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A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of Buntanetap in Participants with Mild to Moderate Alzheimer's Disease

Protocol Short Title:

A dose-ranging study to investigate efficacy of buntanetap in mild to moderate AD participants

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Confidentiality Statement

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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 regionαSYN Alpha-synuclein
αSYN	Alpha Synuclein
Aβ	Amyloid Beta
AChE	Acetylcholinesterase
AD	Alzheimer's diseases
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ADCS-CGIC	Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change
AE	Adverse Event
ANOVA	Analysis of variance
APP	Amyloid Precursor Protein
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BChE	Butyrylcholinesterase
BDNF	Brain derived neurotrophic factor
BP	Blood pressure
CA	Competent Authority
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	Confidence Interval
CLBP	Chronic low back pain
Cmax	Maximum plasma and CSF concentration
ChE	Cholinesterase
C-SSRS	Columbia Suicide Severity Rating Scale
CNS	Central Nervous System
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficients of variation
CVD	Cerebrovascular Dementia
DNA	Deoxyribonucleic Acid
DS	Down Syndrome
DSMB	Data Safety Monitoring Board
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FCR	Fractional clearance rate
FDA	Food and Drug Administration
FSR	Fractional Synthesis Rate
FWA	Federal wide Assurance
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GFAP	Glial fibrillary acidic protein

GI	Gastrointestinal
GRAS	Generally recognized as safe
GWAS	Genome Wide Association Studies
HbA1c	Hemoglobin A1C
HEK 293	Human embryonic kidney cells
HEENT	Head/ears/eyes/nose/throat
hERG	Human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HPMC	Hydroxypropyl methylcellulose
ICH	International Conference on Harmonization
IDMB	Independent Data Monitoring Board
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRE	Iron-responsible element
IRP1	Iron Regulatory Protein 1
LAR	Legally authorized representative
MAD	Multiple Ascending Dose
MCI	Mild Cognitive Impairment
MDS-UPDRS	MDS-United Parkinson's Disease Rating Scale
MedRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent to Treat
MMRM	Mixed model for repeated measures
MMSE	Mini-Mental State Examination
mRNA	Messenger Ribonucleic Acid
NFL	Neurofilament light
NG	Neurogranin
NIA	National Institute on Aging
NIA-AA	National Institute on Aging and Alzheimer's Association
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
NPH	Normal Pressure Hydrocephalus
OHRP	Office for Human Research Protections
p-tau	Phosphorylated tau
PD	Parkinson's disease
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetic
POC	Proof of Concept
PS1	Presenilin 1
QD	Once a Day
QID	4 Times a Day
QT	Interval seen in electrocardiogram (ECG) test
QTc	Interval seen in QT (ECG) test
RA	Regulatory Authority
SAD	Single Ascending Dose
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SH-SY-5Y	Human Derived Cell Line

SILK™	Stable Isotope Labeling and Kinetics
$SNCA^{a53t}$	Synuclein alpha
SNRI	Selective Norepinephrine Reuptake Inhibitor
SOC	Standard of care / System organ class
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
Tmax	Time to peak drug concentration
TMF	Trial Master File
TDP-43	TAR DNA-binding Protein 43
TG	transgenic
WAIS-IV	Wechsler Adult Intelligence Scales, 4^{th} edition
WHO	World Health Organization

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1.0 PROTOCOL SYNOPSIS

PROTOCOL TITLE	A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter Study of Buntanetap in Participants with Mild to Moderate Alzheimer's Disease
STUDY DESIGN	The study will be a 12-week, placebo-controlled and double-blind: participants, investigators and the sponsor will be blinded to the participants' treatment. Qualified participants will be randomly assigned at a 1:1:1:1 ratio to one of the four treatment arms: buntanetap 7.5 mg, buntanetap 15 mg, buntanetap 30mg, and placebo, through an Interactive Randomization System, after a screening period of up to 42 days. ADAS-Cog 11, ADCS-CGIC, ADCS-ADL, DSST, 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 participants will be assessed by the same clinician throughout the study. One interim analysis is planned. It will take place when 90 enrolled participants (~30%) have completed the Week 6 assessments to reassess the sample size. No interim analyses are planned for the purpose of stopping the study early for futility.
DURATION OF STUDY PARTICIPATION	Each participant will have up to a 42-day screening period, a baseline visit, followed by 12 weeks of treatment at home, followed by an in-clinic visit. The total duration of study participation will be 4-5 months.
SUMMARY OF INVESTIGATIONAL PRODUCT	Buntanetap 7.5mg, 15 mg, 30mg, or placebo capsules, taken orally once a day for 12 weeks.
SUMMARY OF KEY ELIGIBILITY CRITERIA	• Diagnosis of AD • Age 55 to 85 • MMSE 14-24
PRIMARY OUTCOME MEASURES	Aim 1. ADAS-Cog11 Aim 2. ADCS-CGIC
SECONDARY OUTCOME MEASURES	Aim 1. ADCS-ADL Aim 2. DSST Aim 3. MMSE
EXPLORATORY OUTCOME MEASURES	Aim 1. Plasma Biomarkers Aim 2. Pharmacokinetics

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 participants, 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 lowering 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 α-Synuclein (αSYN), Amyloid Precursor Protein (APP), its fragments, and tau. Although APP and its downstream products (Ab oligomers, c-terminus peptide, and amyloid plaques), and tau neurofibrillary tangles have been well documented to be culprits of AD, recent research has shown that other misfolded proteins are also part of the equation. For example, increased levels of αSYN and TDP-43 have been shown to be correlated with deficits in cognitive functions in AD participants. Therefore, it is reasonable to hypothesize that inhibiting expression of all the above neurotoxic proteins should lead to a better efficacy outcome in AD participants than inhibiting just one.

αSYN, APP, tau, and TDP43 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 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 also restores colonic motility in a human $SNCA^{A53T}$ transgenic (tg) mouse model of early PD.

Buntanetap's safety has been established in three Phase 1 clinical studies by Maccecchini et al (2012). Importantly, buntanetap normalized levels of APP, tau and αSYN, as well as inflammatory markers in the cerebrospinal fluid (CSF) of mildly cognitively impaired (MCI) participants 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 participants (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 AD, 14 participants were recruited and randomized into 80mg QD buntanetap or placebo for 25±2 days. CSF biomarker results show that buntanetap lowered multiple neurotoxic proteins levels (sAPPa, sAPPb, total Tau, phosphorylated Tau), 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). Buntanetap also improved AD participants ADAS-Cog 11 score as well as WAIS coding score (Fang 2022).

In PD, 54 participants 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 NFL and improved synaptic density shown by NG. Although sample size was not powered to see efficacy, buntanetap improved PD participants WAIS coding scores at all doses including 5mg QD. Buntanetap also improved PD participants MDS-UPDRS Part III, IV and Total score (Fang 2022).

In this study, we want to confirm buntanetap's efficacy in a diverse population of mild to moderate AD participants. We only tested 80mg QD in our Phase2a study in AD participants. During the dose-finding Phase 2a PD study, we saw a dose-response curve between 0 and 10/20 mg QD. Therefore, we want to do a similar dose-ranging trial to test the efficacy of 7.5mg, 15mg and 30 mg QD buntanetap.

2.1. OBJECTIVES

Study objectives include assessing buntanetap' s efficacy and safety in participants with mild to moderate AD.

Study drugs will be 7.5 mg, 15mg, 30mg of buntanetap, or matching placebo capsules, taken once per day in the morning right before food. Eligible participants will be randomly assigned at a 1:1:1:1 ratio to one of the four treatment arms: buntanetap 7.5 mg, buntanetap 15 mg, buntanetap 30mg, and placebo, through an Interactive Randomization System, after a screening period of up to 42 days. The total duration of the study will be 4-5 months. ADAS-Cog11, ADCS-CGIC, DSST, ADCS-ADL, MMSE will be assessed by clinicians who have successfully

completed the requisite certifications/trainings for each assessment. All efforts will be made to ensure participants will be assessed by the same clinician throughout the study.

2.2. ENDPOINTS

Primary Endpoints:

1. **ADAS-Cog11**
   Change in Alzheimer's Disease Assessment Scale-Cognitive Subscale 11 (ADAS-Cog 11) from baseline to the end of treatment period (12 weeks). ADAS-Cog 11 measures cognitive functions and non-cognitive functions such as mood and behavior. Total scores range from 0-70, with higher scores indicating greater cognitive impairment.

2. **Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)**
   ADCS-CGIC is a validated categorical measure of change in the participant's clinical condition between baseline and follow-up visits. It measures whether the effects of active treatment are substantial enough to be detected by a skilled and experienced clinician on the basis of a clinical interview and examination. It relies on both direct examination of the participant and an interview of the study partner. A skilled and experienced clinician who is blinded to treatment assignment rates the participant on a 7-point Likert scale, ranging from 1 (marked improvement) to 7 (marked worsening). Lower scores indicate better improvement.

Secondary Endpoints:

1. **Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living Scale (ADCS-ADL)**
   The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire answered by the participant's study partner. The ADCS-ADL measures both basic and instrumental activities (instrumental activity items 6a, 7-23) of daily living by participants with a lower score indicating greater severity.

2. **Mini Mental State Examination (MMSE) Score**
   MMSE is a brief screening instrument used to assess cognitive function (orientation, memory, attention, ability to name objects, follow verbal/written commands, write a sentence, and copy figures). Total score ranges from 0 to 30 with a lower score indicating greater disease severity.

3. **Digital Symbol Substitution Test (DSST)**
   In the digital symbol substitution test (DSST) 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 and higher scores indicate better performance.

Exploratory Endpoints:

1. **Plasma biomarkers**

Potential biomarkers to be measured in plasma are Aβ42/40 ratio, pTau181, pTau217, Neurofilament Light (NFL), Glial fibrillary acidic protein (GFAP), TDP43.

2. Pharmacokinetics

The following PK parameters will be determined: 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 (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 2020). In summary, buntanetap is a translational inhibitor of APP and aSYN and fully restores function at doses that are very low and very safe, and the plasma levels seen are attainable with low oral dosing in humans.

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.

Four-week 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. 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 in 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 participants 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 participants 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 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 participant 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 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 MCI 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 participants 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 4-5 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 sAPPα and β, tau, αSYN and a series of inflammatory markers. The concentration and persistence of buntanetap in the brain suggests 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 part one, early AD participants were given 80 mg QD buntanetap or placebo for 25 days. In the second part, early PD participants were given 5 mg, 10 mg, 20 mg, 40 mg, 80mg QD buntanetap or placebo for 25 days. In all doses and in both AD and PD participants, 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 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 participants' CSF levels of sAPPα, sAPPβ, total 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 participants' CSF levels of αSYN and a series of inflammatory markers (YKL-40, GFAP, sTREM2, Complement C3). Buntanetap also improved PD participants' axonal integrity shown by NFL and synaptic function shown by NG.

Further, buntanetap treatment improved AD participants' cognition shown by ADAS-Cog11 and WAIS coding test and improved PD participants' movement shown by MDS-UPDRS and WAIS coding test in our Phase2a studies.

4.0 BACKGROUND AND STUDY RATIONALE

4.1. Background

Although APP and its downstream products (Aβ oligomers, c-terminus peptide, and amyloid plaques), and tau neurofibrillary tangles have been well documented to be culprits of AD, recent research has shown that other misfolded proteins are also part of the equation. In AD, in addition to Aβ and tau, increased levels of αSYN and TDP-43 have been shown to be correlated with deficits in cognitive functions. A high load of inflammation and microglia activating factors that contribute to neurodegeneration are also common in AD.

Buntanetap (Posiphen) is the (+) enantiomer of phenserine, but 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 decreased sAPPα and β, tau, p-tau and aSYN 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 APP and aSYN, as well as other neurotoxic aggregating proteins, it might have a broader spectrum of activity than AD and PD. By protecting neurons from dying, it has a disease-modifying effect in AD, PD as well as other neurodegenerative disorders.

4.2. Study Overview

Study population: The study will be conducted in a diverse population of participants with mild to moderate AD.

Dose selection: Qualified participants will be randomly assigned at a 1:1:1:1 ratio to one of the four treatment arms: buntanetap 7.5 mg, buntanetap 15 mg, buntanetap 30mg, and placebo.

Study Design: 320 mild to moderate AD participants will be randomized to 7.5 mg, 15 mg, 30mg of buntanetap QD or placebo. If they provide informed consent, they will undergo a Screening Visit, and if they are considered eligible per the inclusion and exclusion criteria, they will proceed to participate in the treatment period. Randomized participants will visit the clinic for the first-time dosing in clinic, followed by an at home dosing period of 12 weeks, with daily administration of 7.5 mg, 15 mg, or 30 mg of buntanetap or placebo. Participants will be required to visit clinics Day 0 (baseline), 6 weeks, and 12 weeks (end-of-trial), 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) and psychometric tests (ADAS-Cog11, ADCS-CGIC, ADCS-ADL, DSST, MMSE). At the end of blood sampling, the participants will need to stay for a minimum of 1 hour of observation. After all end-of-study procedures are complete, the participant will be discharged to home. A 24-hour follow-up call will occur after all clinical visits to assess the participants current condition and if there are any additional adverse events or questions.

Participants who drop out during the initial 9 weeks at home treatment period will be discontinued and complete an early discontinuation visit as soon as possible following discontinuation. Participants that drop out after the initial 9 weeks will be scheduled for an end of trial visit. If 4 participants are discontinued due to severe adverse events a DSMB safety review will be conducted without interrupting the study.

4.3. Outcome Measures

Efficacy outcome measures: Buntanetap has shown to improve AD participants' cognition. ADAS-Cog 11 and MMSE will be measured to assess its improvement on AD participants' cognition, ADCS-ADL will be measured to assess its improvement on AD participants daily living functions. ADCS-CGIC will also be measured to assess its effect in AD participants' performance. DSST will be measured to assess AD participant's CNS dysfunction.

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 participants will be administered the MMSE (Folstein 1975) for determination of inclusion into the study. The ADAS-Cog11 (Rosen 1984) and MMSE will be administered for participants' cognitive function. The ADCS-ADL (Galasko 1997) will be administered for participants' daily activity. ADCS-CGIC (Guy 1976) will be administered for participants cognitive and daily functions. The DSST (WAIS-IV; Wechsler 2008) will serve as a sensitive measure of CNS dysfunction.

Exploratory measures: Buntanetap has shown to reduce neurotoxic proteins, reduce inflammation and preserve axonal integrity and synaptic functions in previous Phase 2a studies. In this study we potentially plan to measure plasma Aβ42/42 ratio, GFAP, NFL, p-Tau 181, p-Tau217 and TDP43.

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 participants other than receiving medical and selective functional and cognitive evaluations.

The clinical investigator must advise all potential participants 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). No adverse effects were observed in dogs given doses up to 20 mg/kg/day for 36 weeks.

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. 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 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 four weeks 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 plus an additional four weeks. Male study participants should not donate sperm and female study participants should not donate eggs during the whole duration of the trial and four weeks after.

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 participants 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 (COVID19) vaccination is not prohibited. If appropriate, SARS-CoV-2 (COVID19) vaccination should be considered as a concomitant medication.

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 320 participants (1:1:1:1 randomized to 7.5mg, 15mg, 30mg buntanetap and placebo respectively) is planned to be randomized.

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

Participants who have signed an informed consent and meet screening eligibility requirements will be randomly assigned to the active and placebo treatment groups at 1:1:1:1 ratio. The randomization methodology used is permuted block randomization.

6.2. Power and Sample Size Determination

Qualified participants will be randomized at a 1:1:1:1 ratio to one of the following three treatment groups: 7.5 mg, 15 mg, 30 mg QD buntanetap and placebo. A sample size of 280 (210 combining all three buntanetap-treatment groups and 70 in control) will have a 90% power to detect a treatment difference for the primary efficacy variable ADAS-Cog11 at a two-sided significance level of 0.05, assuming a delta of 2.7 between the treatment (pooling all three treatment arms together) and placebo, and a common standard deviation of 6.0. This sample size will also have an 89% power to detect a significant difference for the co-primary efficacy variable ADCS-CGIC at a two-sided significance level of 0.05, assuming a delta difference 0.23 between the treatment (pooling all three treatment arms together) and placebo, and a common standard deviation of 0.5. Approximately 320 participants will be randomized (approximately 80 per arm) to account for an expected 12.5% dropout rate.

6.3. Safety and Tolerability Analysis

Safety and tolerability will be assessed with physical examinations, vital signs, clinical laboratory values, 12-lead ECG, use of concomitant medications, and AE reports. The frequencies of adverse events, serious adverse events, and laboratory abnormalities between the participants across the treatment groups will be compared.

Participants who dropout during the initial 9 weeks at-home treatment period will be discontinued and invited to an Early Discontinuation visit. Participants that drop out after the initial 9 weeks will be scheduled for an end-of-trial visit. If 4 participants are discontinued due to serious adverse events a DSMB 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 participants' 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 participants (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-participant coefficients of variation (CV) will be calculated.

6.5. Criteria for Termination of the Trial

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

An independent Data Monitoring Board (DSMB or IDMB) will be formed to safeguard the participants' wellbeing. The responsibilities of IDMB will be established in the IDMB Charter. The study will have a safety analysis when 90 randomized participants (about 30% of the targeted sample size) have been treated for 6 weeks.

6.6. Statistical Analysis

Continuous variables will be summarized using the following descriptive statistics: number of subjects, mean, median, standard deviation (SD), standard error (SE), minimum, and maximum. Unless otherwise specified, means, medians and confidence intervals (CIs) will be presented to one more decimal place than the raw data, and the SD and SE will be presented to two more decimals than the raw data. In general, the maximum number of decimal places is 4. Wherever possible, data will be decimally aligned.

Categorical variables will be summarized by the number of subjects and the percentage of subjects in each category. Categories with zero counts will not have zero percentages displayed. For demographic summaries, percentages will be calculated by using the total number of subjects in the given treatment group as the denominator. Percentages will be presented with one decimal place.

Unless otherwise specified, all statistical tests will be 2-sided at the significance level of 5% and all the Cis will be 2-sided 95%. P-values will generally be presented to 4 decimal places; values less than 0.0001 will be presented as <0.0001.

6.7. Study Participants and Demographics

6.7.1 Population Analysis Set

Enrolled Analysis Set: The enrolled population will include all participants who signed Informed Consent and meet all inclusion and exclusion criteria.

Randomized Analysis Set: The Randomized Analysis Set (RAS) consists of all participants who were randomized. Subjects will be classified according to the randomized treatment assignments.

Safety Analysis Set: The Safety Analysis Set (SAS) consists of all randomized participants who received at least one dose of study drug. Subjects will be analyzed according to the actual treatment.

Full Analysis Set: The Full Analysis Set (FAS) consists of all participants who were randomized, received at least one dose of study drug, and have both a baseline and at least one post-baseline value for the ADAS-Cog11 or ADCS-CGIC score after taking study drug. Subjects will be analyzed according to the treatment they were randomized.

Per Protocol Analysis Set: The Per-protocol Analysis Set consists of all participants in the FAS who do not have major protocol deviation. The membership of this analysis set will be determined prior to database lock.

6.7.2 Disposition and Withdrawals

The numbers of participants 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 participants in each analysis population will be reported.

6.7.3 Protocol Deviations

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

6.7.4 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.

6.7.5 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 participants taking each medication, classified using World Health Organization (WHO) Drug Dictionary Anatomical Therapeutic Chemical (ATC) classes and preferred terms.

6.8 Analysis of Primary Endpoints

The co-primary endpoints are the change from baseline to 12 weeks in ADAS-Cog11 scores and the ADCS-CGIC scores at 12 weeks. The ADAS-Cog11 will be analyzed via mixed models for repeated measures (MMRM). The model for ADAS-Cog11 will include treatment, timepoint, treatment-by-timepoint interaction as the fixed effects, baseline ADAS-Cog11as the covariate, and subjects as random effect. The Model for ADCS-CGIC will include treatment, timepoint, treatment-by-timepoint interaction as the fixed effects , and subjects as random effect. An unstructured covariance matrix will be used and the Kenward-Roger approximation will be used to adjust the denominator degrees of freedom. The change from baseline and the differences in the change from baseline between treatments will be based on the Least Square Means from this model. The two-sided 95% confidence intervals of the treatment differences will be presented.

6.9 Multiplicity Adjustment

The primary study hypothesis is that, the buntanetap-treatment (pooling three treatment arms together) is superior to placebo in reducing the cognitive impairment of AD patients, as assessed by the two co-primary endpoints: change from baseline in the ADAS-Cog11 score at 12-weeks and ADCS-CGIC score at 12-weeks. The two co-primary endpoints will be tested at a two-sided significance level of 5% without multiplicity adjustment. If both test hypotheses are rejected at the 5% level, the test will continue onto secondary endpoints in a gatekeeping sequential order, at a two-sided significance level of 5%.

The study is also designed to explore the effectiveness of three buntanetap-treatment dose level. Nominal p-values will be provided for these test hypotheses of each dose arm vs. placebo, without multiplicity adjustment.

6.10 Interim Analysis

An interim sample size re-estimation will be performed after a total of $n1$ = 90 evaluable participants across four treatment arms have 6 weeks of assessments for the co-primary efficacy endpoints ADAS-Cog11 and ADCS-CGIC. Evaluable participants are defined as randomized subjects who received the study drug and have baseline and Week 6 values of one or both co-primary efficacy endpoints. The aim of the interim sample size review is to re-assess the size of the estimated mean difference between the treatment (pooling three treatment arms together) and placebo, and standard deviations of the co-primary endpoints ADAS-Cog11 and ADCS-CGIC to ensure sufficient power at the final analyses.

No Interim analyses are planned for the purpose of stopping the study early for success or futility.

6.10.1 Re-estimation of Sample Size

The initial planned sample size was determined for ADAS-Cog11 based on a targeted power of 90% to detect a delta of 2.7 between the treatment (pooling three arms together) and placebo, with a common standard deviation of 6.0 at a two-sided significance level alpha of 5%. This sample size will also have a power of 89% to detect a significant difference for the co-primary effectiveness variable ADCS-CGIC at a two-sided significance level of 5%, assuming a delta of 0.22 with a common standard deviation of 0.5. Accounting for an expected drop-out rate of 12.5%, a sample size of approximately 320 participants (80 per treatment arm) was calculated to achieve 280 evaluable participants (70 per treatment arm).

To guarantee sufficient power for the primary trial objectives, sample size will be re-estimated based on the calculated conditional power at the interim analyses. The conditional power for each co-primary endpoint will be calculated at the significance level of 0.05 separately, according to the methodology and equation from Mehta and Pocock (2011). The sample size will only be increased if the conditional powers for both co-primary endpoints are >50% (and <90%), otherwise, the trial will continue as planned, i.e., no decrease in sample size or stopping the trial early for futility or efficacy success at the interim analysis. The target power is 90% and maximum sample size per group is set to be 100 participants per arm. Specifically, if both conditional powers at interim analysis are >50%, then each arm will be increased to 100 participants. Otherwise, the trial will continue as is.

Chen, Lan and Demets (2004) have shown that, when conditional power >=50%, one may increase sample size to $n2*$ and the conventional test statistics and critical values can be used at the final analysis, the overall type I error rate will not be inflated. Further, Chen, Yuan and Li (2018) demonstrated that the conventional maximum likelihood estimate, and coverage error of its conventional confidence interval are generally small following sample size adjustment. Therefore, conventional point estimate and confidence interval are recommended to be used when applying the 50% conditional power principle for sample size re-estimation, to keep consistent statistics in both hypothesis test and statistical inference.

6.10.2 Communication of Interim Results

The study team at the Sponsor will be blinded to the interim results and only decisions on sample size re-estimation will be communicated to the sponsor. A blinded Sponsor clinical scientist may have access to blinded aggregated ADAS-Cog11 and ADCS-CGIC 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

All safety summary analyses will be performed using the actual treatment for the Safety Analysis by each treatment group and by the pooled buntanetap-treatment group.

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

No formal statistical comparisons will be performed for safety endpoints.

6.12 Adverse Events

Adverse events (AEs) will be coded using MedDRA dictionary, Version 25.1 or newer.

An AE will be considered as a treatment-emergent AE (TEAE) if started after first dose and no later than last dose date + 30 days, or started prior to first dose, but worsened in severity post dose.

The event counts, number and percentage of subjects reporting TEAEs in each treatment group will be tabulated by system organ class (SOC) and preferred term (PT); by SOC, PT and maximum severity; by SOC, PT and relationship to study drug and by descending frequency of PT (within treatment group). If more than one TEAE occurs with the same PT for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summary. The display in these tables will be sorted alphabetically by SOC and then by descending frequency of PT (within treatment group) within each SOC.

The incidence of most frequently reported (PT frequency >=5% in any group) TEAEs, SAEs reported after treatment start, TEAEs leading to drug withdrawn, and TEAEs related to study drug will be summarized by SOC and PT.

An AE listing by subject will display all events, and will include the verbatim term in addition to the MedDRA SOC and PT. This listing will also include all relevant eCRF data associated with the event: date of onset, date resolved, date of last dose, severity, frequency, outcome and relationship to study drug and action taken with study drug. Separate listings will be presented for subjects with treatment-emergent SAEs, related TEAEs, TEAEs leading to drug withdrawn, fatal TEAEs (if any).

6.12.1 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, and the pooled buntanetap-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 participants 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.

6.12.2 Electrocardiogram (ECG)

12-lead ECGs are collected throughout the study. Observed change from baseline of ECG endpoints at each assessment timepoint will be summarized by each treatment group, and the pooled buntanetap-treatment group. Observed QTc will also be categorized into the following categories (msec) and the number and percentage of subjects in each category will be summarized at each timepoint and the overall post-baseline maximum:

- Observed: <=450, 451-480, 481-500, and >500; >450; >480
- Change from Baseline: <=10, 11-30, 31-60, and >60; >30

For ECG interpretations, the number and percentage of subjects with ECG results that are determined as normal, abnormal will be summarized at each timepoint. The overall post-baseline worst interpretation will also be summarized. Shift tables from baseline to each timepoint and from baseline to overall post-baseline worst interpretation will also be presented.

6.12.3 Vital Signs

Descriptive summaries (mean, SD, SE, 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.

6.12.4 Physical Examination Findings

Physical examination data will be presented in the listings.

6.12.5 Other Safety Parameters: C-SSRS

The number and percentage of participants with suicidal ideation or suicidal behavior based on the C-SSRS will be summarized by treatment group and the pooled buntanetap-treatment group. The distribution of responses for most severe suicidal ideation and most severe suicidal behavior during the participant'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 participant 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 participants who have suicidal ideation or suicidal behavior will also be provided.

7 STUDY DRUG AND CONCOMITANT MEDICATIONS

7.1 Identity of IP and Comparator

Buntanetap will be provided in size 1 orange opaque hydroxypropyl methylcellulose (HPMC, vegetarian source) capsule shells. Capsules contain buntanetap (either 7.5mg, 15mg or 30mg) 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 12 weeks at home. Participants are encouraged to take at least 80% of all doses (across the 12 weeks). Bottles will be examined in clinic at each clinical visit to assess compliance.

7.3 Packaging/Dispensing/Labeling

The study drug (buntanetap capsules and placebo capsules) is manufactured under cGMP, in a manner to preserve the blind, i.e., identical color and shape orange opaque HPMC hard capsule shells and packaged 50 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 all eligibility criteria (including 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 study partner before dispensing the study drug.

All packaging and labelling as well as the production of study medication will be in accordance with cGMP regulations.

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 participants. 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 end of trial visit. Participants are encouraged to maintain a minimum of 80% compliance with study drug administration across the 12 weeks at home dosing period.

Prior to the end of trial visit, site personnel will also contact the participant to remind them of the dose regimen, to ensure that a good level of compliance has been achieved.

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 participant for SAE, the investigator can open the blind without prior consulting with the Medical Monitor. 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.

Aducanumab/Aduhelm and Lecanemab/Leqembi are prohibited for 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 Medical Monitor for further guidance.

Buntanetap is mainly metabolized by CYP3A4 *in vitro*. Therefore, we recommend avoiding concomitant use of strong and 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

Use of the following medications is allowed only if the participants have been stabilized 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 dosage must not exceed the following for these medications:
  Quetiapine ≤50 mg/day, risperidone ≤1.5 mg/day, olanzapine ≤5 mg/day, and 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 course of the study is discouraged, however, if necessary, the site should consult with the Medical Director and Sponsor for further guidance.

This protocol allows concomitant treatment with anti-cholinesterase for 4 weeks or greater prior to screening.

If participants 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 permitted. 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 participants 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 (COVID19) vaccination is not prohibited. If appropriate, SARS-CoV-2 (COVID19) vaccination should be considered as a concomitant medication.

8 STUDY POPULATION

Participants in this study must be in accordance with the criteria specified below. Participants who do not meet all inclusion criteria, disease diagnostic criteria, or who meet any exclusion criteria will not be included in the clinical trial.

8.1 Inclusion Criteria

Participants must meet the following criteria:

1. Diagnosis of Alzheimer's disease according to NIA and NIA-AA criteria for probable AD (McKhann 2011).

2. Male or female aged 55 – 85 years.

3. MMSE 14-24.

4. Have a study partner who will provide written informed consent to participate, is in frequent contact with the participant (defined as at least 10 hours per week) and will accompany the participant to study visits at designated times.

5. Female participants 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 participants 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 participant 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. Participants can provide written informed consent. If PI deems that participant cannot fully understand ICF to give consent, their legally authorized representatives (LARs) can provide written informed consent. Participants can comply with scheduled visits, and other study-related procedures to complete the study with the help of the study partner.

8. No evidence of current suicidal ideation or previous suicide attempt in the past 2 months as evaluated in the Columbia Suicide Severity Rating Scale nor suicidal behavior in the past 6 months as per investigator.

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

   a. Cholinesterase inhibitors and/or memantine medication

   b. Anticonvulsant medications used for epilepsy or mood stabilization, neuropathic pain indications.

   c. Mood-stabilizing psychotropic agents, including, but not limited to, lithium.

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

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

8.2 Exclusion Criteria

Participants 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. Has non-AD dementia, such as vascular dementia, Lewy body dementia, frontotemporal disease, Parkinson disease dementia, B12 and thyroid deficiency caused dementia.

3. History of a seizure disorder, if stable on medication is acceptable.

4. Has a history or current evidence of long QT syndrome, Fridericia's formula corrected QT (QTcF) interval ≥ 450 ms for men and 460 ms for women, or torsades de pointes.

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

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

7. 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).

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

9. 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. Participants 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.

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

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

12. Participation in another clinical trial with an investigational agent and have taken at least one dose of study medication, unless unblinded on placebo, within 4 weeks prior to the start of screening, or five half-lives of the investigational drug, whichever is greater.

The end of a previous investigational trial is the date the last dose of an investigational agent was taken.

13. Participants with learning disability or developmental delay.

14. Participants whom the site PI deems to be otherwise ineligible.

15. Participants 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
Hypromellosee (capsule shells structure)
titanium dioxide (opacifier of the capsule shells)

16. Participant is currently pregnant, breast-feeding and/or lactating.

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

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

9 DESCRIPTION OF STUDY VISITS

Each participant will have a 42-day screening period followed by 12 weeks 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, but all must be done within a week. At PI's discretion, re-testing can be done within 30 days. If the investigator deems re-screening is justified, they must contact Medical Monitor and sponsor for discussion on a case-by-case basis. If/when rescreening MMSE, the test has to be done at least 3 weeks apart from the previous one.

Potential participants or their legally authorized representatives (LAR) if PI deems that participant cannot fully understand ICF to give consent, must sign an informed consent form prior to administration of any study-related procedures. The informed consent process must be performed by the principal investigator or medically qualified sub-investigator. Information regarding the participant's demographics, concurrent medications, and medical history will be collected along with cognitive assessments, physical examination, and neurological examination.

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 participants of childbearing potential. Fasting is required for safety laboratory tests.

Cognitive and functional assessments should not be administered when the participant 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 participant's eligibility before proceeding to Baseline.

9.2 Baseline Visit

Sites should remind participants 1-3 days prior to their onsite visit through a telephone call. Baseline procedures include functional, cognitive, and behavioral assessments, safety assessments and a review of concurrent medications and potential adverse events that might occur. To avoid the learning effect, MMSE should be done at least three weeks after the participant's last MMSE test. The visit will consist of the following: admission procedures, including genetic material collection (blood for ApoE genotype), PK Sampling / administration of first dose, and finally, discharge procedures.

Fasting state is required for safety laboratory tests, however, cognitive, and functional assessments should not be administered when the participant is in a fasted state.

All baseline assessments should be performed on the same day. Details as below.

Participants 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, participants will be provided low-fat light meal before completing functional and cognitive evaluations, a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of the contents of all meals provided to the participants. Following completion of all these procedures, participants who continue to meet all protocol inclusion criteria and no exclusion criteria should be randomized.

If no medical or compliance concerns are identified, the participant will move on to the PK sampling phase, which will entail the following procedures:

1) Collect initial samples of blood (hour 0) (12ml) with venipuncture unless PI deems inappropriate with 2ml in a tube for ApoE genotype* and 10ml in a separate tube for PK.
2) Administer first dose of assigned study drug after the hour 0 sampling.
3) Collect blood (10mL) at the 1hr, 2hrs and 4hrs timepoints. Blood should be taken within ± 10 mins of times.
4) Perform the final safety monitoring.

* ApoE genotype sample can be collected along with any other blood draw during this visit, as deemed appropriate by PI.

Prior to discharge from the clinic, vital signs should be recorded, and a review of AE(s) and concomitant medications should be conducted. Participants will be educated of the study drug compliance and study drug return. Upon determination by the Investigator (or qualified designee) that the participant is stable, the participant will be discharged. If a participant experiences an unstable AE, please contact the Medical Monitor for guidance on the appropriate course of action to be taken.

9.3 Onsite Visit at 6 Weeks

Sites should remind participants 1-3 days prior to their onsite visit through a telephone call. At 6 weeks from the baseline visit, a clinic visit should occur. Clinic visit procedures include functional, and cognitive assessments, safety assessments, and review of concurrent medications and adverse events. Fasting is required for safety laboratory tests.

After safety lab, participants will be provided low-fat light meal before completing functional and cognitive evaluations, a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of the contents of all meals provided to the participants.

Study medication compliance will be reviewed and discussed, and reminders given about the upcoming end of trial visit. The participant should be scheduled for the 12-week clinic visit.

9.4 12 Weeks Visit (End of Trial Visit)

Sites should remind participants 1-3 days prior to their onsite visit through a telephone call. Admission for the end of trial visit should occur 12 weeks 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 cognitive assessments, safety assessments, and review of concurrent medications and adverse events that occur in clinic and blood collection. Fasting state is required for safety laboratory tests, however, cognitive, and functional assessments should not be administered when the participant is in a fasted state.

9.4.1 End of Trial Visit

This constitutes the participants' last clinical visit during the study. The end of trial visit will consist of the following: admission procedures, blood sampling, all psychometric and safety tests, and discharge procedures. Fasting is required for safety laboratory tests.

Participants 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, participants will be provided a low-fat light meal before completing functional and cognitive evaluations, a physical and neurological exam, collecting vital signs, ECG, and reviewing and recording adverse events and concurrent medications. Sites should take detailed notes of the contents of all meals provided to the participants.

If no medical or compliance concerns are identified, the participant will move on to the PK sampling phase, which will entail the following procedures:

1) Collect initial samples of blood 10ml (hour 0) with venipuncture unless PI deems inappropriate.

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

3) Collect blood (10mL) at the 1hr, 2hrs and 4hrs timepoints. Blood should be taken within ± 10 mins of times.

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. Upon determination by the Investigator (or qualified designee) that the participant is stable, the participant will be discharged. If a participant experiences an unstable AE, please contact the Medical Monitor for guidance on the appropriate course of action to be taken.

9.4.2 Post End of Trial Visit 24-Hour Phone Follow-up

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

10 EARLY TREATMENT/STUDY DISCONTINUATION

The investigators at each site will make every reasonable effort to maximize participant retention. However, if an investigator removes a participant from treatment or study, or if a participant declines further treatment or study participation, an early discontinuation visit will be completed as soon as possible following discontinuation.

Participants who discontinue from the study prior to completing all protocol procedures may be replaced in consultation with the Sponsor.

10.1 Reasons for Early Discontinuation

Participants or their LARs 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 or their LARs should inform sites as soon as such a withdraw decision is made. 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 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 participants or their LARs 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.

* The line item above requires the participant to continue to meet study entry criteria after randomization. This means that assessments conducted at visits post-randomization, such as vital signs, ECG, and laboratory tests, with results that fall outside of the parameters outlined in the Inclusion/Exclusion criteria must be discussed with the Medical Monitor and Study Team.

The investigator and Medical Monitor will review the case to determine whether the participant must be discontinued from the study based on the abnormal value or if it is safe for the participant to continue treatment.

11 STUDY-SPECIFIC INSTRUMENTS

The following instruments will be employed to measure states of function, dementia, and movement.

- Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog11)
- Mini-Mental State Examination (MMSE)
- Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL)
- Clinical Global Impression of Change (ADCS-CGIC)
- Digital Symbol Substitution Test (DSST)

12 STUDY-SPECIFIC PROCEDURES

12.1 Safety Assessments

Safety will be evaluated by monitoring for changes in the parameters summarized below, including any AEs/SAEs as reported by participants 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 (baseline and 6-weeks), and the end of trial visit (12-weeks). Refer to the Laboratory Manual for additional details.

CLINICAL SAFETY LAB TESTS		
METABOLIC PANEL	**COMPLETE BLOOD COUNT**	**URINALYSIS**
Sodium (Na)	White Blood Cell Count (WBC)	Color
Potassium (K)	Red Blood Cell Count (RBC)	Appearance
Chloride (Cl)	Hemoglobin (Hb)	Specific Gravity
Carbon Dioxide (CO2)	Hematocrit (HCT)	pH
Blood Urea Nitrogen (BUN)	Mean Corpuscular Volume (MCV)	Blood
Glucose	Mean Corpuscular Hemoglobin (MCH)	Glucose
Calcium (Ca)	Mean Corpuscular Hemoglobin	Protein
Creatinine (Crn)	Concentration (MCHC)	Ketones
Bilirubin (direct and total)	Red Blood Cell Distribution Width	Leukocyte Esterase
Albumin	(RDW)	Nitrite
Protein Total	Mean Platelet Volume (MPV)	Urobilinogen
Glutamic-Oxaloacetic	Platelet Count (PLT)	Bilirubin (total)
Transferase (AST, SGOT)		
Glutamic-PyruvateTransferase	**Screening Visit Only**	
(ALT, SGPT)	Hemoglobin A1c (HbA1c)	
Alkaline Phosphatase (ALP)	Vitamin B12	
eGFR (estimated Glomerular	Thyroid Panel (TSH, Free T4, Free T3)	
Filtration Rate)		

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 participant'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 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. The site PI should keep the same rater for the same subject for the same scales during the whole study. Additionally, the PI will perform or supervise clinical evaluation of all participants and ensure protocol adherence. Additional key personnel will be required, as outlined in the procedure manual.

14 ADVERSE EVENTS (AES)

14.1 Definition

An AE is defined as per the US Code of Federal Regulation, Title 21, Part 312.32 (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 participant or clinical investigation participant administered a pharmaceutical product 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 participant 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) Participant 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 Participant 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 Participant's records, in accordance with the investigator's normal clinical practice, and on the AE case report form.

14.2 Following Up on AEs

The investigator is obliged to follow participants with AEs until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Participants 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 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 participant 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.

16 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 FDA and IRB of any individual case reports of SAEs that are determined to be reportable by the Sponsor (SUSARs). 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 FDA and 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 ADVERSE EVENTS OF SPECIAL INTEREST

Not applicable.

18 PRECAUTIONS/OVERDOSE

If a participant receives a dose exceeding 200 mg of buntanetap, the dose may be considered toxic. Since this is a double-blind study, if a participant swallows 7 or more capsules with the assumption of them being in the 30mg 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 PREGNANCY

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

A pregnancy as such is not an AE, unless there is a possibility that the study drug 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 participant 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 DATA AND SAFETY MONITORING BOARD (DSMB)

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

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

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

21 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

Participant 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 participants.

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 participants 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 participant identification number (Participant 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 participant, except as necessary for trial-related monitoring, audits, IRB review, and regulatory inspection(s), where direct access to source data/documents will be provided.

Information about study participants 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.

If a participant revokes authorization to collect or use protected health information (PHI), the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. Each site PI, under the guidance of his/her IRB, is responsible for ensuring that all applicable GDPR/HIPAA regulations and laws are met.

22 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)

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 US, 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.

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 GCP. 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 participants and their LAR if LAR is required. Consent forms must be in a language fully comprehensible to the prospective participants. Participants and their LARs if LAR is required will be given ample opportunity to inquire about the details of the study. Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or their LAR if LAR is required and by the person who conducted the informed consent discussion. Participants 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 participants will never receive results.

23 STUDY MONITORING

The clinical monitor is responsible for inspecting the case report forms (CRFs) and source documentation at specific time points throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research.

The 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 be conducted to confirm that e.g.:

- The investigational team is adhering to the study protocol
- Informed consent has been obtained from all participants
- AEs have been reported as required
- Data are being accurately recorded in the CRF
- Study drug 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 CRF, source documents and other study-related records will be compared against each other to ensure accurate data that reflect the actual existence of the participant in the study, i.e., source data verification. The Site Investigator will cooperate in the monitoring process by ensuring the availability of the CRF, 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 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 regulatory authority (i.e., FDA) and/or an IRB. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the trial conduct and compliance with the protocol may also occur.

25 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 (21CFR§312.57).

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APPENDIX 1: SCHEDULE OF EVENTS

Study Period	**Screening/Baseline**		**At-Home Treatment**		**Unscheduled Visit[k]**	**Early Discontinuation Visit**
Visit Timing	**Day -42 to 0**		**6 weeks ± 7 days**	**12 weeks ± 7 days (end-of-trial) [b]**		
Procedure	**Screening [j] (up to 42 days before Day 0)**	**Baseline (Day 0)**	**Clinic Visit -**	**Clinic Visit -**	**Clinic Visit**	**Clinic Visit**
Informed consent	X					
Inclusion and exclusion criteria	X	X				
Demography information	X					
Full physical and neurological examination	X	X	X	X	X	X
Height, Weight, BMI	X					
Medical and psychiatric history (includes substance use)	X					
Urine pregnancy test (WOCBP only)	X	X	X	X	X	X
MMSE [l]	X	X		X		X
ADCS-CGIC		X[d]	X[e]	X[e]		X[e]
ADAS-Cog11		X	X	X		X
ADCS-ADL		X	X	X		X
DSST		X	X	X		X
C-SSRS	X	X	X	X	X	X
Safety laboratory tests [c]	X	X	X	X	X	X
12-lead ECG	X	X	X	X		X
Vital signs[a]	X	X	X	X	X	X

Study Period	**Screening/Baseline**		**At-Home Treatment**		**Unscheduled Visit[k]**	**Early Discontinuation Visit**
Visit Timing	**Day -42 to 0**		**6 weeks ± 7 days**	**12 weeks ± 7 days (end-of-trial) [b]**		
Procedure	**Screening [j] (up to 42 days before Day 0)**	**Baseline (Day 0)**	**Clinic Visit -**	**Clinic Visit -**	**Clinic Visit**	**Clinic Visit**
Randomization		X				
Genetic sample (ApoE)		X				
Study intervention		X[g]	X[h]	X[I]		
Study intervention compliance review			X	X		
AE/SAE review	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
PK sampling		X		X		
Sampling for blood biomarkers		X		X		
24-hour phone follow-up		X	X	X	X	X

[a] Vital sign will include sitting blood pressure, pulse, temperature, respiration rate.

[b] Participants that drop out before the initial 9 weeks of study treatment will complete the Early Discontinuation visit and participants that drop out after the initial 9 weeks of study treatment will complete the End-of-Trial visit.

[c] Safety labs should be taken fasted.

[d] ADCS-CGIC evaluation only.

[e] ADCS-CGIC evaluation and scoring the scale.

[g] Participants are given one pill during the visit after taking pre-dose (0h) blood samples and the pills for the remaining 6 weeks at the end of the visit.

[h] Participants are given pills for the remaining 6 weeks at the end of the visit.

[I] Participants are given one pill during the visit after taking pre-dose (0h) blood samples.

[J] At PI's discretion, re-testing can be done within 30 days. If the investigator deems re-screening is justified, they must contact Medical Monitor and sponsor for discussion on a case-by-case basis. If/when rescreening MMSE, the test must be done at least 3 weeks apart from the previous one.

[K] Investigator will determine the extra assessment if any is needed.

[l] To avoid the learning effect, all MMSEs should be done at least 3 weeks apart.