs leading to study discontinuation
    - Electrocardiogram findings
    - Clinical laboratory test results
    - Vital sign measurements
    - Physical and neurological examination findings

Secondary Endpoints:

1. **Change from Baseline to Month 6 in the sum of MDS-UPDRS Part II+III (OFF-state)**

    Change in the Sum of the Score from the Activities of Daily Living (ADL) Scale and Motor Examination in the MDS-UPDRS (Parts II+III, a UPDRS Subtotal) from Baseline to the End of Trial.

    MDS-UPDRS Part II (Motor experiences of daily living) has 13 items and the score ranges from 0–52, with higher score reflecting greater severity MDS-UPDRS Part III (motor examination) has 18 items and ranges from 0-132, with higher scores reflecting greater severity. The sum of Part II+III will be 0-184, with higher scores reflecting greater severity.

2. **Change from Baseline to Month 6 in the MDS-UPDRS Part III (OFF-state)**

    MDS-UPDRS Part III (motor examination) has 18 items and ranges from 0-132, with higher scores reflecting greater severity.

3. **Change From Baseline to Month 6 in The Sum of MDS-UPDRS Total Score (OFF-state)**

    The MDS-Unified Parkinson's Disease Rating Scale (UPDRS) is a 50-item rating scale designed to assess Parkinson's disease-related disability and impairment. The scale comprises four parts: Part I evaluates mentation, behavior, and mood symptoms; Part II evaluates activities of daily living (ADL); Part III evaluates motor function; and Part IV evaluates complications of dopaminergic therapy. The Total score is the sum of the subscale scores for Parts I to III and ranges from 0 to 236, with higher scores reflecting greater severity.

4. **Percentage of Responders with "Much Improved" or "Very Much Improved" on Participant Global Impression of Change (PGIC) (ON-state)**

The PGIC is the participant-reported outcome. The qualitative assessment of meaningful change will be determined by the participant in response to the question, "Compared to your condition at the beginning of treatment, how much has your condition changed?" Scores are: 1=very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; and 7=very much worse. Percentage of responders with much improved and very much improved on PGIC scale will be assessed. PGIC will be taken at home while the subject is during ON-state (with their SOC for Parkinson disease).

5. **Change From Baseline to Month 6 on Change on Clinical Global Impression of Severity (CGIS) (OFF-state)**

The Clinical Global Impressions Scale on the severity of movement impairment as assessed by the site rater. Site raters will be asked: Considering your total clinical experience with the Parkinson disease population, how ill is the patient at this time? Answers were based on a 7-point scale, with 1=not assessed, 2= very mild, 3= mild, 4= moderate, 5= moderate severe, 6= severe, 7=extremely severe.

Exploratory Endpoints:

1. **Changes From Baseline to Month 6 in The Plasma Biomarker Measured**

Potential biomarkers to be measured in plasma are Neurofilament Light (NFL), Glial fibrillary acidic protein (GFAP) and TDP43.

2. Change From Baseline to Month 6 in WAIS Coding Test (OFF-state)

In the digital symbol coding test individuals are asked to record associations between different symbols and numbers within time limits. The Total score is the sum of all the correctly coded numbers.

3. Change From Baseline to Month 6 in MMSE (OFF-state)

The Mini-Mental State Exam (**MMSE**) is a 30-point test, widely used test of cognitive function.

4. **Pharmacokinetics**

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

3.0 COMPLETED STUDIES

The following is a summary of the available information on buntanetap. Detailed information can be found in the current buntanetap Investigational Drug Brochure.

3.1. Summary of Non-Clinical Findings

In APP transgenic AD mice, buntanetap 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 buntanetap 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, buntanetap 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 buntanetap fully restored axonal transport *in vitro* and *in vivo* (Chen 2021). In summary, buntanetap is a translational inhibitor of APP and aSYN and fully restores function at doses that are very low and very safe.

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

The cardiac electrophysiological properties of buntanetap tartrate were negative *in vitro* using human ether-a-go-go related gene (hERG) transfected human embryonic kidney cells (HEK 293). Buntanetap 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. Buntanetap readily crosses the blood-brain barrier. The signs/symptoms noted at high doses of buntanetap may be related to cholinergic manifestations. In *in vitro* assays, buntanetap showed minimal inhibition of AChE or BChE (Butyrylcholinesterase) activity, however, a metabolic product of buntanetap, N1-norposiphen demonstrated acetyl cholinesterase inhibitory activity (Yu 2013). There were no effects on the reproductive organs associated with 4-week exposure to buntanetap in male or female rats or dogs.

Repeat Oral dose Toxicity Study of buntanetap in male and female rats giving 10, 20 and 40 mg/kg for 26 weeks showed that NOAEL dose was 40 mg/kg for both male and female rats. Repeat Oral dose Toxicity Study of buntanetap in male and female dogs giving 5, 10 and 20 mg/kg for 39 weeks showed that NOAEL dose was 20 mg/kg for both male and female dogs.

3.2. Summary of Clinical Findings

Three Phase 1 studies and two Phase 2a study have been conducted with buntanetap. For the three Phase 1 studies, 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). One Phase1/2 study (Discover) was to test the safety, tolerability, PK and PD of buntanetap in subjects with early Alzheimer's disease (Protocol

QR12005). The other Phase 2a study was a double study for both early AD and early PD subjects to test buntanetap's safety, pharmacokinetics, biomarkers and efficacy (Protocol ANVS-12003).

In the SAD trial, buntanetap was administered orally in doses of 10, 20, 40, 80, and 160 mg. Limiting side effects observed following the 160 mg dose resulted in curtailment of the study without administration of the 320 mg dose. The 160 mg dose was associated with an increased incidence of nausea and vomiting (four subjects were nauseous and three vomited). Adverse events were either mild or moderate; none were severe. Buntanetap 80 mg was determined as the no observed adverse effect level.

Following oral administration, peak concentration was achieved rapidly, with mean observed T_{max} between 1.3 and 1.6 hours for both males and females at all doses. C_{max} increased disproportionately with increasing dose, as did the various measures of AUC. Differences in mean observed C_{max} and AUC between males and females at each dose appeared to be related to body weight rather than gender differences.

In the MAD trial, buntanetap was administered orally in doses of 20, 40, and 60 mg 4 times a day (QID). The first two treatments were dosed 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.

Buntanetap 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 buntanetap was measured after 10 days of administration (4x60 mg) over 12 hours in CSF and plasma of the AD participants. The pharmacodynamics of a number of biomarkers was compared for 12 hours before the first dose at day 0 and after the last dose at day 11 of buntanetap administration. We found that the plasma concentrations of buntanetap 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 buntanetap levels measured in plasma.

Because a substantial proportion of the adverse events observed in AD subjects treated with cholinesterase inhibitors appear to reflect the cholinomimetic properties of molecules in this

class, buntanetap's highest tolerated dose is determined by the levels of the N1-metabolite in blood and brain.

While the $t_{1/2}$ of buntanetap 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. The concentrations of buntanetap in the brain, extrapolated from blood and CSF, were 8 times higher than in plasma. 10 days of treatment with buntanetap normalized CSF levels of sAPP, tau, αSYN and a series of inflammatory markers. The concentration and persistence of buntanetap in the brain suggest that much lower doses of drug administered once daily could achieve the desired pharmacological effect.

For the Phase 2a trial (Protocol ANVS-12003), there are two parts of the study. In the first part, early AD and PD subjects were given 80 mg QD buntanetap or placebo for 25 days. In the second part, early PD subjects were given 5 mg, 10 mg, 20 mg, 40 mg QD buntanetap or placebo for 25 days. In all doses and in both AD and PD subjects, buntanetap was safe and well tolerated. No SAE was reported.

Buntanetap was absorbed rapidly after oral administration, achieving maximum plasma and CSF concentration (C_{max}) within 1-2 hours. For the 80 mg doses, with fully defined plasma profiles, the mean terminal $t_{½}$'s were 2.76 ± 2.668 hours. The half-life ($t_{½}$) of the plasma concentrations at the lower doses (5 & 10 mg) could not be calculated accurately. The C_{max} increased disproportionally with dose (15.31, 40.19 and 112.31 ng.h/mL after a single dose of 20, 40 and 80 mg, respectively).

Consistent with Phase 1 POC study, 80mg QD buntanetap reduced AD subjects' CSF levels of sAPPa, sAPPb, tau, phosphorylated tau (tau181), αSYN and a series of inflammatory markers (YKL-40, GFAP, sTREM2, Complement C3). Buntanetap also improved axonal integrity shown by Neurofilament light (NFL) and synaptic function shown by neurogranin (NG). Similarly, 80 mg QD buntanetap reduced PD subjects' CSF levels of αSYN and a series of inflammatory markers (YKL-40, GFAP, sTREM2, Complement C3). Buntanetap also improved PD subjects' axonal integrity shown by NFL and synaptic function shown by NG.

Further, buntanetap treatment improved AD subjects' cognition shown by ADAS-Cog11 and WAIS coding test and improved PD subjects' movement shown by MDS-UPDRS and WAIS coding test.

4.0 BACKGROUND AND STUDY RATIONALE

4.1. Background

A major pathological hallmark of PD is the appearance in the gut and in the brain of aSYN aggregates that form Lewy bodies. 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 other neurotoxic proteins such as TDP43 may also contribute to neuropathology of PD. A high load of inflammation and microglia activating factors that contribute to neurodegeneration are also common in PD.

Buntanetap is the (+) enantiomer of phenserine, an orally available small molecule. While phenserine inhibits AChE, buntanetap has no AChE activity itself and develops some activity in vivo with the metabolism to N1-bisnorposiphen. *In vivo*, phenserine has about 10-20 times more AChE inhibitory activity than buntanetap's metabolite N1-bisnorposiphen.

Buntanetap 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 8 to 16 times lower than the levels causing cholinomimetic effects.

Buntanetap 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 buntanetap stabilizes the complex, thereby inhibiting the translation of these mRNAs.

As buntanetap 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

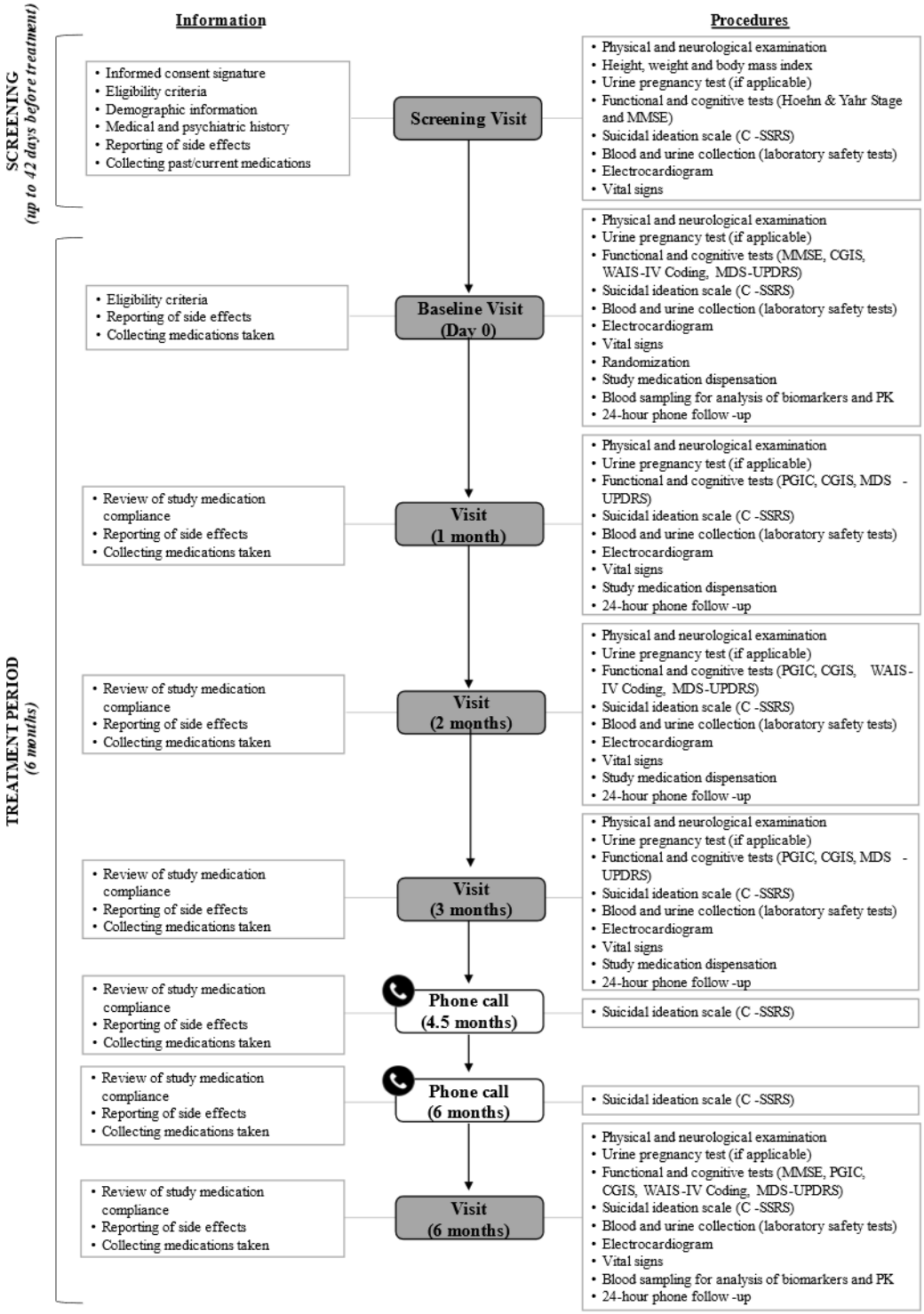
Study population: The study will be conducted in subjects with early PD.

Dose selection: Qualified subjects will be randomly assigned at a 1:1:1 ratio to one of the three treatment arms: buntanetap 10 mg, buntanetap 20 mg, and placebo.

Study Design: 450 early PD subjects will be randomized to 10 mg, 20 mg of buntanetap QD 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. Randomized participants will visit the clinic for the first-time dosing with administration of 10 mg or 20 mg of buntanetap or placebo, followed by an at home dosing period of 6 months, with daily administration of 10 mg or 20 mg of buntanetap or placebo. Participants will be required to attend clinic visits at 1 month, 2 months, 3 months, and 6 months (end-of-trial) time points, where they will undergo study procedures that include safety assessments (AE and concomitant medication monitoring, 12-lead ECGs, clinical laboratory testing, vital signs assessments, and physical/neurological examinations), psychometric tests (MDS-UPDRS, WAIS, MMSE) and PGIC and CGIS. After all end-of-study procedures are complete, the subject will be discharged to home. A 24-hour follow-up call will occur after all clinic visits to assess the participants current condition and if there are any additional adverse events to report.

Subjects who drop out during the initial 5 months at home treatment period will be discontinued and should complete an Early Discontinuation visit as soon as possible following discontinuation. Subjects that drop out after the initial 5 months, will be scheduled for an End of Trial visit. If 4 subjects are discontinued due to serious adverse events, a safety review will be conducted without interrupting the study. Unscheduled visits are allowed and investigators will perform safety assessments and AE/SAE and concomitant medication reviews as needed.

The following figure shows how many times and when these procedures will be performed throughout the approximately 7 months of the study duration:


SCREENING
(up to 42 days before treatment)
TREATMENT PERIOD
(6 months)
Information
Procedures
• Informed consent signature
• Eligibility criteria
• Demographic information
• Medical and psychiatric history
• Reporting of side effects
• Collecting past/current medications
Screening Visit
• Physical and neurological examination
• Height, weight and body mass index
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (Hoehn & Yahr Stage and MMSE)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Eligibility criteria
• Reporting of side effects
• Collecting medications taken
Baseline Visit (Day 0)
• Physical and neurological examination
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (MMSE, CGIS, WAIS-IV Coding, MDS-UPDRS)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Randomization
• Study medication dispensation
• Blood sampling for analysis of biomarkers and PK
• 24-hour phone follow -up
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Visit (1 month)
• Physical and neurological examination
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (PGIC, CGIS, MDS - UPDRS)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Study medication dispensation
• 24-hour phone follow -up
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Visit (2 months)
• Physical and neurological examination
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (PGIC, CGIS, WAIS-IV Coding, MDS-UPDRS)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Study medication dispensation
• 24-hour phone follow -up
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Visit (3 months)
• Physical and neurological examination
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (PGIC, CGIS, MDS - UPDRS)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Study medication dispensation
• 24-hour phone follow -up
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Phone call (4.5 months)
• Suicidal ideation scale (C -SSRS)
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Phone call (6 months)
• Suicidal ideation scale (C -SSRS)
• Review of study medication compliance
• Reporting of side effects
• Collecting medications taken
Visit (6 months)
• Physical and neurological examination
• Urine pregnancy test (if applicable)
• Functional and cognitive tests (MMSE, PGIC, CGIS, WAIS-IV Coding, MDS-UPDRS)
• Suicidal ideation scale (C -SSRS)
• Blood and urine collection (laboratory safety tests)
• Electrocardiogram
• Vital signs
• Blood sampling for analysis of biomarkers and PK
• 24-hour phone follow -up

4.3. Outcome Measures

Efficacy outcome measures: Buntanetap has shown to improve PD subjects' mobility. MDS-UPDRS sum of scores of Part II, Part III, Part II+III, and total score of first three parts will be measured to assess its improvement on PD subjects.

Safety outcome measures: Reports of adverse events (AEs) and serious adverse events (SAEs) during exposure to buntanetap will be collected to evaluate if there are any significant clinical safety issues for the study population. Extensive clinical and laboratory safety data already exist for buntanetap; therefore, these safety measures will be sufficient in the proposed study.

Clinical, functional and cognitive assessment measures: The subjects will be administered the Hoehn & Yahr (1967) and the MMSE (Folstein 1975) for determination of inclusion into the study. The MDS-UPDRS (Goetz 2008), Clinical Global Impression of Severity (CGIS, Hurst 2004), and Participant Global Impression of Change (PGIC, Hurst 2004) will be administered for subjects' movement and daily function. The Coding subtest from the Wechsler Adult Intelligence Scales, 4th edition (WAIS-IV; Wechsler 2008) will serve as a sensitive measure of CNS dysfunction. MMSE will also be measured to assess subjects' cognitive change.

Exploratory measures: Buntanetap has shown to reduce inflammation and preserve axonal integrity and synaptic functions as well as neurotoxic proteins in previous Phase 2a studies. In this study we plan to measure plasma GFAP, NFL and potentially TDP43 depending on assay availability.

5.0 POTENTIAL RISKS AND BENEFITS OF INVESTIGATIONAL PRODUCT AND STUDY PROCEDURES

5.1. Risks and Benefits Associated with Buntanetap 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 placebo are not uncommon but are obviously not due to a pharmacological agent as an industry standard placebo (inactive ingredients) will be provided. The placebo used for the study consists of standard (non-lactose) pharmaceutical excipients which are generally recognized as safe (GRAS), with no known side effects anticipated.

Buntanetap has been tested in animal safety studies. No adverse effects were observed in rats given doses up to 40 mg/kg/day for 26 weeks. Drug-related effects observed in dogs included severe tremors at ≥20 mg/kg/day, ataxia and gastrointestinal erosion/ulcer/inflammation at ≥30

mg/kg/day, convulsions at ≥60 mg/kg/day, and duodenal necrosis and death at 100 mg/kg (equivalent to a human dose of 3,350 mg).

In clinical studies to date, buntanetap 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 AChE 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 buntanetap and also in the placebo group. There was a tendency, but no definitive pattern of increased incidence of AEs with increasing dose of buntanetap. There have been no SAEs in prior clinical studies with buntanetap.

Definitive reproductive and developmental toxicity studies have not been conducted with buntanetap. As a result, women of childbearing potential will be excluded from participating in this study unless they agree to be on contraceptive for the whole duration of the trial and one month after. Female partners of male participants of childbearing potentials will also need to agree to be on contraceptive for the whole duration of the trial and one month after. Male study participants should not donate sperm and female study participants should not donate eggs during the whole duration of the trial and one month after.

At this time, there is no controlled clinical data available for anyone receiving SARS-CoV-2 (COVID-19) vaccination while being treated with buntanetap. However, based on the intended mechanism of actions and currently available data for these vaccine candidates and for buntanetap, it is not believed that there are specific risks to consider in subjects participating in this study who have received SARS-CoV-2 (COVID-19) vaccination or who are planning to receive the vaccination. As such, SARS-CoV-2 (COVID-19) vaccination is not prohibited. If appropriate, SARS-CoV-2 (COVID-19) vaccination should be considered as a concomitant medication (see Section 7.8.2).

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.

6.0 SAMPLE SIZE AND STATISTICAL PLAN

A sample size of up to 450 subjects (1:1:1 randomized to 10mg, 20mg buntanetap and placebo respectively) is planned.

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 at 1:1:1 ratio.

6.2. Power and Sample Size Determination

Qualified subjects will be randomized at a 1:1:1 to one of the following three treatment groups: 10 mg, 20 mg QD buntanetap and placebo. A sample size of 360 (120 per treatment group) will have 90% power to detect a treatment difference at a two-sided 0.025 significance level. In the sample size calculation, it was assumed a treatment difference of 2.55 and a common standard deviation of 5.59 based on historical data of MDS-UPDRS Part II+III (details will be provided in the Statistical Analysis Plan (SAP). Approximately 450 subjects will be randomized (approximately 150 per arm) to account for 112 patients calculated from the power analysis plus screen failures and dropout rates.

Based on FDA recommendations, the primary endpoint was changed into MDS-UPDRS Part II after enrollment ended. The current enrolled subject number gives us 90% power to detect a treatment difference of 3 points and a common standard deviation of 8 points of MDS-UPDRS Part II.

6.3. Safety and Tolerability Analysis

Safety and tolerability will be assessed with physical/neurological 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.

Subjects who dropout during the initial 5 months at-home treatment period will be scheduled early discontinuation visit. Subjects who drop out after the initial 5 monthswill be scheduled for an end-of-trial visit. If 4 subjects are discontinued due to serious adverse events a safety review will be conducted without interrupting the study.

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 calculated on Cmax and AUC as appropriate.

Plasma concentration-time data for buntanetap 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. Criteria for Termination of the Trial

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

6.6. Statistical Analysis

Unless otherwise indicated, all testing of statistical significance will be 2-sided, and a difference resulting in a p value of less than or equal to 0.05 will be considered statistically significant. Furthermore, the baseline will be the last assessment before the first dosing of the study drug.

Summary statistics will be provided for the variables described in the following sections. For continuous variables, these statistics will typically include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will typically include the number and percentage of subjects in each category.

6.7. Study Subjects and Demographics

6.7.1. Disposition and Withdrawals

The numbers of subjects screened, randomized, completing, discontinuing treatment, and withdrawing, along with reasons for discontinuation or withdrawal, will be tabulated overall and by treatment group. The number of subjects in each analysis population will be reported.

6.7.2. Protocol Deviations

Major protocol deviations will be classified and documented by TFS before database lock and will be discussed in the CSR. All protocol deviations, both minors and majors, will be presented in a data listing.

6.7.3. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, and height) will be summarized for each treatment group and for the overall population by descriptive statistics.

6.7.4. Medical History and Concomitant Medications

Medical history will be listed. Prior and concomitant medications will be summarized by treatment group, by the number and percentage of subjects taking each medication, classified using World Health Organization (WHO) Drug Dictionary Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

6.8. Analysis of Primary Endpoint

The primary endpoint is the change from baseline to Month 6 in of MDS-UPDRS Part II scores. The primary endpoint will be analyzed via a mixed model for repeated measures (MMRM). The model will include treatment, timepoint, treatment-by-timepoint interaction as the fixed effects

and baseline MDS-UPDRS Part II as the covariate. The covariate will assume to be unstructured. The treatment effects and the differences of the treatment effects will be estimated. The two-sided 95% confidence intervals of the treatment differences will be presented.

6.9. Multiplicity Adjustment

There are two active treatment groups (10 mg and 20 mg) in the study. Each of the two active treatments will be compared to the control (two hypothesis tests for the primary endpoint). Hochberg step-up procedure will be used to control the familywise Type I Error. Details are described in the SAP.

6.10. Interim Analysis

An interim sample size review will be performed after in total n_1 = 150 evaluable patients (50 patients per treatment group) have primary endpoint data, i.e., MDS-UPDRS part II+III at month 2. Evaluable patients are defined as randomized and having received at least once treatment with the study drug. The aim of the interim sample size review is to re-assess the size of the estimated mean and standard deviations of the primary effectiveness variable (MDS-UPDRS part II+III). No interim analyses are planned for the purpose of stopping the study early for futility.

The initial sample size estimation provides statistical power to demonstrate effectiveness among patients treated with buntanetap. A potential sample size adjustment is to assure that this trial will have the intended precision. The decision of sample size adjustment will be made based upon the estimates of MDS-UPDRS part II+III at baseline and after two months of treatment calculated for the first 150 evaluable patients with primary endpoint data. Sample size will not be decreased regardless of the results of this evaluation. To warrant the originally intended >90% power of the study at the 0.025 alpha level (2-sided), the evaluable sample size may be increased to a maximum of n_{max}=200 enrolled patients per treatment group. The sample size re-estimation will be evaluated for the efficacy endpoint based on the observed interim mean and standard deviation of treatment difference of the MDS-UPDRS part II+III score.

The sample size re-estimation method is based on evaluation of conditional power in relationship to pre-specified decision rules defined by ranges of attainable conditional power values. Only an increase in sample size is possible under this approach when observed conditional power falls within the 'promising zone' as described below (Mehta and Pocock 2011).

The conditional power at the interim analysis ($CP_{\delta 1}$ (z_1, $\tilde{n}_2$)) can be defined by the following equation from Mehta and Pocock (2011):

$$CP_{\delta 1}\,(z_1, \tilde{n}_2) = 1 - \Phi(((z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1})/\sqrt{\tilde{n}_2}) - (z_1\sqrt{\tilde{n}_2}/\sqrt{n1})) + \Phi(((-z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1})/\sqrt{\tilde{n}_2})) - (z_1\sqrt{\tilde{n}_2}\sqrt{n_1})$$

where $\tilde{n}_2 = n_2 - n_1$, $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$, and z_1 is the value of the cumulative Wald statistic as computed at the interim analysis of n_1= 50, n_2= 150 evaluable patients. Define the estimated treatment difference, $\delta_1 = \hat{\mu_1} - \mu_0$ at interim analysis, where $\hat{\mu_1}$ is mean and proportion at interim analysis and μ_0 is the null hypothesis correspondingly.

The targeted conditional power at the first interim review is 90%, however we pre-specify a range of conditional power values below 90% that would deem our interim results promising and

warrant a sample size re-estimation. Table 1 provides cut-off values from Mehta and Pocock (2011) for the lower bound of the promising zone, CP_{min}, under some typical two-stage adaptive designs. CP_{min} is 0.42 (42%) for the parameter choices ($n_{max}/n_2 = 1.5$, $n_1/n_2 = 0.33$) in this study.

Table 1. CP_{min} cut-off values for some typical two-stage adaptive designs with no early stopping either for efficacy or futility

Sample size ratios		**CP_{min} values for targeted conditional power**	
Maximum allowed (n_{max} / n_2)	**At interim look (n_1 / n_2)**	**80 per cent**	**90 per cent**
1.5	**0.25**	0.42	**0.42**
1.5	0.5	0.41	0.41
1.5	0.75	0.38	0.38
2	0.25	0.37	0.37
2	0.5	0.36	0.36
2	0.75	0.33	0.33
3	0.25	0.32	0.32
3	0.5	0.31	0.31
3	0.75	0.30	0.27
∞	0.25	0.32	0.28
∞	0.5	0.31	0.27
∞	0.75	0.30	0.25

Table 2 summarizes the sample size re-estimation decision based on the conditional power observed at interim analysis. The sample size is re-estimated when the interim conditional power falls within the promising zone of 0.42 to 0.90 (42% to 90%).

Table 2. Sample Size Re-Estimation Decision

Conditional power	**Decision**
Less than 42%	"Unfavorable zone" – No change to sample size
42% to 90%	"Promising zone" – Increase sample size
At least 90%	"Favorable zone" – No change to sample size

The re-estimated cumulative final sample size (n_2*) is computed using the following equation (equation (9) from Mehta and Pocock (2011)) and will be increased by a factor based on a re-assessed attrition rate as per the initial sample size calculation:

$n_2* = \min(n_2', n_{max})$, where $\tilde{n}_2'$ satisfies the condition $CP_{\delta 1}(z_1, \tilde{n}_2') = 1 - \beta$, $\beta = 90\%$,

and n_2' is the estimated new sample size computed as $n_1 + \tilde{n}_2'$.

Based on Mehta and Pocock (2011), this condition is satisfied by the function:

$\tilde{n}_2' = ([n_1/z_1^2][(z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}\sqrt{n_2} - n_1 + z_\beta]^2)$, where $z_{\alpha/2} = \Phi^{-1}(1-\alpha/2)$, $z_\beta = \Phi^{-1}(1-\beta)$,

and z_1 is the cumulative Wald statistic as computed at the interim analysis.

The new sample size s increased to:

$$n_{2*} = \min(n_2' , n_{max}) ,$$

where $\tilde{n}_2'$ satisfies the condition $CP_{\delta 1}(z_1, \tilde{n}_2') = 1 - \beta$, $\beta = 90\%$, and n_2' is the estimated new sample size computed as $n_1 + \tilde{n}_2'$ (Details see SAP).

The study team at the Sponsor will be blinded to interim results. A blinded Sponsor clinical scientist may have access to blinded subject-level and aggregated MDS-UPDRS results (pooled trial data) for the purpose of data review and will have no other responsibilities associated within the study. These results will be provided by the external unblinded statistician.

6.11. Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Population.

Safety and tolerability will be assessed through TEAEs; hematologic, biochemical, and urinalysis laboratory parameters; physical/neurological examination findings; and vital signs measurements.

No formal statistical comparisons will be performed for safety endpoints.

6.11.1. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities reporting system. The number and percentage of subjects with TEAEs will be displayed for each treatment group by SOC and preferred term. Additionally, TEAEs will be tabulated for each treatment group by severity and by relationship to the study drug. A listing of SAEs will be provided if applicable.

6.11.2. Clinical Laboratory Evaluations

For continuous laboratory parameters, descriptive statistics will be presented for each visit and for the changes from Baseline to each subsequent visit by treatment group.

Additionally, clinical laboratory parameters will be categorized as low, normal, or high according to laboratory range specifications and the number and percentage of subjects in each category will be presented in shift tables.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges.

6.11.3. Vital Signs

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from Baseline will be calculated for systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and oral temperature.

6.11.4. Physical/Neurological Examination Findings

Physical/neurological examination data will be presented in the listings.

6.11.5. Other Safety Parameters: C-SSRS

The number and percentage of subjects with suicidal ideation or suicidal behavior based on the C-SSRS will be summarized by treatment group. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the subject's lifetime, during the double-blind treatment period, and during the safety follow-up period will also be presented by treatment group for the Safety Population. Supportive listings will be provided and will include the subject number, study center number, lifetime history, and post-baseline values. Intensity of suicidal ideation, suicidal behavior type, and lethality of suicidal behavior will also be included in these listings. A listing of all AEs occurring in subjects who have suicidal ideation or suicidal behavior will also be provided.

7.0 STUDY DRUG AND CONCOMITANT MEDICATIONS

7.1. Identity of IP and Comparator

Buntanetap will be provided in size 1 white opaque hydroxypropyl methylcellulose (HPMC, vegetarian source) capsule shells. Capsules contain buntanetap (either 10mg or 20mg) formulated with inert inactive (non-lactose) pharmaceutical excipients generally recognized as safe for human pharmaceutical use. Matching placebo capsules will be prepared with the same inert inactive ingredients and look exactly like the buntanetap capsules.

7.2. Dosage

The study drug is to be taken orally; one capsule, once a day in the morning right before food, for 6 months at home.

Participants are encouraged to take a minimum of 80% of all doses (across 6 months). Returned IMP will be examined at each clinic visit to assess compliance overall.

7.3. Packaging/Dispensing/Labeling

The study drug (buntanetap capsules and placebo capsules) has been manufactured under cGMP, in a manner to preserve the blind, i.e., identical color and shape white opaque HPMC hard capsule shells and packaged 40 capsules per bottle.

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

Sites should order IP only after successful confirmation of eligibility criteria (usually after receipt of positive lab results) during screening period and well ahead of baseline visit.

The dosing schedule and storage requirements will be clearly explained to the participants and caregiver before dispensing the study drug.

All packaging and labelling as well as the production of study medication will be in accordance with US FDA regulations and EudraLex volume 4, Annex 13 "Good manufacturing practices for Medicinal products for human and veterinary use" and applicable local regulatory requirements.

7.4. Storage

Both buntanetap capsules and the matching placebo capsules must be stored at room temperature (not to exceed 25°C/77°F), protected from light and 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) will be shipped back to the contracted depot 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 relevant study visits. Participants are encouraged to take a minimum of 80% of all doses at home (6 months) depending on the end of trial date. Site personnel will count capsules and evaluate compliance from the bottle at each clinic visit.

Prior to the end of trial visit, site personnel will also contact the participant to remind them of the dose regimen, to ensure that the necessary level of compliance has been achieved to continue with the end-of-trial visit procedures. It is possible that subjects will be discontinued early from the study due to insufficient study drug compliance.

Site personnel will assess compliance at each clinic visit and again at the time of admission for the end of trial visit. .

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 SAE, the investigator can open the blind without prior consulting with the Medical Monitor and the Project Directors. If the blind is broken, whether it be by accident or for the welfare of the participant, the investigator MUST contact the Medical Monitor at the earliest opportunity and the entire process shall be recorded in the study documents, together with the procedures for the management of the SAE. Refer to the study procedures manual for detailed procedures related to breaking the blind and reporting.

7.8. Concomitant Medications

7.8.1. Prohibited Concomitant Medications

Investigational agents are prohibited 4 weeks or five half-lives, whichever is greater, 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.

Buntanetap is mainly metabolized by CYP3A4 in vitro. Therefore, we recommend avoiding concomitant use of strong or moderate CYP3A4 inhibitor/inducers, examples see below according to FDA guidance on drug development and drug interactions.

CYP3A4 inhibitors	Itraconazole, Ketoconazole, Azamulin, Troleandomycin, Verapamil
CYP3A4 inducers	Rifampicin

7.8.2. Permitted Concomitant Medications

This protocol allows concomitant treatment with anti-parkinsonian medications at stable doses for 4 weeks or greater prior to screening.

Use of the following medications is allowed only if the patients have been stable on them for at least 4 weeks before screening and will continue to be stable throughout the study:

- tricyclic antidepressants
- antipsychotics prescribed for any reason. However, the prescribed dose must be equal to or less than the following doses for each listed medication: quetiapine 50 mg/day, risperidone 1.5 mg/day, olanzapine 5 mg/day, aripiprazole 10 mg/day. If the subject is on other antipsychotics besides the ones mentioned above, please consult the MM before screening the subject.
- psychostimulants

Discontinuation and/or change of any of the above medication during the study is discouraged and should consult with the Medical Director and Sponsor for further guidance.

If subjects are taking any 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, are allowed. 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.

At this time, there is no controlled clinical data available for anyone receiving SARS-CoV-2 (COVID19) vaccination while being treated with buntanetap. However, based on the intended mechanism of actions and currently available data for these vaccine candidates and for buntanetap, it is not believed that there are specific risks to consider in subjects participating in this study who have received SARS-CoV-2 (COVID19) vaccination or who are planning to receive the vaccination. As such, SARS-CoV-2 (COVID-19) vaccination is not prohibited.

8.0 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 will not be included in the clinical trial. Membership in the analysis populations will be determined before unblinding.

The following analysis populations are planned for this study:

- Enrolled Population: The enrolled population will include all subjects who signed Informed Consent and meet all inclusion and exclusion criteria.
- Randomized Population: The randomized population will include all subjects who are randomized to a treatment arm.
- Modified Intent-to-Treat (mITT) Population: the mITT will consist of all subjects who are randomized, take at least 1 dose of the study drug, and have at least 1 post-Baseline assessment. The mITT population will be analyzed to support the primary efficacy analyses.
- Intent-to-Treat (ITT) Population: the ITT will consist of all subjects who are randomized. The primary efficacy analysis will be based on the ITT population.
- Safety Population: The Safety Population will be the primary safety analysis population and will include all subjects who receive at least 1 dose of the study drug. The safety analyses will be based on the Safety Population.

- Per Protocol Population: The Per Protocol Population will include all mITT subjects who do not have any major protocol deviations.

8.1. Inclusion Criteria

Subjects must meet the following criteria:

1. Diagnosis of idiopathic PD according to MDS Clinical Diagnostic Criteria for Parkinson's Disease (Postuma 2015).

2. H&Y score =1, 2 or 3 during ON-state & OFF-state <2hrs per day.

3. Male or female aged 40 – 85 years.

4. MMSE score between the range of 22-30 during screening visit (ON-state) and subjects can live independently without a caregiver.

5. Female subjects of childbearing potential* must have a negative urine pregnancy test at Screening, must be non-lactating and must agree to use a highly effective method of contraception (i.e., a method resulting in a failure rate of less than 1% per year when used consistently and correctly) during the trial and for 4 weeks after the last dose of trial treatment, such as:

    - Oral, intravaginal, or transdermal combined (estrogen plus progestogen) hormonal contraception associated with inhibition of ovulation
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner (a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the participant, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used)
    - Sexual abstinence (sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant)

    *Non-childbearing potential includes surgically sterilized or postmenopausal with no menstrual bleeding for at least one year prior to study start.

6. Male subjects must be sterile or sexually inactive or agree not to father a child during the study and one month after the last dose of study medication and must agree to use a barrier method for contraception. Female partners of male subject must adopt a highly effective method of contraception with a failure rate of less than 1% per year when used consistently and correctly such as:

    - Oral, intravaginal, or transdermal combined (estrogen plus progestogen) hormonal contraception associated with inhibition of ovulation
    - Oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion

7. General cognition and functional performance sufficiently preserved that the subject can provide written informed consent.

8. No evidence of current suicidal ideation or previous suicide attempt in the past month as evaluated in the Columbia Suicide Severity Rating Scale.

9. Stability of permitted medications prior to screening for at least 4 weeks.

10. At screening subjects do not need to but may be on the following medication:
    - Standard of Care anti-parkinsonian medication
    - Anticonvulsant medications used for epilepsy or mood stabilization, neuropathic pain indications
    - Mood-stabilizing psychotropic agents, including, but not limited to, lithium.

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

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

13. Subjects previously exposed to buntanetap can still be included in the study after a 28- day wash out period.

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, if stable on medication is acceptable.

3. Has a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 450 ms for men and 460ms for women, 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 (CKD-EPI <60 mL/min/BSA (body surface area)) or hepatic impairment (ALP > 2.0 ULN and/or total bilirubin > 2.0 ULN).

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

10. Alcohol / Substance use disorder, moderate to severe, in the last 5 years according to the most current version DSM.

11. 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.

12. Subjects with learning disability or developmental delay.

13. Subjects whom the site PI deems to be otherwise ineligible.

14. Subjects with a known allergy to the investigational drug or any of its components. Here are all the inactive ingredients of the IMP:

Silicified Microcrystalline Cellulose
Dibasic Calcium Phosphate Dihydrate
Mannitol
Magnesium Stearate
Hypromellose (capsule shells structure)
Titanium Dioxide (opacifier of the capsule shells)

15. Subject is currently pregnant, breast-feeding and/or lactating.

16. Subject is currently taking strong or moderate CYP3A4 inhibitors and/or inducers. See examples below:

CYP3A4 inhibitors	Itraconazole, Ketoconazole, Azamulin, Troleandomycin, Verapamil
CYP3A4 inducers	Rifampicin

17. Subject is currently receiving deep brain stimulation treatment.

9.0 DESCRIPTION OF STUDY VISITS

Each subject will have a 42-day screening period followed by 6 months 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. Participants do not need to stop their Parkinson's disease SOC medications for screening visit.

Potential participants 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. With investigator's permission, lab re-testing is allowed within a month. If investigator deems re-screening is justified, they must contact Medical Monitor and sponsor for discussion at case-by-case basis.

Safety assessments will include an 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, and urinalysis as listed in Section 12.1.3. Urine dipstick

pregnancy test will be completed for female subjects. Fasting is required for safety laboratory tests.

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.

9.2. Baseline Visit

Baseline procedures include functional, cognitive, and behavioral assessments, safety assessments, and review of concurrent medications and potential adverse events that might occur. Fasting is required for safety laboratory tests. Participants should stop all Parkinson's disease SOC 12 hours prior to the visit to ensure a clinical OFF-state. For patients who are not on any Parkinson's disease SOC, their natural state will be considered OFF-state and since they won't have ON-state, it should be documented accordingly in the source documents.

Baseline visit should be completed in one day except for the intense PK sub-group.

Day 1:

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

After safety lab, patients will be provided low-fat light meal before completing functional and cognitive evaluations (completed in an OFF state after holding PD meds for 12 hours prior to arrival at site), a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of contents of all meals provided to the patients. Following completion of all these procedures, subjects who continue to meet all protocol inclusion criteria and no exclusion criteria should be randomized. Patients can take their SOC medication at this point if needed.

For sparse PK group (i.e. any subject that is not participating in the intense PK sub-study), if no medical or compliance concerns are identified, the subject will move on to the PK sampling phase, which will entail the following procedures:

1) Collect initial samples of blood (hour 0) with venipuncture unless PI deems inappropriate.

2) Administer first dose of assigned study drug after the hour 0 sampling.

3) Collect blood (10mL) at the 1.5hr timepoint. Blood should be taken within ± 10 mins of times.

4) Perform the final safety monitoring.

For sparse PK group, prior to discharge from the clinic, vital signs should be recorded, and a review of AE(s) and concomitant medications should be conducted as the final safety monitoring. Patients will be educated of the study drug compliance and study drug return. 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, the PI shall manage the event without prior consulting with the Medical Monitor. The MM shall be informed as soon as possible, and the management of the AE shall be reported in the Study documents.

For intense PK group, if no medical or compliance concerns are identified following the Day 1 procedures, subjects will be scheduled for the next day PK sampling, unless patients prefer to finish PK in one day.

Day 2 (Intense PK group only)

Patient should arrive in clinic fasted in the morning after an overnight fast but does not need to be in OFF state. The subject will start PK sampling phase, which entails the following procedures.

1. Place an intravenous line for blood sampling.
2. Collect initial sample of blood (hour 0).
3. Administer first dose of assigned study drug after the hour 0 sampling.
    a. For 16 subjects per group, blood samples (10mL) will be collected at 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr,7hr, 8hr, 9hr, and 10hr timepoints. Blood should be collected within ± 10 mins of scheduled times.
    b. Perform periodic safety monitoring during the collection period. Participants should be asked about pain, redness or swelling at the blood collection site.
    c. Patients will be provided low-fat light meals after 2hr, 6hr and 10hr PK sampling. Sites should take detailed notes of contents of all meals provided to the patients.
4. Perform the final safety monitoring.

Prior to discharge from the clinic, vital signs should be recorded, and a review of AE(s) and concomitant medications should be conducted as the final safety monitoring. Patients will be educated of the study drug compliance and study drug return. 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, the PI shall manage the event without prior consulting with the Medical Monitor. The MM shall be informed as soon as possible, and the management of the AE shall be reported in the Study documents.

9.3. ONSITE VISIT AT 1 MONTH, 2 MONTH AND 3 MONTHS

At 1 month, 2 months and 3 months (+/- 7 days) from the baseline visit, a clinic visit should occur. Participants should stop all Parkinson's disease SOC 12 hours prior to the visit to ensure a clinical OFF-state. Clinic visit procedures include functional, and behavioral assessments, safety assessments, and review of concurrent medications and adverse events that occur in clinic and during blood collection. Fasting is required for safety laboratory tests. After safety lab, patients will be provided low-fat light meal before completing functional and cognitive evaluations (completed in an OFF state after withholding PD meds for 12 hours prior to arrival at site), a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of contents of all meals provided to the patients.

Study medication compliance will be reviewed and discussed, and reminders given about the upcoming end of trial visit.

A post-visit safety phone follow up will be conducted approximately 24 hours following each clinic visit.

9.4. 4.5 months Telephone Contact

A telephone call will be conducted at 4.5 months +/- 7 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 end of trial visit.

9.5. End of Trial Visit

End of trial is when the last subject of the study finishes last clinical visit. End of trial visit is each subject's last clinical visit during the study. The end of trial visit should occur 6 months +/- 7 days following the first dose of study medication. A pre-visit phone call will be conducted 1-3 days prior to admission and a post-visit phone follow-up will be conducted approximately 24 hours following discharge. End of trial visit procedures include functional, and behavioral assessments, safety assessments, and review of concurrent medications and adverse events that occur in clinic and blood collection. Participants should stop all Parkinson's disease SOC 12 hours prior to the visit to ensure a clinical OFF-state.

9.5.1. Pre-visit Telephone Contact

A telephone call will be conducted at 1-3 days prior to end of trial to assess for any changes in status, adverse events, or concomitant medications. Study medication compliance will be discussed, and reminders given about the upcoming end of trial visit.

9.5.2. End of Trial Visit

This constitutes the subjects' last clinical visit during the study for all patients who have participated over 5 months. Early drop-out patients will be invited to participate early discontinuation visit. The end of trial visit will consist of the following: admission procedures, Time 0 blood

sampling, administration of last dose of study drug, 1.5hr after-dose blood sampling except for the subgroup of subjects participating in the intense PK sub-study, who will have PK samples for 10 hours, all psychometric and safety tests, and discharge procedures. Fasting is required for safety laboratory tests. End of trial visit should be done in one day except for the intense PK subgroup.

For the subgroup of subjects who will have intense PK samples, blood samples will be drawn at 0hr, 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr, and 10hr timepoints.

Day 1:

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

After safety lab, patients will be provided low-fat light meal before completing functional and cognitive evaluations (completed in an OFF state after holding PD meds for 12 hours prior to arrival at site), a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of contents of all meals provided to the patients. Patients can take their SOC medication at this point if needed.

For sparse PK group, if no medical or compliance concerns are identified, the subject will move on to the PK sampling phase, which will entail the following procedures:

1) Collect initial samples of blood (hour 0) by venipuncture unless PI deems inappropriate.
2) Administer last dose of assigned study drug after the hour 0 sampling.
3) Collect blood (10mL) at the 1.5hr timepoint. Blood should be taken within ± 10 mins of times.
4) Perform the final safety monitoring.

For sparse PK group, prior to discharge from the clinic, vital signs should be recorded, and a review of AE(s) and concomitant 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, the PI shall manage the event without prior consulting with the Medical Monitor. The MM shall be informed as soon as possible, and the management of the AE shall be reported in the Study documents.

For intense PK group, if no medical or compliance concerns are identified, the subject will be scheduled for the next day PK sampling unless patients prefer to complete end-of-trial visit in one day.

Day 2 (Intense PK only)

Patient should arrive in clinic fasted in the morning after an overnight fast but do not need to be in OFF state. The subject will start PK sampling phase, which entails the following procedures.

5. Place an intravenous line for blood sampling for the subgroup that will collect 10-hour blood samples.
6. Collect initial samples of blood (hour 0).
7. Administer last dose of assigned study drug after the hour 0 sampling.
    a. For 16 subjects per group, their blood samples (10mL) will be collected at 1hr, 1.5hr, 2hr, 3hr, 4hr, 5hr, 6hr,7hr, 8hr, 9hr, and 10hr. Blood should be taken within ± 10 mins of times.
    b. Perform periodic safety monitoring during the collection period. Participants should be asked about pain, redness or swelling at the blood collection site in the arm.
    c. Patients will be provided low-fat light meal after 2hr, 6hr and 10hr PK sampling. Sites should take detailed notes of contents of all meals provided to the patients.
8. Perform the final safety monitoring.

Prior to discharge from the clinic, vital signs should be recorded, and a review of AE(s) and concomitant medications should be conducted as the final safety monitoring. 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, the PI shall manage the event without prior consulting with the Medical Monitor. The MM shall be informed as soon as possible, and the management of the AE shall be reported in the Study documents.

9.5.3. Post End of Trial Visit 24-Hour Phone Follow-up

Approximately 24 hours following the end of trial visit the subject will be contacted by phone to confirm the subject's well-being and to query about any new AEs.

9.5.4. After The Trial

The subject will continue the standard of care of Parkinson's disease under the supervision of the treating physician.

10.0 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.

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 must 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 discontinuation. This may include abnormal laboratory values.
- Death.
- Safety risk: Any participant who becomes a safety risk to themselves or others during the trial will be withdrawn.
- Protocol violation: The participant fails to meet protocol entry criteria during the study after being randomized or does not adhere to protocol requirements.
- Development of suicidal or homicidal ideation requiring hospitalization or confinement.
- Consent is withdrawn. The participant wishes to withdraw from the study.
- 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.

11.0 STUDY-SPECIFIC INSTRUMENTS

The following instruments will be employed to measure states of function, dementia, and movement. Copies of the instruments are provided in Appendix 2.

- Mini-Mental State Examination (MMSE)
- Patients' Global Impression of Change (PGIC)
- Clinical Global Impression of Severity (CGIS)
- Wechsler Adult Intelligence Scales, 4th edition (WAIS-IV)

- Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

12.0 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 using 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 these time points: the screening visit, each clinical visit (1 month, 2 months and 3 months), and the end of trial visit. Refer to the Laboratory Manual for additional details.

CLINICAL SAFETY LAB TESTS		
METABOLIC PANEL	**COMPLETE BLOOD COUNT**	**URINALYSIS**
Sodium (Na) Potassium (K) Chloride (Cl) Carbon Dioxide (CO2) Blood Urea Nitrogen (BUN) Glucose Calcium (Ca) Creatinine (Crn) Bilirubin (direct and Total) Albumin Protein - Total Glutamic-Oxaloacetic Transferase (AST, SGOT) Glutamic-PyruvateTransferase (ALT, SGPT) Alkaline Phosphatase (ALP) eGFR (estimated Glomerular Filtration Rate)	White Blood Cell Count (absolute and percentage): basophils, eosinophils, lymphocytes, monocytes, neutrophils Red Blood Cell Count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC) Red Blood Cell Distribution Width (RDW) Mean Platelet Volume (MPV) Platelet Count (PLT) **Screening Only** Hemoglobin A1C (HbA1c)	Color Appearance Specific Gravity pH Blood Glucose Protein Ketones Leukocyte Esterase Nitrite Urobilinogen Bilirubin (total)

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. Plasma for Biomarkers and Pharmacokinetics

Plasma samples will be collected at the baseline visit, and during the end of trial visit for analysis of biomarkers and PK, as described in the Laboratory Manual.

13.0 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.

14.0 ADVERSE EVENTS (AES)

14.1. Definition

An AE is defined as per the US Code of Federal Regulation, Title 21, Part 312.32 (2016) and ICH E2A: International Conference on Harmonization - Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994).

Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Collection of adverse events will begin once informed consent is signed and will continue until the 24-hour phone follow-up after the subject is discharged from the clinic at the end of study visit or discontinues from the study. 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.

15.0 SERIOUS ADVERSE EVENTS (SAE)

15.1. Definition

An SAE is defined as per the US Code of Federal Regulation, Title 21, Part 312.32 (2016) and ICH E2A: International Conference on Harmonization - Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (1994).

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 be monitored throughout the trial. All SAEs must be reported to the Medical Monitor and the Sponsor 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. The Sponsor will work with the Coordinating Center personnel to submit any SAEs according to the EU local country requirements.

16.0 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION

16.1. Definition

A suspected unexpected serious adverse reaction (SUSAR) is an AE that is assessed as serious, related, and unexpected.

16.2. Reporting of Suspected Unexpected Serious Adverse Reactions

The Sponsor is responsible for informing the Competent Authority (CA), the European Medicines Agency and the IECs as well as the Regulatory Authority (RA), the FDA and IRB of any individual case reports of SAEs that are determined to be reportable by the Sponsor (SUSARs) in Europe and the US, respectively. The Investigator will ensure that all relevant information is provided to the Sponsor to allow the Sponsor to meet their obligations to report the SUSAR to the CA/RA and IEC/IRB. For a SUSAR that is fatal or life-threatening, this should be reported as soon as possible and not later than 7 days after the Sponsor was first advised, for any other SUSAR this should be within 15 days.

17.0 ADVERSE EVENTS OF SPECIAL INTEREST

Not applicable.

18.0 PRECAUTIONS/OVERDOSE

If a subject receives a dose exceeding 200 mg of buntanetap, the dose may be considered toxic. Since this is a double-blind study, if a subject swallows more than 10 capsules with the assumption of them being in the 20mg buntanetap group, this will be considered an overdose, and in such case, the information will be collected following the same timeframe and procedures as for a SAE, even if the overdose is not associated to any AE/SAE. No specific treatment is recommended apart from appropriate supportive measures.

19.0 PREGNANCY

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

A pregnancy as such is not an AE, unless there is a possibility that the IMP has interfered with the efficiency of any contraceptive measures. However, the Investigator should report pregnancies according to the procedures and timelines described for reporting of SAEs (Section 15.2). The pregnancy report form should be used instead of the SAE form.

The pregnant subject or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE or SAE (if it fulfils SAE criteria).

The outcome of the pregnancy must be reported on the pregnancy report form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE.

20.0 DATA AND SAFETY MONITORING BOARD (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be formed to safeguard the subjects' wellbeing. The responsibilities of DSMB will be established in the DSMB Charter. The 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. First DSMB meeting will be when 75 patients (17% of the targeted sample size) received 1 month of treatment.

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.

21.0 RECORDING AND COLLECTION OF DATA

21.1. 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.

21.2. 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 trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), where direct access to source data/documents will be provided.

Information about study subjects will be kept confidential and managed according to the requirements of the General Data Protection Regulation (GDPR) of 2018, and the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

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/IEC, is responsible for ensuring that all applicable GDPR/HIPAA regulations and applicable laws are met.

22.0 ETHICS AND REGULATORY CONSIDERATIONS

22.1. 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 ethical principles of the latest revision of the Declaration of Helsinki as adopted by the World Medical Association, 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.

22.2. Institutional Review Board (IRB) / Independent Ethics Committee (IEC)

In the US, IRBs 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.

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 shall notify the IRB of deviations from the protocol or SAEs occurring at the site, in accordance with local procedures.

In Europe, this protocol and any amendments will be submitted to a properly constituted IEC and Competent Authority (if applicable), in accordance with the International Conference on Harmonization (ICH) guidelines, the applicable European Directives and local legal requirements, for approval/favorable opinion of the study. Approval/favorable opinion must be obtained in writing before the first subject can be recruited.

22.3. 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/GDPR authorizations signed before protocol procedures are conducted. 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. Consent forms must be in a language fully comprehensible to the prospective subjects. Subjects and their relatives 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 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 are part of the study analysis, and subjects will never receive results.

23.0 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.

Centralized monitoring of the original electronic source records will take place where available, however on-site monitoring inspections will continue to take place to perform monitoring activities that cannot be performed remotely.

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

Monitoring visits will include but not be limited to confirming:

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

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

24.0 AUDIT

In accordance with ICH E6 R2 (Good Clinical Practices) representatives of the Contract Research Organization (CRO) 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 that will be suitable for inspection at any time by the CRO, the Sponsor, its designees, a RA/CA and/or an IRB/IEC. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the trial conduct and compliance with the protocol may also occur.

25.0 RECORD RETENTION

The Sponsor shall retain the records and reports required for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified (US 21CFR§312.57).

Trials in which data are used to support a marketing authorization have additional requirements and the TMF must be retained for at least 15 years after completion or suspension of the trial or at least two years after the last marketing authorization has been granted in the European Community (where no marketing authorization applications are pending or foreseen in the EC) or at least two years after the formal suspension of the clinical development of the investigational product (Directive 2003/63/EC).

26.0 LITERATURE CITED

Folstein M.F., Folstein, S.E., McHugh, P.R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research,* 12(3), 189-198.

Goetz CG, Tilley BC, Shaftman SR, Stebbin GT, et al. (2008). Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Movement Disorders.* Vol. 23, No. 15, pp. 2129–2170.

Hoehn MM, Yahr MD (1967). Parkinsonism: onset, progression, and mortality. *Neurology.* Vol. 17. No. 5.

Hurst H, Bolton J (2004). Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther* 27:26-35.

Kadir A., Andreasen N., Almkvist O., Wall A., Forsberg A., Engler H., HagmanG., Lärksäter M.,Winblad B., Zetterberg H., Blennow K., Längström B., Nordberg A. (2008). Effect of Phenserine Treatment on Brain Functional Activity and amyloid in Alzheimer 's disease. *Ann Neurol* 621-631.

Kuo YM, Nwankwo EI, Nussbaum RL, Rogers J, Maccecchini ML (2019). Translational inhibition of α-synuclein by Posiphen normalizes distal colon motility in transgenic Parkinson mice. *Am J Neurodegener* Dis 8(1):1-15.

Li X, Herrmann C, Rauch G (2020). Optimality criteria for futility stopping boundaries for group sequential designs with a continuous endpoint. *BMC Med Res Methodol* 20, 274.

Lilja AM, Röjdner J, Mustafiz T, Thome CM, Storelli E, Gonzalez D, Lithner CU, Greig NH, Nordberg A, Marutle A (2013). Age-Dependent Neuroplasticity Mechanisms in Alzheimer Tg2576 Mice Following Modulation of Brain Amyloid-β Levels. PLoS ONE 8(3): e58752. doi:10.1371/journal.pone.0058752.

Maccecchini ML, Chang MY, Pan C, John V, Zetterberg H, Greig N (2012). Posiphen as a candidate drug to lower CSF amyloid precursor protein, amyloid-b peptide and s levels: target engagement, tolerability and pharmacokinetics in humans. *J Neurol Neurosurg Psychiatry,* 83:894-902.

Marutle A, Ohmitsu M, Nilbratt M, Grieg NH, Nordberg A, Sugaya K (2007). Modulation of human neural stem cell differentiation in Alzheimer (APP23) transgenic mice by phenserine. *PNAS* 104(30).

Mehta, C. R., & Pocock, S. J. (2011). Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statistics in medicine, 30(28), 3267-3284.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marke K, Litvan I, Lang AE, Halliday G, Goetz CG, Gasser T, Duboie B, Chan P, Bloem BR, Adler CH, Deuschl G (2015). MDS Clinical Diagnostic Criteria for Parkinson's Disease. *Movement Disorders*, Vol. 30, No. 12, p1591-1599.

Teich AF, Sharma E, Barnwell E, Zhang H, Staniszewski A, Utsuki T, Padmaraju V, Mazell C, Tzekou A, Sambamurti K, Arancio O, Maccecchini ML (2018). Translational inhibition of APP by Posiphen: Efficacy, pharmacodynamics, and pharmacokinetics in the APP/PS1 mouse. *Alzheimers Dement Transl Res Clin Interv* 4:37–45.

Wechsler D (2008). Wechsler Adult Intelligence Scale—Fourth Edition Administration and Scoring Manual. San Antonio, TX: Pearson (**only available under license agreement**)

Yu QS, Reale M, Kamal M.A., Holloway H.W., Luo W., Sambamurti K., Ray B., Lahiri D.K., Rogers JT, Greig NH (2013). Synthesis of the Alzheimer drug posiphen into its primary metabolic products (+)-N1-norposiphen, (+)-N8-norposiphen and (+)-N1,N8-bisnorposiphen, their inhibition of amyloid precursor protein, a Synuclein synthesis, interleukin-1β release and cholinergic action. *Antiinflamm Antiallergy Agents Med Chem.* 12:117-28.

APPENDIX 1: SCHEDULE OF EVENTS

Study Period	**Screening/Baseline Up to 42 Days**		**Double-Blind Trial Treatment Period 6 Months[e]**						**Unscheduled Visit [h] (USV)**	**Early Discontinuation Visit**
Visit Timing	**Day -42 to 0**		**1 month ± 7 days**	**2 months ± 7 days**	**3 months ± 7 days**	**4.5 months ± 7 days**	**1-3 days prior to end of trial visit**	**6 months ± 7 days (end of trial visit) [J]**		
Procedure	**Screening[I] (up to 42 days before Day 0)**	**Base line [J] (Day 0)**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone**	**Phone**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**
Informed consent	**X**									
Inclusion and exclusion criteria	**X**	**X**								
Demography information	**X**									
Full physical examination and neurological examination	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Height, Weight, BMI	**X**									
Medical and psychiatric history (includes substance use)	**X**									

Study Period	**Screening/Baseline Up to 42 Days**		**Double-Blind Trial Treatment Period 6 Months[e]**						**Unscheduled Visit [h] (USV)**	**Early Discontinuation Visit**
Visit Timing	**Day -42 to 0**		**1 month ± 7 days**	**2 months ± 7 days**	**3 months ± 7 days**	**4.5 months ± 7 days**	**1-3 days prior to end of trial visit**	**6 months ± 7 days (end of trial visit) [J]**		
Procedure	**Screening[I] (up to 42 days before Day 0)**	**Base line [J] (Day 0)**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone**	**Phone**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**
Urine pregnancy test (WOCBP only)	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Hoehn & Yahr Stage	**X**									
MMSE	**X**	**X**						**X**		
PGIC			**X**	**X**	**X**			**X**		
CGIS		**X**	**X**	**X**	**X**			**X**		
WAIS-IV		**X**		**X**				**X**		
MDS-UPDRS		**X**	**X**	**X**	**X**			**X**		
C-SSRS	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Clinical Laboratory safety tests[d&g]	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
12-lead ECG	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Vital signs[a]	**X**	**X**	**X**	**X**	**X**			**X**	**X**	**X**
Randomization		**X**								
Study intervention dispensed		**X**	**X**	**X**	**X**			**X[f]**		

Study Period	**Screening/Baseline Up to 42 Days**		**Double-Blind Trial Treatment Period 6 Months[e]**						**Unscheduled Visit [h] (USV)**	**Early Discontinuation Visit**
Visit Timing	**Day -42 to 0**		**1 month ± 7 days**	**2 months ± 7 days**	**3 months ± 7 days**	**4.5 months ± 7 days**	**1-3 days prior to end of trial visit**	**6 months ± 7 days (end of trial visit) [J]**		
Procedure	**Screening[I] (up to 42 days before Day 0)**	**Base line [J] (Day 0)**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**	**Phone**	**Phone**	**Clinic Visit**	**Clinic Visit**	**Clinic Visit**
Study intervention compliance review			**X**	**X**	**X**	**X**	**X**	**X**		**X**
AE/SAE review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant medication review	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PK sampling[c]		**X**						**X**		
Sampling for blood biomarkers		**X**						**X**		
24-hour phone follow-up[b]		**X**	**X**	**X**	**X**			**X**	**X**	**X**

a=Vital signs include sitting blood pressure, pulse, temperature, respiration rate.
b=Phone follow-up should occur approximately 24 hours after baseline, each clinic visit and after discharge from the end of trial or early discontinuation visits.
c=Sampling Times: 0 (pre-dosing) and 1.5hrs after dosing, except for 16-people per group who will go through 10hr sampling timepoints at 0, 1hr, 1.5hr, 2hr, 3hr, 4hr,5hr, 6hr, 7hr, 8hr, 9hr, and 10hr (±10 mins for all collection timepoints). Intense PK subgroup is only in the US.
d=Safety labs at all clinic visits should be taken fasted.

e=Subjects who drop out after the initial 5 months of study treatment will complete the full End of Trial visit. Subjects who dropped out prior to the initial 5 months of study treatment will complete the Early Discontinuation Visit assessments.
f=The study intervention dispensing on the end of trial visit is only for the one pill given on that day.
g=Blood and urine samples will be obtained for clinical safety lab assessments as described in the Laboratory Manual.
h= Investigator will determine the extra assessment if any is needed.
i= With investigator's permission, lab re-testing is allowed within a month.
j= For the intense PK subgroup participants, baseline visit and end-of-trial visit can be done in 2 days.

APPENDIX 2: INSTRUMENTS USED IN THE STUDY

Copies of the following instruments used in the study are provided here.

- Mini-Mental State Examination (MMSE)
- Patients' Global Impression of Change (PGIC)
- Clinical Global Impression of Severity (CGIS)
- Wechsler Adult Intelligence Scales, 4th edition (WAIS-IV)
- Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS).