EIP PHARMA, INC

CLINICAL STUDY PROTOCOL

Title	A Double-Blind, Placebo-Controlled 16-Week Study of the Cognitive Effects of the Oral P38 Alpha Kinase Inhibitor Neflamapimod in Dementia with Lewy Bodies (DLB)
Investigational Product	Neflamapimod
Development Phase	2
EIP Study Number	EIP19-NFD-501
IND Number	125198
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Date (Version)	12 April 2019 (Version 1.0)
Sponsor Address	EIP Pharma, Inc. 210 Broadway, Suite 201 Cambridge MA 02139 USA

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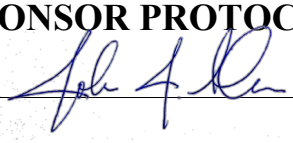

Signature

John J. Alam, M.D.

Sponsor Responsible Person

President and CEO

Title

12 April 2019

Date

INVESTIGATOR'S SIGNATURE OF AGREEMENT PAGE

I have read the protocol and, on behalf of my institution, agree to comply with all the conditions and instructions contained in this the protocol and with all applicable regulations.

Signature

Principal Investigator (printed name):
Title:
Institution:
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Date

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SYNOPSIS

Study Title	A Double-Blind, Placebo-Controlled 16-Week Study of the Cognitive Effects of the Oral P38 Alpha Kinase Inhibitor Neflamapimod in Dementia with Lewy Bodies (DLB)
Protocol Number (date, Version)	EIP19-NFD-501
Study Phase	2
Study Centers	Approximately 20 study centers in the United States (US) and 2 study centers in the Netherlands
Indication	Dementia with Lewy Bodies (DLB)
Study Objective	The primary objective is to evaluate the effect of neflamapimod on cognitive function as assessed in a study-specific Neuropsychological Test Battery (NTB) comprised of: • Cogstate Detection test (DET) • Cogstate Identification test (IDN) • Cogstate One Card Learning test (OCL) • Cogstate One Back test (ONB) • Letter Fluency Test • Category Fluency Test (CFT) The secondary objectives are to: • Evaluate the effects of neflamapimod on informant/caretaker evaluation of cognition and function, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB). • Assess the effects of neflamapimod on general cognition, as assessed by the Mini Mental State Examination (MMSE). • Assess the effects of neflamapimod on episodic memory, as assessed by the International Shopping List Test (ISLT). • Assess the effects of neflamapimod on select domains of the 10-item Neuropsychiatric Inventory (NPI-10), including depression (dysphoria), anxiety, hallucinations, and agitation/aggression. • Evaluate the effects of neflamapimod on motor function as assessed by the Timed Up and Go Test (TUG). • Evaluate the effects of neflamapimod on quantitative electroencephalography (EEG) parameters.

Study Endpoints	Primary endpoints: • Change in the composite score of the NTB, including assessments of attention, executive function, and visuospatial function in neflamapimod treated-subjects as compared to the placebo-treated subjects. Secondary endpoints: • Change in CDR-SB in neflamapimod-treated subjects compared to placebo-recipients. • Change in MMSE in neflamapimod-treated subjects compared to placebo-recipients. • Change in NPI-10 domains in neflamapimod-treated subjects compared to placebo-recipients. • Change in International Shopping List Test immediate & delayed recall and recognition in neflamapimod-treated subjects compared to placebo-recipients. • Change in Timed Up and Go Test. • Change in EEG parameters.
Number of Subjects	80 subjects are planned to be enrolled
Subject Population	Subjects aged ≥55 years with mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria (McKeith et al, 2017), including a positive DaTscan™, who are currently receiving cholinesterase inhibitor therapy. If the DaTscan is negative, but the subject has historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), this will also qualify as probable DLB.
Inclusion Criteria	1. Men and women aged ≥55 years. 2. Subject or subject's legally authorized representative is willing and able to provide written informed consent. 3. Probable DLB and identified cognitive deficits, according to current consensus criteria (McKeith et al, 2017), specifically one core clinical feature and a positive DaTscan. If a negative DaTscan, but the subject has historical PSG-verified RBD, the subject would also qualify. 4. MMSE score of 15-28, inclusive, during Screening. 5. Currently receiving cholinesterase inhibitor therapy, having received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization. Except for reducing the dose for tolerability reasons, the dose of cholinesterase inhibitor may not be modified during the study. 6. Normal or corrected eye sight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments. 7. No history of learning difficulties that may interfere with their ability to complete the cognitive tests. 8. Must have reliable informant or caregiver.

Exclusion criteria	1. Diagnosis of any other ongoing central nervous system (CNS) condition other than DLB, including, but not limited to, post-stroke dementia, vascular dementia, Alzheimer's disease (AD), or Parkinson's disease (PD). 2. Suicidality, defined as active suicidal thoughts within 6 months before Screening or at Baseline, defined as answering yes to items 4 or 5 on the C-SSRS, or history of suicide attempt in previous 2 years, or, in the Investigator's opinion, at serious risk of suicide. 3. Ongoing major and active psychiatric disorder and/or other concurrent medical condition that, in the opinion of the Investigator, might compromise safety and/or compliance with study requirements. 4. Diagnosis of alcohol or drug abuse within the previous 2 years. 5. Poorly controlled clinically significant medical illness, such as hypertension (blood pressure >180 mmHg systolic or 100 mmHg diastolic); myocardial infarction within 6 months; uncompensated congestive heart failure or other significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would interfere with assessment of drug safety. 6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5. 7. Known human immunodeficiency virus, hepatitis B, or active hepatitis C virus infection. 8. Participated in a study of an investigational drug less than 3 months or 5 half-lives of an investigational drug, whichever is longer, before enrollment in this study. 9. History of previous neurosurgery to the brain. 10. If male with female partner(s) of child-bearing potential, unwilling or unable to adhere to contraception requirements specified in the protocol. 11. If female who has not has not reached menopause >1 year previously or has not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy, has a positive pregnancy test result during Screening and/or is unwilling or unable to adhere to the contraception requirements specified in the protocol.
Study Drug Details	Neflamapimod 40 mg capsule or matching placebo capsules.
Duration of treatment	Screening window of 21 days (unless DaTscan is required, in which case Screening window may be extended to 35 days), 16 weeks of treatment, a 2-week follow-up visit for a total of 21 weeks study duration.
Study Design and Methods	This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of-principle study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with DLB. Subjects weighing <80 kg will receive 2 capsules per day (in divided doses) and those weighing ≥80 kg will receive 3 capsules per day (in divided doses). Subjects receiving two capsules per day will be administered 1 capsule, twice daily (BID) with food (i.e., with the morning and evening meals), either neflamapimod 40 mg or placebo. Subjects receiving 3 capsules per day will be

	administered 1 capsule three times daily (TID) with food (i.e., with the morning, mid-day, and evening meals), either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart. Following completion of informed consent procedures, subjects will enter the Screening phase of the study. One to two Screening visits are planned, during which safety screening measures will be undertaken, a practice NTB will be performed, and the required diagnosis and cognitive impairment will be confirmed. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan™ is required to determine study eligibility, Screening may be extended to 35 days. Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Randomized subjects will be stratified by International Shopping List Test (ISLT) Total Recall score at Baseline ($\leq$ 21 vs. >21), i.e. by wheter patients have an episodic memory defect at baseline or not. Subjects will receive study drug for 16 weeks. Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Final Study Visit (i.e. Follow-Up Visit) will be conducted 2 weeks (+/-3 days) after completion of study drug or after the Early Termination (ET) visit. The NTB, ISLT, and NPI-10 will be conducted at Screening, Baseline (Day 1), Week 4 (Day 28), Week 8 (Day 56), and Week 16 (Day 112) or ET if early termination. The CDR-SB and TUG will be conducted at Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. The MMSE will be conducted at Screening, Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. EEGs will be conducted at Baseline (Day 1) and Week 16 (Day 112) or ET. Samples for plasma biomarkers will be obtained at Screening, Baseline (Day 1) and Week 16 (Day 112) or ET.
Therapy	Neflamapimod 40 mg capsule(s) or matching placebo capsules will be administered orally, BID or TID depending on weight, with food for 16 weeks. All subjects will be administered 1 capsule, BID or TID, with food. Doses must be taken within 30 minutes following a meal or snack. Doses should be taken at approximately same times each day throughout the study and at least 3 hours apart. All subjects will receive matched (by size and color) capsules that contain 40 mg neflamapimod, or placebo, respectively. Subjects weighing less than 80 mg will receive one 40 mg neflamapimod capsule or one placebo capsule to be taken BID with food (i.e., with the morning and evening meals); subjects weighing 80 mg or more will receive one 40 mg neflamapimod capsules or one placebo capsule to be taken TID (i.e., with the morning, mid-day, and evening meals). Subjects will be randomized 1:1 placebo or neflamapimod.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APOE	Apoliprotein E
APP	Amyloid-precursor-protein
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	bis in die (twice a day)
CDR-GS	Clinical Dementia Rating Scale-Global Score
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
CFT	Category Fluency Test
CL	Clearance
CNS	Central nervous system
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CYP	Cytochrome P450
DET	Cogstate Detection test
DLB	Dementia with Lewy Bodies
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalography
ET	Early Termination
FDA	Food and Drug Administration
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDN	Cogstate Identification Test

Abbreviation	Definition
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
ISLT	International Shopping List Test
LFT	Liver function test
MAP	Mitogen-activated protein
MAPKα	p38 mitogen activated protein kinase alpha
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
MWM	Morris-Water-Maze
NPI-10	10-item Neuropsychiatric Inventory
NTB	Neuropsychological Test Battery
OCL	Cogstate One Card Learning test
ONB	Cogstate One Back Test
p38α	Mitogen-activated protein kinase 14
PD	Parkinson's disease
PK	Pharmacokinetic
PSG	Polysomnography
qEEG	Quantitative electroencephalograph
RBD	REM sleep behavioral disorder
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SPECT	Single-photon emission computed tomography
TID	Three times daily
TUG	Timed Up and Go Test
ULN	Upper limit of normal
US	United States

1. INTRODUCTION

1.1. Scientific Rationale

This is a double-blind, placebo-controlled 16-week treatment study of neflamapimod 40 mg administered twice daily (BID) or 3 times daily (TID), based on subject weight, in subjects with Dementia with Lewy Bodies (DLB). The primary objective of this proof-of-concept study is to determine whether neflamapimod can improve cognitive function in subjects with DLB, as assessed by a neuropsychological test battery (NTB).

DLB is common, representing 10-20% of the dementia population, with an estimated 1.4 million affected individuals in the United States (US). There is evidence that the prognosis is even more severe than other dementia disorders, including Alzheimer's disease (AD). DLB is characterized by progressive dementia and fluctuating cognition (deficits in memory, attention) and is also associated with sleep disturbances, visual hallucination, and Parkinsonism (tremor, gait disturbance). DLB has now been identified as a separate disease, although it remains difficult to differentiate it from the related dementias of AD and Parkinson's disease (PD) dementia (McKeith et al, 2017; Walker et al, 2015).

The clinical presentation of DLB demonstrates progressive cognitive decline accompanied by mild-to-moderate motor symptoms that are similar to those seen in PD (Park et al, 2011). DLB is a progressive disorder with average time from diagnosis to death approximately 7 years. There are no treatments approved for the underlying disease process and only symptomatic treatments for parkinsonian symptoms. Although not approved for DLB, cholinesterase inhibitors are often used.

Neflamapimod is a highly specific inhibitor of the intra-cellular enzyme mitogen-activated protein kinase 14 (p38α) that is currently being evaluated in a phase 2b clinical study in early AD. In the brain, p38α regulates inflammation through effects on microglia. Moreover, under conditions of stress and disease, p38α is also expressed in neurons and of the various p38 isoforms, the α isoform is the most important regulator of the stress response in neurons (Lawson et al, 2013). In the neuron, p38α also appears to play a critical role in inflammation-driven toxicity to synapses (Watterson et al, 2013; Prieto et al, 2015). As a result of this understanding, p38 mitogen activated protein kinase alpha (MAPKα) has been recognized as a leading therapeutic target to improve synaptic function and synaptic plasticity for a broad range of central nervous system (CNS) disorders (Corrêa et al, 2012; Sandersen et al, 2016).

More recently, using selective inhibitors of p38α, two groups have demonstrated that short-term (2-3 weeks) treatment reverses spatial learning deficits in the Radial Arm Water Maze and Morris-Water-Maze (MWM) tests in the Alzheimer's APP/PS1 transgenic mouse (Roy et al, 2015) and the Aged Rat (Alam, 2015) models, respectively. Further, genetic reduction of neuronal p38α in amyloid-precursor-protein (APP) overexpressing transgenic mice improves synaptic transmission and plasticity (i.e., prevents synaptic dysfunction), reduces memory loss, and reduces amyloid pathology (Colié et al, 2017). Genetically knocking down p38α in neurons also protected mice from developing age-related hippocampal dysfunction and decline in neurogenesis (Cortez et al, 2017).

Regarding neflamapimod in preclinical and early phase studies, it has been shown to reverse spatial learning deficits, as assessed in the Morris-Water-Maze test, in aged rats (Alam et al, 2015). The spatial learning deficits in the aged rat is considered to be the result of inflammation-induced hippocampal synaptic dysfunction. Moreover, in Phase 2a clinical studies in patients with early AD, neflamapimod demonstrated medium to large effect size within-subject improvement in performance on tests of

immediate and delayed recall (i.e., tests of episodic memory). These preliminary clinical results are being evaluated in a 24-week placebo-controlled study in early AD that is ongoing.

Neflamapimod has not been evaluated previously in DLB. However, though patients present with a broader set of cognitive deficits (e.g., visual-spatial deficits), episodic memory deficits attributable to hippocampal dysfunction are prominent, though generally considered qualitatively different from that in in AD (Park, et al 2011; Galvin, 2015; Adamowitz et al, 2017). As a result, based on the prior rationale for p38α kinase inhibition to address hippocampal dysfunction as well the preliminary clinical evidence with neflamapimod in patients with AD, neflamapimod could be expected to improve episodic memory in patients with DLB.

In addition, based on the potential to impact broadly the disease pathogenesis of DLB, neflamapimod might be expected to impact synaptic dysfunction regions outside the hippocampus as well. For example, with respect to underlying disease pathogenesis, based on genetic evaluation, DLB appears to be overlapping with disease pathogenesis for both AD and PD (Guerreiro et al, 2016). Apoliprotein E (APOE) genotype variants are associated with both DLB and AD, while the major biologic impact of the disease-associated APOE4 variant is to augment the neuroinflammatory response (Keene et al, 2011). As such, inflammation-induced synaptic dysfunction, regardless of the brain region impacted, is likely to be drivers of disease in both settings; a concept that is supported by the finding of elevated markers of inflammation in the brain of both disorders (Mrak and Griffin, 2007). With respect to disease pathogenic mechanisms that are common to DLB and PD, the most important is considered to be the neurotoxicity of α-synuclein, the constituent of "Lewy bodies" that is the major pathologic correlate of both diseases. Importantly, p38 kinase has been linked to the neurotoxicity of α-synuclein in a range of in vitro and in-vivo model systems (Obergasteiger, et al, 2018; Chen et al, 2018).

The primary objective of this study is to assess the impact of neflamapimod on cognitive function domains (attention, executive function, visuospatial function) that depend on proper synaptic function in the frontal and parieto-occipital regions of the brain. A secondary objective is to evaluate the effects of neflamapimod on episodic memory function, which depends primarily on hippocampal synaptic function.

1.2. Pre-Clinical Pharmacology Results

To obtain preclinical proof-of-principle for an effect on hippocampal synaptic dysfunction, neflamapimod was tested in the aged rat model of age-related cognitive decline. When tested in a MWM test, rats show cognitive deficits starting at 20 to 22 months of age. This deficit has been shown to be a result of inflammation-induced impairment of synaptic plasticity in the hippocampus (Kelly, 2003; Lynch, 2010).

The published results (Alam, 2015) showed that neflamapimod administered for 3 weeks fully reversed the spatial learning deficits in the MWM test in 20- to 22-month old rats with identified cognitive deficits, with the performance of aged rats treated with neflamapimod at the optimal dose being significantly better than vehicle (placebo)- treated aged rats ($P = 0.007$) and being similar to that of young rats. These data combined with dose-response data in previous animal and clinical studies, were then utilized to identify doses for the Phase 2a clinical studies in early AD.

Neflamapimod also was studied in an induced-stroke model in rats: transient ischemia of sufficient duration was induced such that significant neurologic disability developed without mortality and the neurologic disability did not substantially reverse during follow-up without therapy. These rats were then treated with vehicle (control) or neflamapimod. Starting at 48-hours after stroke, administration of

neflamapimod for 6 weeks led to substantial improvement on multiple parameters of neurologic function compared to vehicle controls (P <0.001 for each of global neurologic scores, motor- and sensory-specific tests). As recovery after stroke is dependent on neuronal and synaptic plasticity (Chollet, 2013), these results further confirm that neflamapimod is active in reversing impaired synaptic plasticity in animal models.

Based on the scientific rationale and emerging mechanistic understanding of the effects of inhibition of neuronal p38α (refer to Section 1.1), the demonstrated positive pharmacological effects of neflamapimod may be due to reversing proteostasis defects within neurons, including impaired autophagy and endolysosomal dysfunction (Alam & Scheper, 2016). The proteostasis-reversing potential of neflamapimod was recently confirmed in a human *in vitro* system (Down Syndrome fibroblasts), where neflamapimod at concentrations below 10 nM reversed endosomal abnormalities and improved lysosomal function (confidential data on file).

1.3. Prior Clinical Experience

Neflamapimod has been tested clinically in AD and also in earlier studies in rheumatoid arthritis and the risks to date are well documented.

With respect to completed clinical studies, neflamapimod has been given to 90 healthy volunteers in single-dose studies, 16 healthy volunteers in multiple-dose studies for 10 days, 56 patients (57 courses of therapy, because 1 patient participated in 2 studies) with rheumatoid arthritis for up to 123 days, 5 patients with myelodysplastic syndrome (MDS) for 9 to 60 days, and 25 patients with early AD for up to 12 weeks. The highest dose levels have been evaluated in patients with rheumatoid arthritis, at doses up to 750 mg BID for one month and 250 mg BID for 12 weeks. In addition, 161 patients have been enrolled in a 24-week, double-blind placebo controlled (1:1 randomization) Phase 2b clinical study in patients with mild AD.

In clinical studies prior to those conducted in patients with AD, headache, common cold, gastroenteritis, diarrhea, and sleeplessness/ insomnia were the most common adverse events (AEs) reported. Gastroenteritis and diarrhea, which have been primarily mild, appear to have the strongest association with neflamapimod treatment.

During 12 weeks of dosing at 250 mg BID in 44 patients with rheumatoid arthritis elevations in liver transaminase levels were noted in 6 patients (14% of 44), 3 of whom were discontinued prematurely from treatment due to these findings. Patients were asymptomatic, there were no associated increases in bilirubin, and the elevations resolved with treatment discontinuation.

Twenty-five patients received neflamapimod at either 40 mg or 125 mg BID in Phase 2a studies of 6- or 12-weeks neflamapimod dosing in patients with early AD. One patient discontinued prematurely, attributed primarily to persistent cerebrospinal fluid (CSF) leakage after pre-dosing baseline CSF collection because the patient discontinued due to vomiting within 4 days of starting dosing. There were no severe or serious adverse events (SAEs) reported. The most common AEs across the 2 studies were mild somnolence (sleepiness or drowsiness) reported in 5 patients, and self-limited mild diarrhea (loose stools) reported in 4 patients. There were no abnormalities in liver function tests (LFTs), nor any trends in changes in LFT parameters, noted in either study in patients with early AD.

In the 12-week Phase 2a study in patients with early AD, though the magnitude of changes were not clinically significant, statistically significant overall increases for heart rate, body weight, and body mass index, and decreases for systolic and diastolic blood pressures were observed.

In the ongoing blinded Phase 2b clinical study of neflamapimod in mild AD, 2 SAEs have been reported, one a severe unrelated hypokalemia and the other a mild, possibly related non-cardiac chest pain. With the exception of the case of severe hypokalemia, all other events were mild to moderate in nature and primarily unrelated. The events deemed at least possibly related and reported more than once include rash, thrombocytopenia, headache, anxiety and lethargy (each reported twice).

Given the potential benefits to patients with DLB, the safety margin relative to animal toxicity findings, and the prior clinical experience at substantially higher dose levels, the benefit/risk profile is favorable for the planned study at a dose of 40 mg given BID or TID, based on subject weight.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate the effect of neflamapimod on cognitive function as assessed in a study-specific Neuropsychological Test Battery (NTB) comprised of:

- Cogstate Detection test (DET)
- Cogstate Identification test (IDN)
- Cogstate One Card Learning test (OCL)
- Cogstate One Back test (ONB)
- Letter Fluency Test
- Category Fluency Test (CFT)

2.2. Secondary Objectives

The secondary objectives are to:

- Evaluate the effects of neflamapimod on informant/caretaker evaluation of cognition and function, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)
- Assess the effects of neflamapimod on general cognition, as assessed by the Mini Mental State Examination (MMSE)
- Assess the effects of neflamapimod on episodic memory, as assessed by the International Shopping List Test (ISLT).
- Assess the effects of neflamapimod on select domains of the 10-item Neuropsychiatric Inventory (NPI-10), including depression (dysphoria), anxiety, hallucinations, and agitation/aggression.
- Evaluate the effects of neflamapimod on motor function as assessed by the Timed Up and Go Test (TUG).
- Evaluate the effects of neflamapimod on quantitative electroencephalography (EEG) parameters.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, proof-of-principle study of neflamapimod versus matching placebo (randomized 1:1) administered with food for 16 weeks in subjects with DLB. Subjects will be randomized to neflamapimod BID/placebo or neflamapimod TID/placebo depending on weight, with subjects weighing <80 kg receiving capsules BID and those weighing ≥80 kg receiving capsules TID. Subjects receiving study drug BID will be administered 1 capsule, BID with food (i.e., with the morning and evening meals), either neflamapimod 40 mg or placebo. Subjects receiving study drug TID will be administered 1 capsule TID with food (i.e., with the morning, mid-day, and evening meals), either neflamapimod 40 mg or placebo. Doses should be administered at least 3 hours apart.

3.1.1. Screening

Following completion of informed consent procedures, subjects will enter the Screening phase of the study.

One to two Screening visits are planned, during which safety screening measures will be undertaken, a practice NTB will be performed, and the required diagnosis and cognitive impairment will be confirmed. Screening will be conducted within 21 days before Baseline (Day 1). If a DaTscan™ is required to determine study eligibility, Screening may be extended to 35 days.

3.1.2. Treatment Period

Once eligibility is confirmed during the Screening period and before the first dose of study drug, subjects will be randomly assigned on a 1:1 basis to placebo or neflamapimod for the 16-week treatment period. Investigators and subjects will be blinded to the treatment assignment. Randomization will be stratified by ISLT Total Recall score at Baseline (≤ 21 vs. > 21), i.e. by wheter patients have an episodic memory defect at baseline or not.

Subjects will receive study drug for 16 weeks. Dosing will start on Day 1 following completion of all baseline procedures. During the 16-week treatment period, subjects will return to the clinic every 2 weeks for the first month and then every 4 weeks thereafter. A Follow-Up will be conducted 2 weeks (±3 days) after completion of study drug or after the Early Termination visit.

The NTB, ISLT, and NPI-10 will be conducted at Screening, Baseline (Day 1), Week 4 (Day 28), Week 8 (Day 56), and Week 16 (Day 112) or ET if early termination. The CDR-SB and TUG will be conducted at Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. The MMSE will be conducted at Screening, Baseline (Day 1), Week 8 (Day 56), and Week 16 (Day 112) or ET. EEGs will be conducted at Baseline (Day 1) and Week 16 (Day 112) or ET. Samples for plasma biomarkers will be obtained at Screening, Baseline (Day 1) and Week 16 (Day 112).

3.1.3. Early Termination (ET)

Subjects who prematurely discontinue study drug for any reason will be asked to return to the clinic for an Early Termination (ET) visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the ET visit should

be conducted at that time. These subjects will also be asked to return to the clinic for a Follow-up Visit 2 weeks (±3 days) following the last study drug dose.

Every effort should be made to ensure a subject returns for this visit.

Refer to Section 4.3 for details regarding removal of subjects from treatment.

3.2. Discussion of Study Design

Several design features are employed to minimize bias, including the study being double-blind, placebo-controlled, randomized, and multi-centered. The use of placebo control permits blinded prospective comparison between treatment groups. Random assignment of subjects to study treatment avoids bias and helps support both known and unknown risk factors being distributed evenly between treatment groups. Furthermore, randomization is stratified by ISLT Total Recall score at Baseline ($\leq$ 21 vs. > 21; i.e. by wheter patients have an episodic memory defect at baseline or not) to further balance characteristics of subjects receiving neflamapimod versus placebo. The multi-center nature of the study provides assurance that the results are likely to have general applicability.

3.2.1. Rationale for Dose Selection

3.2.1.1. Efficacy Considerations

The 40 mg BID regimen was initially chosen as the most likely active dose for the prior Phase 2a clinical studies in AD based on the results of the effects of neflamapimod on hippocampal synaptic dysfunction (assessed in the MWM test) in aged rats, which demonstrated that the optimal dose in aged rats was 1.5 mg/kg. The 1.5 mg/kg dose was then correlated to dose-response in rat arthritis models and in human clinical studies in rheumatoid arthritis to derive the predicted dose of 40 mg BID. Furthermore, plasma drug levels obtained in the aged rat at 1.5 mg/kg correspond to those that were seen subjects with AD at 40 mg BID. The predicted cognitive effect at 40 mg BID has been preliminarily demonstrated in humans, as there were statistically significant improvement from baseline in tests of episodic memory function in both phase 2a clinicals studies utilizing this dose. As well there was evidence of target engagement and pharmacological activity at this dose level in the two phase 2a studies, i.e., reductions in amyloid plaque load by PET scan and reductions in interleukin-8 levels in CSF, respectively.

Interim pharmacokinetic results from a Phase 2b clinical study in early AD indicate the median 12-hour plasma drug concentration exposure of neflamapimod in the minority of subjects who weigh ≥80 kg is approximately 33% lower that seen in subjects who weigh <80 kg. The median 12-hour plasma drug exposure was 65 ng*hr/mL in subjects weighing 80 kg or more, and 98 ng*hr/mL in those weighing less than 80 kg. As a higher proportion of subjects with DLB compared to AD are male, and therefore a higher proportion of subjects are expected to weigh ≥80 kg, to achieve consistent target plasma drug concentrations in the current study subjects who weigh ≥80 kg will receive 40 mg TID (i.e., 120 mg per day, rather than 80 mg per day) of neflamapimod. The median 12-hour plasma drug concentration exposure by utilizing this approach is expected to be approximately 100 ng*hr/mL (i.e., 0.1 µg*hr/mL).

3.2.1.2. Safety Considerations

Based on the clinical experience to date at higher doses and the results from animal toxicology studies, the neflamapimod doses of 40 mg BID in those weighing <80 kg and 40 mg TID in those weighing ≥80 kg is expected to be well tolerated and to have a low risk of drug toxicity.

Dose-limiting toxicity in clinical studies, defined as elevations in liver transaminase levels, was noted in 6 patients of 44 subjects (14%) with RA treated with neflamapimod 250 mg BID (a dose level that achieved median 12-hours plasma drug concentration exposure of 453 ng*hr/mL); 3 of the 6 subjects with transaminase elevations were discontinued prematurely from treatment due to these findings. Patients were asymptomatic, there were no associated increases in bilirubin, and the elevations resolved with treatment discontinuation.

In the Phase 2a studies (Study 303) of 6- or 12-weeks neflamapimod dosing in patients with early AD, a total of 25 subjects were enrolled. With regard to safety, neflamapimod was well tolerated, with 24 of 25 subjects completing their scheduled dosing period (8 completed 6 weeks of neflamapimod administration, and 16 completed 12 weeks of neflamapimod administration). The one subject who discontinued early did so within the first week of study drug administration due to an AE of vomiting, attributed primarily to persistent CSF leakage after the predose/baseline CSF collection. There were no severe or serious AEs reported. The most common AEs across the 2 studies were mild somnolence (sleepiness or drowsiness) reported in 5 patients, and self-limiting mild diarrhea (loose stools) reported in 4 patients. There was also one event of moderate diarrhea, which was considered not related, as the event did not recur during additional 8 weeks of treatment after having resolved during a brief treatment interruption. No treatment-related or clinically relevant trends in the analysis of safety laboratory and 12-lead electrocardiogram (ECG) parameters were observed. More specifically, there were no abnormalities in LFTs nor any trends in changes in LFT parameters noted in either study. LFT abnormalities, specifically increases in liver transaminases, were seen in 10% to 15% of patients in a prior study in patients with RA at a dose of 250 mg BID for 3 months. Due to the use of higher doses and different formulations in the RA studies, the plasma drug concentrations were 4- to 5-fold higher than in the Phase 2a mild AD studies.

A Phase 2b study of neflamapimod in early AD (MMSE 20 to 28) is ongoing. A total of 161 patients have been randomized on a blinded basis to either placebo or 40 mg capsules BID with food for 24 weeks. As of November 12, 2018, the annual data safety cutoff date, blinded data were available for 101 patients. As of that date, a total of 70 AEs had been reported across 43 patients. There were two SAEs reported, one a severe unrelated hypokalemia and the other a mild, possibly related non-cardiac chest pain. With the exception of the case of severe hypokalemia, all other AEs were mild to moderate in nature and primarily unrelated. The events deemed at least possibly related and reported more than once include rash, thrombocytopenia, headache, anxiety and lethargy (each reported twice). This study is ongoing and all data are blinded.

The expected plasma drug concentrations in the current study provides a 5-fold margin based on plasma drug levels to no adverse effect level in long term animal toxicity studies and 10-fold margin to minimal and/or equivocal findings for hematological, hepatic and neuropathological changes (evidence of axonal damage) in chronic (9- and 12-month) dog toxicology studies. Further details are provided in the Investigator Brochure (IB).

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Subjects meeting all of the following criteria are eligible for enrollment in this study:

1. Men and women aged ≥55 years.
2. Subject or subject's legally authorized representative is willing and able to provide written informed consent.
3. Probable DLB and identified cognitive deficits, according to current consensus criteria (McKeith et al, 2017), specifically one core clinical feature and a positive DaTscan. If a negative DaTscan, but the subject has historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), the subject would also qualify.
4. MMSE score of 15-28, inclusive, during Screening.
5. Currently receiving cholinesterase inhibitor therapy, having received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization. Except for reducing the dose for tolerability reasons, the dose of cholinesterase inhibitor may not be modified during the study.
6. Normal or corrected eye sight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments.
7. No history of learning difficulties that may interfere with their ability to complete the cognitive tests.
8. Must have reliable informant or caregiver.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for enrollment in this study:

1. Diagnosis of any other ongoing CNS condition other than DLB, including, but not limited to, post-stroke dementia, vascular dementia, AD, or PD.
2. Suicidality, defined as active suicidal thoughts within 6 months before Screening or at Baseline, defined as answering yes to items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or history of suicide attempt in previous 2 years, or, in the Investigator's opinion, at serious risk of suicide.
3. Ongoing major and active psychiatric disorder and/or other concurrent medical condition that, in the opinion of the Investigator, might compromise safety and/or compliance with study requirements.
4. Diagnosis of alcohol or drug abuse within the previous 2 years.

5. Poorly controlled clinically significant medical illness, such as hypertension (blood pressure >180 mmHg systolic or 100 mmHg diastolic); myocardial infarction within 6 months; uncompensated congestive heart failure or other significant cardiovascular, pulmonary, renal, liver, infectious disease, immune disorder, or metabolic/endocrine disorders or other disease that would interfere with assessment of drug safety.
6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.
7. Known human immunodeficiency virus, hepatitis B, or active hepatitis C virus infection.
8. Participated in a study of an investigational drug less than 3 months or 5 half-lives of an investigational drug, whichever is longer, before enrollment in this study.
9. History of previous neurosurgery to the brain.
10. If male with female partner(s) of child-bearing potential, unwilling or unable to adhere to contraception requirements specified in the protocol.
11. If female who has not has not reached menopause >1 year previously or has not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy, has a positive pregnancy test result during Screening and/or is unwilling or unable to adhere to the contraception requirements specified in the protocol.

4.3. Removal of Subjects from Treatment

In accordance with the current revision of the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution. A subject's participation may also be discontinued by the Investigator or Sponsor due to compliance, safety, or other administrative reason (see also Section 6.2.13).

The subject **must** be discontinued from the study for the occurrence of an unacceptable toxicity, including any of the following:

- Any clinically significant infection. (Clinically significant is defined as any infection requiring hospitalization and/or intravenous antibiotics and/or considered to be opportunistic.)
- ALT or AST >8×ULN; ALT or AST >5×ULN for >2 weeks; or ALT or AST >3×ULN and total bilirubin >2×ULN or INR >1.5; or ALT or AST >3×ULN with the appearance of worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

Refer to Section 3.1.3 for details regarding follow-up after early discontinuation. Additional care and treatment will be provided to subjects once study discontinuation, including any required follow-up visits for resolution for study-related AEs, is completed.

5. TREATMENTS ADMINISTERED

Neflamapimod 40 mg capsules or matching placebo capsules will be administered orally, BID or TID with food for 16 weeks. Subjects will follow the BID regimen if weighing <80 kg or the TID regimen if weighing ≥80 kg.

Furthermore, all subjects will be administered 1 capsule, BID or TID, with food:

- Subjects following the BID regimen will receive one 40 mg neflamapimod capsule or one placebo capsule to be taken twice daily with food (i.e., with the morning and evening meals);
- Subjects following the TID regimen will receive one 40 mg neflamapimod capsules or one placebo capsule to be taken three times daily (i.e., with the morning, mid-day, and evening meals).

Doses must be taken within 30 minutes following a meal or snack. Doses should be taken at approximately same times each day throughout the study and at least 3 hours apart.

The first dose of study drug in each treatment period will be administered at the study center.

The Investigator or other designated, qualified site personnel should review dosing instructions with the subject. Subjects will be instructed to return all study containers, regardless of whether empty or containing unused study drug.

If a subject misses 1 study drug dose (i.e., 1 capsule), the subject should resume dosing at the next scheduled administration time, at which time both the missed dose and the current dose (i.e., 2 capsules) are to be taken. If the subject misses 2 study drug doses (i.e., 2 capsules), the subject should take 2 doses (i.e., 2 capsules) at the next scheduled administration time. Subjects may not take more than 2 doses (i.e., 2 capsules) at any given administration time.

5.1. Packaging and Labeling

EIP Pharma will supply placebo or neflamapimod capsules via blister packs on an individual subject basis.

Both neflamapimod and placebo capsules are opaque in color. Label details will be in accordance with local and national requirements.

5.2. Study Drug Supply, Storage, and Handling

Study drug will be supplied to the site on an individual subject basis. Both neflamapimod and placebo capsules are opaque in color. Study drug is labeled in accordance with local and national requirements.

Neflamapimod capsules should be stored at room temperature.

While at the clinical site, study drug access should be limited to the Investigator and other qualified site personnel.

5.3. Drug Accountability, Disposal, Return, or Retention of Unused Study Drug

The site designated pharmacist or other qualified personnel will document receipt from Sponsor, dispensing to subjects, and return to the study center from subject on the drug accountability log(s).

Subjects will be instructed to return all blister packs to the study center, regardless of whether empty or containing unused study drug. EIP Pharma or designee will review accountability records throughout the conduct of the study.

The site should maintain all study drug containers (used and unused) until final review of accountability is conducted by the EIP Pharma or designee, and instructions regarding return or disposal, as applicable, are provided.

5.4. Method of Assigning Subjects to Treatment Group

After subjects have completed the Screening Visit and are deemed eligible, they will be randomized on a 1:1 basis in a blinded manner to receive either placebo or 40 mg neflamapimod utilizing an automatically generated random code. Randomization will be stratified by ISLT Total Recall score at Baseline ($\leq$ 21 vs. > 21), i.e. by wheter patients have an episodic memory defect at baseline or not. Randomization and stratification will be administered via Interactive Response Technology (IRT).

Subjects will follow the BID regimen if weighing <80 kg or the TID regimen if weighing ≥80 kg.

Study drug for the entire 16-week period will then be sent on a per subject basis to the site.

5.5. Study Blinding and Breaking the Blind

Subjects and site personnel associated with study conduct will be blinded to treatment assignment.

During the conduct of the study, the blind should be broken on an individual subject basis in the event of an emergency where it is necessary for the Investigator to know which treatment the subject is receiving before the subject can be treated. The code may also be broken if someone not in the study uses study drug (e.g., if a child in the participant's household takes study drug, the blind may be broken to determine treatment for the child).

When it is necessary to break the blind, the researcher may unblind the treatment immediately (i.e., without prior notice to the Medical Monitor, sponsor, or other) but must notify the Independent Ethics Committee (IEC) per local regulations and Sponsor as soon as possible, preferably by telephone and then in writing, regarding the necessity of code breaking.

If the code is broken for a subject, this must be documented in the electronic case report form (eCRF) and source documents, together with the reasons for breaking the code.

5.6. Dose Modification for Toxicity

No dose modifications are permitted during the study. If a subject is unable to tolerate the assigned study drug dose then the subject should be discontinued from study drug treatment (Section 4.3).

5.7. Prior and Concomitant Therapy

Any medications taken from Screening through the Final Study Visit (i.e. Follow-Up Visit), including all prescription and over-the-counter medications as well as supplements, will be documented in the subject's source document and in the eCRF.

While drug-drug interaction studies have not been conducted, in vitro testing indicates that neflamapimod is metabolized by oxidation in the liver by the cytochrome P450 (CYP) system (combination of CYP3A4

and CYP2C19 isozymes). Until the metabolism is better characterized, **concomitant strong inhibitors of CYP3A4 are prohibited** and **strong inducers of CYP3A4 should be used with caution** in subjects receiving neflamapimod, as the use of such drugs could impact neflamapimod metabolism in subjects who have an underlying CYP2C19 genotypic variant that impacts activity of that CYP2C19.

The following medications are prohibited during study participation:

- Strong CYP3A4 inhibitors (see Table 5-1).
- Any other investigational drug. If a subject has previously participated in a study of an investigational drug, last dosing must have occurred 3 months or 5 half-lives of the investigation drug, whichever is longer, before enrollment in this study.

The Medical Monitor should be contacted with any questions regarding concomitant use of medications that are thought to modulate CYP3A4 activity.

Table 5-1: CYP3A4 Inhibitors

Prohibited: **Strong Inhibitors** **≥5-fold increase in AUC** **or >80% decrease in CL**	**Allowed:** **Moderate inhibitors** **≥2 but <5-fold increase in AUC** **or 50-80% decrease in CL**	**Allowed:** **Weak inhibitors** **≥1.25 but <2-fold increase in AUC** **or 20-50% decrease in CL**
boceprevir cobicistat clarithromycin conivaptan danoprevir/ritonavir diltiazem elvitegravir/ritonavir grapefruit juice idelalisib indinavir/ritonavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir paritaprevir/ritonavir/ombitasvir posaconazole ritonavir saquinavir/ritonavir telaprevir tipranavir/ritonavir troleandomycin voriconazole	Aprepitant cimetidine ciprofloxacin clotrimazole crizotinib cyclosporine dronedarone erythromycin fluconazole fluvoxamine imatinib tofisopam verapamil	chlorzoxazone cilostazol fosaprepitant istradefylline ivacaftor lomitapide ranitidine ranolazine tacrolimus ticagrelor

Abbreviations: AUC, area under the concentration-time curve; CL, clearance.

Table 5-2: CYP3A4 Inducers

Use with Caution: Strong Inducers ≥80% decrease in AUC	Allowed: Moderate Inducers 50-80% decrease in AUC	Allowed: Weak Inducers 20-50% decrease in AUC
carbamazepine enzalutamide mitotane phenytoin rifampin St. John's wort	bosentan efavirenz etravirine modafinil	armodafinil rufinamide

Abbreviations: AUC, area under the concentration-time curve.

5.8. Contraception and Pregnancy

This section should be read in conjunction with the selection criteria that relate to age and contraception:

- Exclusion criteria #10 and #11 (Section 4.2)

No signs of embryo-fetal toxicity or teratogenic effects of neflamapimod were observed in rats. Testing in rabbits was not performed due to lack of exposure following administration of the neflamapimod formulation. No human studies of effects of neflamapimod on conception, pregnancy, or lactation have been performed. Females should not be exposed to neflamapimod if pregnant, breastfeeding, or attempting to conceive. The following guidelines for contraception should be followed from before first dose on Day 1 through 91 days following the last dose of study drug:

Female subjects of child-bearing potential (have not experienced menopause and have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy) or female subjects who have experienced menopause within the previous year must have a negative pregnancy test during Screening and must use at least 1 of the following contraceptive methods: complete abstinence regardless of menstrual cycle timing, contraceptive (oral, transdermal, injectable, or implantable), intrauterine device, or barrier method of contraception.

Male subjects with female partners of child-bearing potential must use at least 1 of the following contraceptive methods: hormonal contraceptives (oral, injectable, patch, intrauterine devices), male sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the subject.

- Abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments when this is the preferred and usual lifestyle of the subject.

  Note that periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception.

Any pregnancy should be reported to the Investigator, and, in turn, the pregnancy should be reported to Worldwide Clinical Trials within 24 hours of the Investigator's awareness of the pregnancy. If a female

subject becomes pregnant, study drug will be permanently discontinued and the subject will be discontinued from the study.

With proper informed consent (separate pregnancy informed consent form), the subject or partner will be followed through the completion of the pregnancy and outcome of the pregnancy reported, and the infant will be followed for 12 months after birth.

5.9. Treatment Compliance

Treatment compliance will be assessed by reviewing the count of returned capsules at each visit. Any apparent discrepancies between quantity of capsules returned and the number expected based on dosing schedule will be discussed with the subject to ensure an understanding of dosing instructions.

Repeated non-compliance with dosing instructions may necessitate discontinuation from the study, based on the Investigator's judgment (Section 4.3).

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Schedule of Assessments

The schedule of assessments is presented in Table 6-1.

Table 6-1: Schedule of Assessments

	Study Period / Week / Study Day								
	Screening	Treatment Period						Early Termination	Follow-Up
	Screening Visit[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[d]
Assessment	**Within 21-35 days of D1**	**D1[b]**	**D14 (±3)**	**D28 (±3)**	**D56 (±5)**	**D84 (±5)**	**D112 (±5)**	**Within 3 days after last dose**	**Within 14 days (±3) of last dose**
Informed Consent	X[e]								
Medical history review	X								
Pregnancy testing	X[f]								
Physical examination[g]	X						X	X	X
Vital signs[h]	X	X	X	X	X	X	X	X	X
Hematology and chemistry[i]	X	X		X	X	X	X	X	
Coagulation studies[i]	X				X				X
12-lead electrocardiogram[j]	X								
DaTscan™, if needed	X[k]								
CT/MRI	X[l]								
C-SSRS	X	X		X	X	X	X	X	
MMSE[m]	X	X			X		X	X	
NTB[m], International Shopping List Test (ISLT)	X	X		X	X		X	X	
CDR-SB		X			X		X	X	
NPI-10	X	X		X	X		X	X	
Timed Up and Go (TUG)		X			X		X	X	
EEG[n]		X					X	X	
Dispense study drug		X	X	X	X	X			
Pharmacokinetic sampling[o]			X	X	X				
Plasma sample for protein biomarker testing[p]	X[q]	X					X	X	

	Study Period / Week / Study Day								
	Screening	Treatment Period						Early Termination	Follow-Up
	Screening Visit[a]	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16	ET Visit[c]	Follow-Up Visit[d]
Assessment	Within 21-35 days of D1	D1[b]	D14 (±3)	D28 (±3)	D56 (±5)	D84 (±5)	D112 (±5)	Within 3 days after last dose	Within 14 days (±3) of last dose
Prior/concomitant medication	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X
Final study drug reconciliation							X	X	

CDR-SB: Clinical Dementia Rating Scale – Sum of Boxes; C-SSRS: Columbia-Suicide Rating Scale; CT: Computed tomography; D=day; MMSE: Mini-Mental State Examination; MRI: Magnetic resonance imaging; NPI-10: 10-item Neuropsychiatric Inventory; NTB: Neuropsychological Test Battery.

a. One to two Screening visits are planned during which safety screening procedures are to be completed and reviewed, including a practice NTB and the required diagnostic and cognitive impairment procedures. Screening will be conducted within 21 days before Baseline (Day 1); if a DaTscan and/or MRI or CT scan is required to determine study eligibility, Screening may be extended to 35 days. (If necessary, a second visit may be conducted on a different day to allow for scheduling purposes.) All screening assessments should be conducted within 21-35 days of Day 1 and can be condensed to one visit.
b. On Day 1, all procedures should be conducted prior to first dose of study drug.
c. Subjects who prematurely discontinue study drug for any reason will be asked to return to the study center for an Early Termination visit within 3 days following the last study drug dose; if it is determined that the subject will discontinue study drug while at the study center for a scheduled visit, then the Early Termination visit should be conducted at that time.
d. The Follow-up Visit should be conducted within 14 (±3) days of the last dose of study drug for subjects who complete the study or discontinue early.
e. Informed consent procedures, including signing of informed consent, must be completed before any study-specific procedures are performed.
f. Female subjects who have reached menopause in the previous year must have a serum or urine pregnancy test performed during Screening; subjects with positive results are not eligible for study participation.
g. Refer to Section 6.2.8 for details regarding physical examination.
h. Vital signs include blood pressure, pulse, respiratory rate, and body temperature. Vital signs should be measured after the subject has been in sitting position for 5 minutes.
i. Details of clinical laboratory sampling for chemistry, hematology, and coagulation studies are discussed in Section 6.2.10.
j. Details of 12-lead ECG assessment are discussed in Section 6.2.9.
k. Subjects are required to have a prior DaTscan. If a DaTscan has not been performed within the previous 2 years, it is to be performed during Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization. Note that if DaTscan results are negative (i.e., no evidence of

reduced uptake in the basal ganglia), the subject is required to have historical PSG-verified RBD to be eligible for study participation.

l. If MRI or CT has not been performed within 3 years before Screening and/or results are not available, MRI or CT scan must be performed to exclude other disease as part of Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization (see Section 6.2.2).

m. Refer to Section 6.2.4 for details regarding cognitive function tests.

n. EEG need not performed at the ET visit for subjects who discontinue prior to Week 4 (Day 28).

o. Refer to Section 6.2.11 for details regarding PK sampling.

p. Refer to Section 6.2.12 for details regarding plasma biomarker sampling.

q. Only plasma Aβ42/40 ratio is required at Screening.

6.2. Study Assessments

The subject or subject's legally authorized representative must provide written informed consent before the performance of any study-related procedures.

6.2.1. Baseline and Disease Characteristics

Details regarding DLB history, including method(s) of diagnosis will be collected during Screening, as specified in the eCRF. Subjects without documentation of prior diagnostic DLB tests (DaTscan and/or known amyloid biomarker status) are to have such tests performed during Screening (see Section 6.2.3).

6.2.2. Computed Tomography (CT) / Magnetic Resonance Imaging (MRI)

The subject must have had MRI or CT scan within 3 years of Screening, with findings negative for evidence of other neurodegenerative or other brain disease that could account for their cognitive symptoms. MRI/CT results should be available and reviewed before Screening diagnostic tests are performed. If MRI or CT has not been performed within 3 years before Screening and/or results are not available, MRI or CT scan must be performed as part of Screening to exclude other disease.

6.2.3. DaTscan (if Required)

Subjects are required to have a prior DaTscan (i.e., single-photon emission computed tomography [SPECT] with Ioflupane I 123 Injection) to be eligible for study participation.

The DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using SPECT brain imaging. Ioflupane I 123 Injection is to be administered and SPECT imaging is to be performed and interpreted per the prescribing information (GE Healthcare, 2015). If a DaTscan has not been performed within the previous 2 years, it is to be performed during Screening **only after** subject has been deemed eligible based on all other inclusion/exclusion criteria (e.g., medical history, laboratory testing) and prior to randomization.

Note that if DaTscan results are negative (i.e., no evidence of reduced uptake in the basal ganglia), the subject is required to have historical PSG-verified RBD to be eligible for study participation.

6.2.4. Cognitive Function Tests

Cognitive function tests include a Neuropsychological Test Battery (NTB) as well as the Letter Fluency Test and Category Fluency Test (CFT), which are all components of the primary objective/endpoint to assess attention, executive function, and visuospatial function.

Cognitive function tests to be performed as components of the secondary objective include the CDR-SB, MMSE, NPI-10, Timed Up and Go (TUG), and International Shopping List Test (ISLT).

At Baseline and on any visits at which both NTB and other cognitive tests are conducted, the NTB should be performed prior to the other tests.

6.2.4.1. Neuropsychological Test Battery (NTB)

The NTB includes:

- Cogstate Detection test (DET)
- Cogstate Identification test (IDN)

- Cogstate One Card Learning test (OCL)
- Cogstate One Back test (ONB)
- Letter Fluency Test: The Letter Fluency Test is a measure of phonemic fluency and is a subtest of the Multilingual Aphasia Examination (Benton et al, 1994). The LFT uses the 3-letter set of F, A, and S or C, F, and L to assess phonemic fluency. Individuals are given 1 minute to name as many words as possible beginning with one of the letters. The procedure is then repeated for the remaining two letters. The administration of phonemic and semantic fluency (CFT) takes approximately 5 minutes. Admissible responses are summed and compared to a normative sample.
- Category Fluency Test (CFT): The CFT is a measure of verbal fluency and is sometimes called semantic fluency. In the standard version of the task, participants are given 1 minute to produce as many unique words as possible within a category. The subject's score is the number of unique correct words.

6.2.4.2. Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)

The Clinical Dementia Rating Scale (CDR) (Hughes, 1982) is a semi-structured interview resulting in a semi-quantitative scoring of cognitive impairment in milder and more progressed forms of dementia. It is sensitive in both AD dementia and Mild Cognitive Impairment, and is an approved regulatory endpoint recognized by the FDA. The CDR yields both a global score (CDR-GS) and Sum of Boxes score (CDR-SB). While the CDR-GS is typically utilized for staging purposes, the CDR-SB score is a more detailed quantitative general index than the CDR-GS and it provides more information than the CDR total score in cases of mild dementia (O'Bryant, et al, 2010).

The CDR interview is to be conducted with the subject and Caregiver by an experienced and certified clinician at the time points specified in Table 6-1.

6.2.4.3. Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al, 1975) consists of 11 tests of orientation, memory (recent and immediate), concentration, language, and praxis. Scores range from 0 to 30, with lower scores indicating greater cognitive impairment. It is based on the performance of the subject and takes approximately 5 to 10 minutes to administer.

Standardized MMSE will be conducted by the Investigator or designee at the time points specified in Table 6-1.

6.2.4.4. International Shopping List Test (ISLT)

Word learning tests have been commonly utilized to assess episodic memory. In DLB, the recognition component is considered to be of particular utility (Wesnes et al, 2015). The ISLT is one such word learning test that has been utilized in a number of proof-of-concept clinical studies with novel therapeutics (Nathan et al, 2013; Maher-Edwards et al, 2015). Immediate and Delayed Recall, as well as Recognition, will be assessed.

6.2.4.5. 10-item Neuro-Psychiatric Inventory (NPI-10)

The NPI-10 is designed to assess psychopathology in the person with dementia and to help distinguish between the different causes of dementia. The NPI-10 examines 10 sub-domains of behavioral functioning: delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy,

disinhibition, irritability/lability, and aberrant motor activity. For this study, the following domains are of specific interest: depression (dysphoria), anxiety, hallucinations, and agitation/aggression. The NPI-10 is administrated to caregivers of dementia subjects. A screening question is asked about each included sub-domain. If the responses to these questions indicate that the subject has problems with a particular sub-domain of behavior, the caregiver is only then asked all the questions about that domain, rating the frequency of the symptoms on a 4-point scale, their severity on a 3-point scale, and the distress the symptom causes them on a 5-point scale (Cummings, 1997).The NPI-10 takes approximately 10 minutes to complete.

6.2.5. Timed Up and Go Test (TUG)

The Timed Up and Go Test is designed to assess mobility. It measures the time in seconds for a person to rise from sitting from a standard arm chair, walk 3 meters, turn, walk back to the chair, and sit down. The subject wears regular footwear and uses his/her customary walking aid. A score of >15 seconds indicates client has increased risk of falls. The test takes 1 to 2 minutes to complete.

The Timed Up and Go Test is to be administered at the time points specified in Table 6-1.

6.2.6. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner et al, 2011). The "Baseline" version of the instrument will be administered to subjects during Screening, and the "Since Last Visit" version will be used at subsequent time points specified in Table 6-1.

6.2.7. Electroencephalography (EEG)

Quantitative electroencephalography (qEEG) will be performed with the subject awake in accordance with the 10-20 International System of Electrode placement at the time points specified in Table 6-1 according to a standard protocol that will be provided in a separate EEG manual. Slowing of the dominant frequency band by qEEG over posterior aspects of the brain has been recognized to be prominent in DLB (Olde Dubbelink et al 2013; Peraza et al, 2018), and various patterns have been identified to differentiate DLB from AD. EEG has also been recognized to be potential biomarker for DLB in the most recent consensus report of the DLB consortium (McKeith et al, 2017).

6.2.8. Physical Examination and Vital Signs

Physical examination will include a review of all body systems and measurement of weight, per each Investigators standard practice. Physical examination findings will be documented in the subject's source documents.

Vital signs include measurement of blood pressure, pulse, respiratory rate, and body temperature. Vital signs are to be measured with the subject in a sitting position after 5 minutes.

Any physical examination finding or vital sign measurement that represents a worsening from Baseline condition and is considered by the Investigator to be clinically significant will be recorded as an AE (see Section 7).

6.2.9. 12-Lead Electrocardiogram

A 12-lead ECG will be performed during Screening using validated machinery available locally to each clinical site. ECG parameters to be captured include heart rate (bpm), PR interval, QRS duration, QT interval, corrected QT interval (using Fridericia's formula) , and RR interval Each report will be reviewed

by the Investigator or qualified sub-investigator and assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant. Abnormal, clinically significant findings are to be reported as part of the subject's medical history.

6.2.10. Clinical Laboratory Assessments

Blood samples will be collected at the time points specified in Table 6-1 for assessment of routine chemistry and hematology analytes. Additional blood samples will be collected for coagulation studies at the time points specified in Table 6-1.

All samples will be analyzed via a central laboratory.

Table 6-2: Clinical Laboratory Analytes

Serum Chemistry

- Albumin
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)
- Glucose
- Blood urea nitrogen
- Calcium
- Bicarbonate/Carbon Dioxide
- Chloride
- Total cholesterol
- Triglycerides
- Creatinine
- Gamma-glutamyl transferase
- Lactate dehydrogenase
- Phosphate
- Potassium
- Sodium
- Total protein
- Uric acid

Hematology

- Differential (absolute and percent)
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils
- Erythrocytes
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Hemoglobin
- Leukocytes
- Platelets

Coagulation Studies

- Prothrombin time
- Partial thromboplastin time
- INR

Clinical laboratory findings that represent a worsening from Baseline value and are considered by the Investigator to be clinically significant will be recorded as an AE (refer to Section 7).

6.2.11. Pharmacokinetics (PK)

Blood samples for PK are to be collected at the timepoints specified in Table 6-1. The actual sample collection time on the designated visit days is per study center / subject convenience. The actual sample collection date and time relative to the most recent study drug dose is to be documented.

6.2.12. Biomarker Testing

Plasma samples for protein biomarker assessment are to be collected at the timepoints specified in Table 6-1. At Screening all subjects will only have the Aβ42/40 plasma ratio assessed from these samples. Subsequent samples will be stored for future protein biomarker testing once applicable assays are identified or developed; note that such samples will be not be used for genetic testing.

For purposes of use during analysis of the clinical results, biomarker status (positive/negative) will be determined by historical amyloid PET, if available. If prior amyloid PET is not available, then biomarker status is to be determined by historical biomarker testing in CSF. If prior CSF is not available, then biomarker status is to be determined by Screening Aβ42/40 plasma ratio.

6.2.13. Withdrawal of Subjects

A subject may be discontinued from study treatment at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or withdrawal of surrogate consent)
- Subject develops suicidal ideations or attempts suicide
- Subject is not compliant with study procedures
- AE that in the opinion of the Investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an AE, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

A subject may be withdrawn from the study at any time if the subject, the Investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the Investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

Refer to Table 6-1 for assessments to be performed for subjects who prematurely discontinue study drug.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS/SAFETY REPORTING

The Investigator is responsible for reporting of events meeting the criteria and definition of an AE or SAE as provided in this protocol.

7.1. Definitions and Criteria

7.1.1. Adverse Events

Per International Council for Harmonisation (ICH) E2A: An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Medical interventions such as surgeries, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment of the AEs.

7.1.2. Serious Adverse Events

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (e.g., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse; malignancy)

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. An SAE is not necessarily severe; e.g., an overnight hospitalization for a diagnostic procedure must be reported as an SAE even though the occurrence is not medically serious. By the same token, a severe AE is not necessarily serious: nausea of several hours' duration may be rated as severe but may not be considered serious.

The following hospitalizations are not considered serious:

- A visit to the emergency room or other hospital department <24 hours, that does not result in admission (unless considered 'important medical event' or event life-threatening).
- Elective surgery, planned prior to signing the informed consent form (ICF).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

7.1.3. Unexpected Adverse Drug Reactions

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the applicable product information (Investigator's Brochure, Package Insert for marketed products). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected." Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

Guidance on reporting AEs and SAEs is described in Section 7.2.

7.1.4. Abnormal Laboratory Values

Any abnormality in a laboratory value that is new in onset or which has worsened in severity or frequency from the baseline condition and meets 1 of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention or diagnostic tests.
- Leads to discontinuation of investigational product.
- Has accompanying or inducing symptoms or signs.
- Is judged by the Investigator as clinically significant.

7.1.5. Assessing Intensity and Relationship

All AEs will be assessed on 2 descriptive parameters: intensity and relationship to the investigational product:

- Intensity refers to the severity of an event and references impact on a subject's functioning.

- Relationship refers to the likelihood that the event being assessed was caused by the investigational product.

Intensity

Each AE will be classified according to the following criteria:

Mild:	The AE does not interfere in a significant manner with the subject's normal level of functioning.
Moderate:	The AE produces some impairment of functioning, but is not hazardous to the subject's health.
Severe:	The AE produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the experience should be noted. If the intensity category changes over a number of days, those changes should be recorded separately (with distinct onset dates).

Relationship

Each AE will be assessed as to its relationship to the investigational product, based on the following criteria. Although the attribution by the Investigator will be collected for reported events, for analytic purposes a temporal association with the use of the investigational product will be assumed sufficient for at least plausible association.

Not related:	No causal relationship exists between the investigational product and the AE, but an obvious alternative cause exists, e.g., the subject's underlying medical condition or concomitant therapy.
Possibly related:	A connection with the administration of the investigational product appears unlikely, but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the investigational product; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the investigational product.
Related:	There is a reasonable/plausible possibility that the AE may have been caused by the investigational product.

When assessing the relationship to the investigational product, the following criteria will be considered:

- Positive rechallenge
- Positive dechallenge (resolution upon stopping suspect the investigational product, in absence of other intervention or treatment)
- Known class effect
- Biological plausibility
- Lack of alternative explanation—concomitant drug or disease

7.2. Reporting Procedures and Requirements

7.2.1. Adverse Events (AE)

AEs occurring from when the subject signs the ICF until the last study event will be recorded. Any AEs occurring before the start of treatment (i.e., before the first dose of the investigational product)" will be recorded in the medical history. Also, the sign, symptom, or disease present before starting the treatment period are only considered AEs if they worsen after starting the treatment period.

If the Investigator detects an AE in a study subject after the last scheduled follow-up visit and considers the event possibly related or related to prior study treatment, the Investigator should report it to Worldwide Clinical Trials.

The Investigator should report all AEs on the AE page(s) of the eCRF and source documents, regardless of seriousness, severity, and causality. Whenever possible, an AE will be reported using a diagnostic term rather than symptoms, (e.g., "common cold" or "upper respiratory infection" rather than "runny nose, cough, mild fever") and should be described with the attributes described in Section 7.1.5.

7.2.2. Serious Adverse Events (SAE)

Each AE will be assessed to determine whether it meets seriousness criteria (Section 7.1.2). If the AE is considered serious, the Investigator should report this event to Worldwide Clinical Trials outlined below and also to the IEC according to its standard operating procedures.

The Investigator must report all SAEs **via an eCRF in the EDC system** within 24 hours of learning about the event regardless of relationship to study drug.

If the Investigator/site experiences a temporary disruption of the EDC system, a back-up paper SAE Report Form will be available for Investigator/site staff to complete. If a paper SAE Report Form is utilized, it must follow the same timelines and be emailed or faxed within 24 hours of learning about the event regardless of relationship to study drug.

SAE Reporting:

E-mail: drugsafety@worldwide.com

Fax: +1-866-387-5539 (US) or +44 208 043 4813 (ROW)

If notification is made via email or fax, site staff must enter the SAE information into the EDC system as soon as the system becomes available. Should a paper SAE form be used, the original SAE form should be kept at the site.

Each SAE should be followed up until resolution or stabilization. For reported deaths, the Investigator should supply Worldwide Clinical Trials and the IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

The Sponsor or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Investigator's responsibility to notify the IEC of all SAEs that occur at the Investigator's site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial.

SAEs that are ongoing at the Follow-up visit should be followed until resolution, until the condition stabilizes, until the subject is lost to follow-up or otherwise explained.

If the Investigator detects an SAE in a study subject after the last scheduled follow-up visit, and considers the SAE related or possibly related to prior study treatment, the Investigator should report it to the Sponsor.

8. DATA MANAGEMENT AND STATISTICAL ANALYSIS

8.1. Data Management and Quality Assurance Considerations

This study will employ eCRFs via an electronic data capture (EDC) system. The site will be trained on specific forms and procedures for source documentation and maintenance of an audit trail of the data that is entered on the eCRF prior to study initiation.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific eCRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by subject number (6 digits: the first 3 for the study center and the last 3 for the subject).

The Investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

If a correction is required for an eCRF, the time and date will be automatically recorded by the EDC system indicating the person updating eCRF data in order to create an audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

Queries will be issued for any inconsistencies, omissions, and discrepancies and will be resolved by the appropriate parties.

Database lock will occur once quality assurance procedures have been completed.

The statistical analysis of this data will be performed by the Sponsor or designee. All AEs will be coded using the latest version of the Medical Dictionary for Regulated Activities (MedDRA). Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting United States Food and Drug Administration (FDA), European Medicines Agency, and ICH guidelines for the handling and analysis of data for clinical studies. Data management details will be outlined in a separate Data Management Plan.

8.2. Sample Size

A total of approximately 80 subjects are planned to be enrolled, of whom 40 are planned to receive neflamapimod and 40 are planned to receive placebo.

As there is no prior experience with neflamapimod in patients with DLB upon which to base assumptions of treatment effect, no formal sample size calculation has been performed. However, based on prior experience with NTB in clinical studies, 40 subjects per treatment arm should provide a reasonably robust first assessment of whether neflamapimod improves cognitive function in patients with DLB.

8.3. Analysis Sets

The safety analysis set will include any subject who receives at least 1 dose of study drug.

The efficacy analysis set will include any subject who receives at least 1 dose of study drug and at least one post-dose cognitive assessment.

Analyses will be fully outlined in a Statistical Analysis Plan finalized prior to the end of enrollment.

8.4. Safety

The incidence of treatment-emergent AE and SAEs, the causal relationship between an AE/SAE, and the Study Drug and severity will be tabulated by treatment (dose) group.

Individual clinically-significant changes in clinical laboratory and ECG parameters will be listed along with median and mean and standard deviation by treatment group.

8.5. Efficacy

The primary efficacy variable is:

- Change in the composite score of the NTB, including assessments of attention, executive function, and visuospatial function in neflamapimod treated-subjects as compared to the placebo-treated subjects.

Secondary efficacy variables are:

- Change in CDR-SB in neflamapimod-treated subjects compared to placebo-recipients.
- Change in MMSE in neflamapimod-treated subjects compared to placebo-recipients.
- Change in NPI-10 domains in neflamapimod-treated subjects compared to placebo-recipients.
- Change in ISLT in neflamapimod-treated subjects compared to placebo-recipients.
- Change in Timed Up and Go Test.
- Change in EEG parameters.

The estimand of this study is the change from baseline to Week 16 in the composite score of the NTB in patients 55 years of age and older with probable DLB, comparing subjects treated with neflamapimod to those treated with placebo. The NTB includes assessments of episodic memory, executive function, visuospatial function, and attention. The primary endpoint will be analyzed using the Mixed Model Repeated Measures (MMRM) analysis method with the NTB change from baseline composite score as the dependent variable, and will use an unstructured covariance matrix. This analysis will be performed on the efficacy analysis population, which will include all subjects who receive at least one dose of study drug and provide at least one post-dose cognitive assessment. Additional covariates to be included in the MMRM model will be provided in the Statistical Analysis Plan (SAP) which will be finalized prior to study unblinding. Z-scores may be calculated and used in order to create standardized change scores to be used for the analysis. Additionally, sensitivity analyses will be performed on the primary endpoint specifically to address different missing data scenarios, both Missing at Random and Missing Not at Random. Further descriptions of the sensitivity analyses, as well as any additional efficacy populations that may be used to assess efficacy will also be provided in the SAP. Secondary efficacy endpoints will utilize the same analysis method and model as the primary endpoint.

8.6. Interim Analysis

No interim analysis is planned.

9. STUDY MANAGEMENT

9.1. Ethics and Consent

9.1.1. Regulations and Guidelines

The study will be performed in accordance with this protocol, United States Investigational New Drug Application regulations (21 CFR 312) or local national laws (as applicable) and ICH guidelines for Good Clinical Practice.

9.1.2. Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC. Approval is required for the study protocol, investigational drug brochure, protocol amendments, ICFs, subject information sheets, and advertising materials. No investigational product will be shipped to a site until written IEC authorization has been received by the Sponsor or its designee.

9.1.3. Informed Consent

For each study subject, written informed consent must be obtained from the subject or subject's legally authorized representative before the performance of any protocol-related activities. As part of this procedure, the Investigator or a designated representative must explain orally and in writing the nature, duration, and purpose of the study, and the action of the investigational product in such a manner that the subject and (if applicable) legally authorized representative are aware of the potential risks, inconveniences, or adverse effects that may occur. Subjects should be informed that they may withdraw from the study at any time. They will receive all information that is required by local regulations and ICH guidelines. The Investigator or a designated representative will provide the Sponsor or its designee with a copy of the IEC-approved ICF before the start of the study.

9.2. Indemnification

The Sponsor's indemnification of the Investigator and institution during the conduct of this study is addressed in a letter of indemnification provided as a separate document. Other indemnification or insurance will be provided as necessary under local regulations.

9.3. Discontinuation of the Study by the Sponsor

The planned study period is approximately 2 years, until the last visit of the last subject (including the follow-up visit). The planned subject participation is approximately 21 weeks, including 16 weeks of treatment. Once the subjects have ended their participation in the study, they will return to their standard of care treatment as determined by their physician.

The Sponsor reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the Sponsor and Investigator. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the subjects enrolled in the study.

- Failure of the Investigator to enter subjects at an acceptable rate.
- Unsatisfactory subject enrollment with respect to quality and/or quantity or data recording is inaccurate and/or incomplete on a chronic basis.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be terminated and/or the site closed for whatever reason, all documentation and investigational product pertaining to the study must be returned to the Sponsor or its designee.

9.4. Study Documentation

By signing a copy of Form FDA 1572 or other country-specific regulatory forms, the Investigator acknowledges that he/she has received a copy of the IB on neflamapimod and assures the Sponsor that he/she will comply with the protocol and the provisions stated in Form FDA 1572 and other country-specific forms. No changes in this protocol can be made without the Sponsor's written approval.

9.5. Study Monitoring and Auditing

This study will be monitored for quality assurance at all stages of its development by the clinical research personnel employed by the Sponsor or its designee. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to the protocol, standard operating procedures, Guidelines of Good Clinical Practice, and applicable regulatory requirements. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. On-site review of eCRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

9.6. Use of Study Findings

By signing the study protocol, the Investigator agrees to the use of results of the study for the purposes of national and international registration. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. Reports covering clinical and biometric aspects of the study will be prepared by the Sponsor or its designee.

9.7. Publications

The clinical study will be registered at www.clinicaltrials.gov and www.clinicaltrialsregister.eu. The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

9.8. Recording, Access and Retention of Source Data

The Investigators must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee) and Regulatory Agency inspectors upon request.

A file for each subject must be maintained that includes the signed Informed Consent and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

All study documents (subject files, signed ICFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

9.9. Protocol Violations

A protocol violation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety, and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

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