EIP PHARMA, INC.

CLINICAL STUDY PROTOCOL

Title	A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease
Investigational Product	Neflamapimod (VX-745)
Development Phase	2
EIP Study Number	EIP-VX17-745-304
IND Number	125198
EudraCT Number	2017-004388-11
Date (Version)	27 August, 2018 (Version 2.0)
Sponsor Address	EIP Pharma, Inc. 210 Broadway, Suite 201 Cambridge, MA 02139 USA

CONFIDENTIAL

NCT03402659

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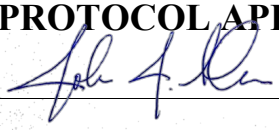

Signature

John J. Alam, MD

Sponsor Responsible Person

President and CEO

Title

27 August 2018

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

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SYNOPSIS

Title	A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease
Study Phase	2
Study centers:	Multi-center study in United States and European Union.
Study Objectives	The primary objective is to evaluate the effects of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the Hopkins Verbal Learning Test – Revised (HVLT-R) in subjects with mild Alzheimer's disease (AD). The secondary objectives are: • To evaluate effects of neflamapimod on immediate and delayed recall of Logical Memory (LM), Verbal Paired Associates (VPA) and Visual Reproduction (VR) components of the Wechsler Memory Scale® (WMS). • To evaluate effects of neflamapimod on the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) and Mini-Mental State Examination (MMSE). • To evaluate the effects of neflamapimod on AD-related cerebrospinal fluid (CSF) biomarkers (total tau, phospho-tau, amyloid-beta peptides, neurogranin, and neurofilament light chain).
Study Endpoints	Primary efficacy endpoints: • Combined change in z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients. Secondary endpoints: • Change in WMS immediate and delayed recall composites in neflamapimod-treated subjects compared to placebo-recipients. • 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 CSF biomarkers (total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, neurofilament light chain) in neflamapimod-treated subjects compared to placebo-recipients.

Number of Subjects	Approximately 152 subjects (76 subjects per dose group).
Subject Population	Subjects aged 55 to 85 years with CSF biomarker confirmed AD, with a CDR global score of 0.5 or 1.0, a CDR memory subscore of at least 0.5, and MMSE scores between 20 and 28, inclusive.
Inclusion Criteria:	1. Men and women age 55 to 85 years, inclusive. 2. Willing and able to provide informed consent. 3. Must have mild cognitive impairment (MCI) or mild AD with evidence of progression ("Mild-AD"), as defined by the following: a. CDR-Global Score of 0.5 or 1.0, with CDR memory subscore of at least 0.5. b. MMSE score ranging from 20 to 28, inclusive. c. Positive biomarker for AD, as defined by a CSF $A\beta_{1-42}$ below the threshold and phospho-tau above the threshold for the assay utilized in the study and assessed by the central laboratory. 4. Computed tomography (CT) or magnetic resonance imaging (MRI) findings within 2 years of Screening that are compatible with AD (i.e., no other pathologic processes that would account for the cognitive deficit). 5. If the subject is taking a single drug for AD (e.g., donepezil or other cholinesterase inhibitors or memantine; dual therapy is excluded), he/she has been on a stable dose for at least 2 months prior to baseline, and the dose must remain unchanged during the study unless required for management of adverse events (AEs). 6. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments. 7. Must have reliable informant or caregiver. In Czech Republic only, the caregiver must be either sharing the same household as the subject or be in personal contact with the subject at least 5 days per week.
Exclusion criteria	1. Evidence that the primary basis for cognitive impairment is neurodegenerative disease other than AD, including, but not limited to, vascular dementia, dementia with Lewy bodies, and Parkinson's disease. 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. History of major and active psychiatric disorder, moderate to severe depressive symptoms, 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. History of cancer within the last 5 years, except basal cell carcinoma, squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years.
6. 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 preclude treatment with p38 mitogen activated protein (MAP) kinase inhibitor and/or assessment of drug safety and efficacy.
7. History of serum B12 abnormality, anemia with hemoglobin ≤10 g/dL, thyroid function abnormality, electrolyte abnormality, or positive syphilis serology that have not been corrected and/or otherwise addressed.
8. History of epilepsy or unexplained seizure within the past 5 years.
9. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5
10. Known human immunodeficiency virus or active hepatitis B or hepatitis C virus infection.
11. Subject participated in a study of an investigational drug less than 3 months or 5 half-lives of the investigation drug, whichever is longer, before enrollment in this study.
12. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements specified in the protocol.
13. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.
    - If a female subject reached menopause within the previous year, a pregnancy test must be performed during Screening and the subject must be willing to adhere to the contraception requirements specified in the protocol. Such subjects with a

positive urine or serum pregnancy test are not eligible for study participation.

14. Requires concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation (see Section 5.7).

Study Drug Details

Neflamapimod 40 mg capsule or matching placebo capsule administered orally according to randomized treatment assignment.

Study Design and Methods

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of neflamapimod 40 mg or matching placebo administered twice daily for 24 weeks in subjects with mild AD.

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

Two Screening visits are planned to allow most screening procedures to be completed and reviewed during the first visit before lumbar puncture to collect CSF is performed during Screening Visit 2.

Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned on 1:1 basis to placebo or neflamapimod treatment. Investigators and subjects will be blinded to the treatment assignment.

Dosing will start on Day 1 following completion of all Baseline procedures.

During the treatment period, subjects will return to the clinic on Days 21, 42, 84, 126, and 168. Telephone contacts will be conducted to determine subject status and assess compliance between Days 42 and 84 (Visits 5 and 6); Days 84 to 126 (Visits 6 and 7); and Days 126 and 168 (Visits 7 and 8).

Episodic memory and other cognitive assessments will be performed at Baseline and Days 42, 84, and 168.

Lumbar puncture will be performed, and CSF collected at Screening Visit 2 and on Day 168.

A Follow-up visit will be conducted 14 (±3) days following the last dose of study drug.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AD	Alzheimer's disease
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
APP	Amyloid-Precursor-Protein
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	bis in die (twice a day)
CDR	Clinical Dementia Rating Scale
CDR-SB	Clinical Dementia Rating Scale-Sum of Boxes
C_{max}	Maximum concentration
CNS	Central Nervous System
CT	Computed tomography
C_{Trough}	Trough concentration
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EF	Effect sizes
FDA	Food and Drug Administration
HVLT-R	Hopkins Verbal Learning Test – Revised
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IL-1beta	Interleukin-1 beta
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LFT	Liver function test
LM	Logical Memory

Abbreviation	Definition
LP	Lumbar puncture
MAP	Mitogen activated protein
MCI	Mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NFT	Neurofibrillary Tangle
p38 alpha	p38 mitogen activated protein kinase alpha
PD	Pharmacodynamic
PET	Positron emission tomography
PK	Pharmacokinetic
PT	Prothrombin time
PTT	Partial thromboplastin time
RA	Rheumatoid arthritis
SAE	Serious adverse event
ULN	Upper limit of normal
VPA	Verbal Paired Associates
VR	Visual Reproduction
WMS	Wechsler Memory Scale

1. INTRODUCTION

1.1. Scientific Rationale

The investigational drug neflamapimod is a highly specific inhibitor of the intra-cellular enzyme p38 mitogen activated protein (MAP) kinase alpha ("p38 alpha"). Neflamapimod (VX-745) was discovered through a proprietary structure-based drug discovery platform at Vertex Pharmaceuticals (Duffy et al, 2011), and was licensed by EIP Pharma for development for the treatment of central nervous system (CNS) disorders. Neflamapimod readily enters the brain, with brain concentrations being approximately 2-fold higher than in peripheral blood.

In the brain, p38 alpha is a major regulator of inflammation through effects on microglia, the major immune cell in the brain. P38 alpha is also expressed in neurons, where it is directly involved in cellular stress-induced inhibition of synaptic plasticity and resulting formation of memory deficits (Lynch, 2010; Prieto, 2015; Sandersen et al, 2016).

Pathologically, Alzheimer's disease (AD) is defined of two distinct abnormalities: amyloid plaques and neurofibrillary tangles (NFTs). The major constituent of amyloid plaques is amyloid-beta, and of NFTs is tau. These 2 proteins have long been considered important in the development of AD. While much scientific controversy exists on the relative contribution of the various pathogenic drivers, there is general agreement that the disease is a result of interplay between those 2 proteins (amyloid-beta and tau), but also with inflammation. In addition, increasingly it appears the convergence point for the three drivers is the synapse, with synaptic dysfunction and loss being the fundamental pathogenic event within the neuron that leads to the defining characteristic of AD, memory deficits (Spires-Jones & Hyman, 2014).

Extensive scientific literature indicates p38 alpha is a critical contributor in the toxicity of amyloid-beta, inflammation (particularly the cytokine interleukin-1 beta [IL-1beta]), and tau to neurons and synapses (Li et al, 2003; Li et al, 2011; Lynch, 2010; Watterson et al, 2013; Birnbaum et al, 2015; Koppensteimer et al, 2016). The most direct evidence of the contribution of p38 alpha in the development of synaptic dysfunction and memory deficits is from distinct animal models in which memory deficits are induced by amyloid-beta, inflammation, or tau, respectively. In these models, the memory deficits are fully reversed with 2 to 3 weeks of treatment (Roy et al, 2015; Alam, 2015; Maphis et al, 2016). These data are consistent with multiple mechanistic *in vitro* studies in which p38 alpha plays a significant role in amyloid-beta and IL-1beta induced impairment of synaptic plasticity (Watterson et al, 2013; Tong et al, 2012; Prieto et al, 2015). Synaptic plasticity otherwise is the basic biochemical process by which information is encoded in the brain and therefore a process that is critical to learning and memory formation.

Three recent scientific publications, in which p38 alpha activity was genetically knocked down by 50% in mice, suggest that p38 alpha activation is involved in hippocampal synaptic dysfunction. In a hypertension-induced cognitive impairment model, mice with reduced p38 alpha activity had improved hippocampal synaptic plasticity (Dai et al, 2016); in another model, similar mice were protected from developing age-related hippocampal dysfunction and decline in neurogenesis (Cortez et al, 2017). In the third report, and perhaps most important, genetic reduction of neuronal p38 alpha in Amyloid-Precursor-Protein (APP) overexpressing transgenic mice resulted in improved synaptic transmission and plasticity in addition to reduced memory loss and amyloid pathology (Colié et al, 2017).

1.2. Pre-Clinical Pharmacology Results

To obtain preclinical proof-of-principle, neflamapimod was tested in the aged rat model of age-related cognitive decline. When tested in a water maze test, rats show cognitive deficits starting at 20 to 22 months of age. This deficit has been shown to be a result of impaired synaptic plasticity that is primarily due to inflammation (Kelly, 2003; Lynch, 2010); however, it also due to increased levels of amyloid beta in the brain due to aging (Church, 2014). Thus, aged rats provided an ideal model system to test whether neflamapimod could reverse impaired synaptic plasticity due to inflammation and amyloid-beta.

The published results (Alam, 2015) showed that neflamapimod administered for 3 weeks fully reversed the spatial learning deficits in the morris-water-maze-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 advance of the Phase 2a clinical studies neflamapimod was also tested in aged-transgenic mice that overproduce APP and develop amyloid plaque. In this model, neflamapimod appeared to decrease amyloid plaque burden in the hippocampus, a finding that provided the rationale for utilizing positron emission tomography (PET) amyloid scanning as a biomarker of drug effect in one of the two phase 2a clinical studies.

More recently, neflamapimod 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 p38 alpha (refer to Section 1.1), the demonstrated of positive pharmacological effects of neflamapimod may be due to reversing proteostasis defects within the neuron 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

Phase 1 studies in healthy subjects and a Phase 2a clinical study in patients with rheumatoid arthritis (RA) were previously conducted by the company that discovered neflamapimod, Vertex Pharmaceuticals. Approximately 150 health volunteers or patients with RA for up to 3 months received neflamapimod in the studies conducted by Vertex.

EIP Pharma licensed neflamapimod from Vertex in 2014 and initiated two phase 2a studies in patients with mild AD in May 2015: Study 302, a 12-week treatment study conducted at VU Medical Center in Amsterdam, Netherlands; and Study 303, a 6-week treatment study conducted at the Early Clinical Phase Unit - Los Angeles, part of Parexel International. Both studies enrolled patients with early AD, defined as patients with either mild cognitive impairment (MCI) with biomarker evidence of AD (i.e., "MCI due to AD") or mild Alzheimer's disease. The Mini-Mental State Examination (MMSE) scores at baseline were between 20 and 28. Neflamapimod doses of 40 mg and 125 mg twice a day (BID) were utilized in Study 302; and effectively only 40 mg was utilized in Study 303 (one subject received 125 mg, but their plasma drug levels were near the middle of the 40 mg recipients in that study).

The major efficacy findings from the Phase 2a clinical studies were:

- Statistically significant improvement in tests of the recall component of episodic memory, as assessed by Wechsler Memory Scale® (WMS) immediate and delayed recall composite measures in Study 302, and Hopkins Verbal Learning Test – Revised (HVLT-R) in Study 303. Though there were no placebo-control in either study, the consistency and magnitude of improvement indicates that there is a true drug effect, particularly in this patient population where the literature indicates there is less practice effects than in a healthy elderly population (see further discussion below).
- Reductions in brain amyloid plaque load at the 40 mg dose level, as assessed in Study 302 by quantitative dynamic amyloid PET scan. As neuronal p38 alpha has been shown to play a "critical role" in amyloid beta generation and plaque production (Schnoder et al, 2016), this result is likely due to inhibition of p38 alpha within the neuron leading to decreased amyloid plaque production; thus, providing evidence of target engagement of neflamapimod in the neuron at the 40 mg dose level. At the higher dose level, this effect is not seen due to anti-inflammatory effect due to inhibition of p38 in microglia that reduces amyloid plaque clearance.
- Definition of 40 mg BID as the optimal dose for neflamapimod in the treatment of AD based on this does level having positive effects on both recall component of episodic memory and amyloid plaque load.
- In addition, neflamapimod at a dose level up to 125 mg BID for 12 weeks was well tolerated in patients with AD. In addition, neflamapimod was confirmed to be blood-brain-barrier penetrant in humans.

Because the episodic memory tests inform directly on the design of the current study, the results are discussed in more detail in this section.

In Study 302 (12-week study in Netherlands), episodic memory was evaluated using the Dutch version of the WMS scale utilizing both verbal and visual information: Logical Memory test, in which subject is read a story; Verbal-Paired Associates, in which subject is given pairs of words and asked remember which words go together; and Visual Reproduction, in which subject is given drawings of specific shapes. Subjects were then asked to recall the information within each test both in an immediate (WMS-Immediate Recall composite) and delayed (WMS-Delayed Recall composite) basis. The WMS was administered at baseline (i.e., before first dose of neflamapimod), after 28 days of treatment, and at end of treatment on Day 84.

Mean WMS immediate recall composite scores increased from 48.4 (±3.8) at baseline to 58.4 (±4.3) at Day 84 (n=15; p=0.005 by Wilcoxon sign rank test for improvement). Mean WMS delayed recall composite scores increased from 13.2 (±2.3) at baseline to 22.1 (±4.1) at Day 84 (p<0.001). Seven of 8 patients in 40 mg group and 6 of 7 in 125 mg group showed improvement from baseline in immediate recall composite score; 8 of 8 patients in 40 mg group and 6 of 7 in 125 mg group showed improvement from baseline in delayed recall composite score.

To further understand the impact of neflamapimod on episodic memory as assessed by WMS, an analysis of the relationship between plasma drug (neflamapimod) concentrations and outcome on WMS immediate and delayed recall tests was conducted. Using a standard linear pharmacokinetic-pharmacodynamic (PK-PD) regression model, a highly significant positive correlation was established between plasma drug levels and level of improvement at Day 84 in combined WMS-immediate and delayed recall (p=0.001). Moreover, plasma drug levels explained 70% (i.e., r^2=.70) of the variance in change (improvement) from baseline to end-of-treatment. These statistics strongly argue that the improvement seen in episodic memory in this study was primarily due to neflamapimod treatment, and not due to chance or practice effects. In addition, the concentration dependency of the effects on episodic memory in the plasma drug levels achieved with the dose range of 40 mg to 125 mg that there is no rationale for going to lower doses, as they would simply lead to lower efficacy; while the difference in plasma drug concentrations achieved with the two doses, and therefore effect on episodic memory, were not substantial.

In Study 303 (6-week study in Los Angeles), the HLVT-R was utilized to assess episodic memory. In this test, 12 specific words from a list are provided verbally, and subject asked to recall ask many words as possible. Two scores are calculated:

- Total (Immediate) Recall Score (0-36): combined score of 3 consecutive trials immediately following provision of words.
- Delayed Recall Score (0-12): Number of words recalled when subject is asked 20-25 minutes after initial trials to recall as many of the words originally provided.

A strength of the HVLT-R is that 5 different validated version exist that incorporate different set of words. Due to the use of these different versions during the course of a clinical study, there is essentially no practice effect (Benedict, et al, 1998) with repeated administration.

Mean Total Recall improved from 19.1 (±1.5) at Baseline to 22.6 (±2.1) at week 6 (p=0.015 for improvement from baseline); Delayed Recall increased from 5.4 (±0.6) to 7.5 (±1.1) (p=0.028 for improvement from baseline). Median increase in Total Recall score was 4.5 (range: -2.5 to +9.5), with only one subject with a decrease during treatment. Particularly with the use of alternate versions that should minimize “placebo effects”, the consistency of improvement and statistics indicates that the improvements in episodic memory seen in Study 303 are due to neflamapimod treatment.

To further evaluate and compare the episodic memory results, treatment effect sizes (ES; called Cohen's d in statistics) were calculated for each study/measure. The results are shown in the following table:

	Study 303 (N=15) (Wechsler Memory Scale)	**Study 303 (N=8) (HLVT-R)**
Immediate Recall	.59	.69
Delayed Recall	.69	.86

The ES calculations show first that the results are very similar between the two studies, i.e., there is a high degree of consistency between the studies despite the use of different measures and tests being applied in different languages/cultures. The magnitude of the ES ranging between 0.59 and 0.86 also argues for a true drug effect, as in MCI and Alzheimer's patient population, ES for improvement in placebo groups are generally <0.2 (Goldberg et al, 2015) in short-term studies, and often show either no change or worsening after 12 weeks or longer follow-up (Scheltens et al, 2011; Hassenstab et al, 2015). In addition, as ES >0.5 is generally taken as being clinically meaningful, ES calculations allows an assessment of whether the magnitude of treatment effect is clinically relevant; which in this case appears to be so.

MMSE scores were evaluated in the 2 studies Though the variability in MMSE results and the samples sizes did not allow one to do statistical analyses, the overall trends were encouraging as 11 of 14 subjects at the 40 mg dose level across the 2 studies that had baseline and end-of-treatment had at least a 1-point improvement in MMSE score.

With the consistent effect on recall component of episodic memory across the 2 studies, and corroboration using 2 different assessment tools in distinct patient populations, the phase 2a clinical data provide preliminary evidence that neflamapimod is pharmacologically active in a manner that is consistent with the scientific rationale and preclinical data that indicate the potential to reverse synaptic dysfunction in the hippocampus. The objective of the current study then is to demonstrate proof-of-concept for neflamapimod by replicating the phase 2a results of improving episodic memory function in a placebo-controlled study. In addition, a general clinical measure of cognition and function (Clinical Dementia Rating Scale [CDR]) will be assessed both to determine whether there is evidence of improvement and estimating potential treatment effects to support Phase 3 study design.

From a mechanism standpoint the expected effect of neflamapimod on episodic memory through reversing synaptic dysfunction, possibly through reversing endolysosmal dysfunction within neurons. In animals, the biomarker of inhibiting reversing synaptic dysfunction through inhibiting neuronal p38α is reduced amyloid beta generation and tau aggregation (Colié et al, 2017; Maphis et al, 2016), which in humans might be expected to lead to reduced CSF Aβ peptides levels and CSF total or phospho-tau. Therefore, to provide additional support of an objective drug effect and to support mechanistic understanding of drug effect, CSF will be collected at baseline and at end-of-treatment to assess effects of neflamapimod on CSF levels of total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, and neurogranin. In addition, neurofilament light chain in CSF, recently identified as potential marker of neurodegenerative diseases associated with proteostasis defects (Bacioglu, 2016) will be evaluated.

2. OBJECTIVES

2.1. Primary Objective

- To evaluate the effect of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the HVLT-R in subjects with mild AD.

2.2. Secondary Objectives

- To evaluate effects of neflamapimod on immediate and delayed recall of Logical Memory (LM), Verbal Paired Associates (VPA) and Visual Reproduction (VR) components of the WMS.
- To evaluate effects of neflamapimod on the CDR-Sum of Boxes (SB) and MMSE.
- To evaluate the effects of neflamapimod on AD-related CSF biomarkers (total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, and neurofilament light chain).

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of neflamapimod 40 mg or matching placebo administered twice daily for 24 weeks in subjects aged 55 to 85 years with CSF biomarker-confirmed AD; with global CDR score of 0.5 or 1.0, with CDR memory subscore of at least 0.5, and MMSE scores between 20 and 28, inclusive.

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

3.1.1. Screening

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

Two screening visits are planned to allow most screening procedures to be completed and reviewed during the first visit before lumbar puncture to collect CSF to be performed on Screening Visit 2.

All screening assessments should be conducted within 42 days of Day 1 (first dose of study drug).

3.1.2. Treatment Period

Once eligibility is confirmed and before the first dose of study drug, subjects will be randomly assigned to receive neflamapimod or placebo; refer to Section 5.4 for details regarding assignment to treatment group.

Dosing will start on Day 1, following completion of all Baseline procedures. During the treatment period, subjects will return to the clinic on Days 21, 42, 84, 126, and 168. Telephone contacts will be conducted to determine subject status and assess compliance between Days 42 and 84 (Visits 5 and 6); Days 84 to 126 (Visits 6 and 7); and Days 126 and 168 (Visits 7 and 8).

3.1.3. Follow Up

A Follow-up Visit will be conducted 14 (±3) days following the last dose of study drug.

3.1.4. Early Discontinuation

Subjects who prematurely discontinue study drug for any reason will be asked to return to the clinical site 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. These subjects will also be asked to return to the clinical site for a Follow-up Visit 14 (±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

The primary objective of assessing episodic memory was chosen to provide a robust assessment of the potential of neflamapimod to reverse hippocampal dysfunction in subjects with mild AD. Defects in episodic memory are a defining characteristic of AD and is one of earliest manifestations of cognitive

dysfunction in the disease process (Gold & Budson, 2008; Tromp et al, 2015). In addition, neflamapimod demonstrated effects on episodic memory in the Phase 2a studies.

The HVLT-R test was chosen as the assessment tool for the primary endpoint because it has alternative versions validated in multiple cultural and language contexts, has high test-retest reliability, and shows good short-term stability (i.e., no practice effects) in subjects with mild AD (Phillips et al, 2012).

3.2.1. Rationale for Dose Selection

The dosing regimen of 40 twice daily for 24 weeks is based on available efficacy (pharmacological activity; Section 3.2.1.1) and safety (Section 3.2.1.2) data.

3.2.1.1. Efficacy Considerations

The 40 mg BID regimen was chosen because PK-PD modeling (plasma drug concentration response) correlations indicated a plasma drug concentration dependency on the effects on episodic memory that argues against going to lower doses and only modest further increase in efficacy with utilizing 125 mg dose level, while the loss of an amyloid plaque load effect at 125 mg dose level provides a specific reason not to increase the dose above 40 mg. The PK-PD modeling was also consistent with the *in vitro* potency of the drug and predicted doses for optimal cognitive effects based on pre-clinical studies (Alam, 2015). Moreover, the 40 mg dose level provides an appropriate safety margin relative to findings in chronic toxicology findings in the dog (Section 3.2.1.2).

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 dose of 40 mg BID and lower is expected to be well tolerated and to have a low risk of drug toxicity.

In the Phase 2a studies (Study 303) of 6- or 12-weeks neflamapimod dosing in patients with mild 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 neflamapimod administration, and 16 completing 12 weeks neflamapimod administration). The one subject who discontinued early did so within the first week of study drug administration due to an adverse event (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-limited 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 liver function tests (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 different formulations in the RA studies, the plasma drug concentrations were 4- to 5-fold higher than in the Phase 2a mild AD studies.

The 40 mg BID dose level provides a 5-fold margin based on plasma drug levels to no adverse effect level and 10-fold margin to minimal and/or equivocal findings for hematological, hepatic and

neuropathological changes in chronic (9- and 12-month) dog toxicology studies. Further details are provided in the investigator brochure.

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 age 55 to 85 years, inclusive.
2. Willing and able to provide informed consent.
3. Must have MCI or mild AD with evidence of progression ("Mild-AD"), as defined by the following:
    a. CDR-Global Score of 0.5 or 1.0, with CDR memory subscore of at least 0.5.
    b. MMSE score ranging from 20 to 28, inclusive.
    c. Positive biomarker for AD, as defined by a CSF $A\beta_{1-42}$ below the threshold and phospho-tau above the threshold for the assay utilized in the study and assessed by the central laboratory.
4. Computed tomography (CT) or magnetic resonance imaging (MRI) findings within 2 years of Screening that are compatible with AD (i.e., no other pathologic processes that would account for the cognitive deficit).
5. If the subject is taking a single drug for AD (e.g., donepezil or other cholinesterase inhibitors or memantine; dual therapy is excluded), he/she has been on a stable dose for at least 2 months prior to baseline, and the dose must remain unchanged during the study unless required for management of AEs.
6. Adequate visual and auditory abilities to perform all aspects of the cognitive and functional assessments.
7. Must have reliable informant or caregiver. In Czech Republic only, the caregiver must be either sharing the same household as the subject or be in personal contact with the subject at least 5 days per week.

4.2. Exclusion Criteria

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

1. Evidence that the primary basis for cognitive impairment is neurodegenerative disease other than AD, including, but not limited to, vascular dementia, dementia with Lewy bodies, and Parkinson's disease.
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. History of major and active psychiatric disorder, moderate to severe depressive symptoms, 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. History of cancer within the last 5 years, except basal cell carcinoma, squamous skin carcinoma, prostate cancer or carcinoma in situ with no significant progression over the past 2 years.
6. 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 preclude treatment with p38 mitogen activated protein (MAP) kinase inhibitor and/or assessment of drug safety and efficacy.
7. History of serum B12 abnormality, anemia with hemoglobin ≤10 g/dL, thyroid function abnormality, electrolyte abnormality, or positive syphilis serology that have not been corrected and/or otherwise addressed.
8. History of epilepsy or unexplained seizure within the past 5 years.
9. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.
10. Known human immunodeficiency virus or active hepatitis B or hepatitis C virus infection.
11. Subject participated in a study of an investigational drug less than 3 months or 5 half-lives of the investigation drug, whichever is longer, before enrollment in this study.
12. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements (Section 5.8)
13. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy.
    - If a female subject reached menopause within the previous year, a pregnancy test must be performed during Screening and the subject must be willing to adhere to the contraception requirements specified in the protocol. Such subjects with a positive urine or serum pregnancy test are not eligible for study participation.
14. Requires concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation (see Section 5.7).

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 6.2.12).

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

- 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 3.1.4 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.

Subjects who withdraw from the study treatment and/or study for a reason prior to Day 21 will be replaced.

5. TREATMENTS ADMINISTERED

Neflamapimod 40 mg capsule(s) or matching placebo capsules will be administered orally, BID with a meal or snack for 24 weeks. Doses should be taken within 30 minutes following a meal or snack (i.e., breakfast and dinner) no less than 8 hours apart and at approximately the same times each day throughout the study.

All subjects will receive matched (by size and color) capsules that contain 40 mg neflamapimod or placebo, respectively.

The first dose of study drug and the morning dose on Day 21 will be administered at the clinical site.

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.

5.1. Packaging and Labeling

EIP Pharma will supply placebo or neflamapimod capsules 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 a per-subject basis.

Capsules will be supplied in blister cards, which each blister card containing 16 capsules (i.e., 1-week supply of study, with two extra capsules). The blister cards will be packaged in cartons containing a 3-week supply of study drug (i.e., 3 blister cards per carton).

Neflamapimod capsules should be stored at 59 to 86°F (15–30°C; controlled room temperature), and should not be exposed to heat in excess of 86°F (30°C) or to high humidity.

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 site from subject on the drug accountability log(s).

Subjects will be instructed to return all blister packs, 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 Screening Visit 2 and are deemed eligible, they will be randomized in a blinded manner to either placebo or neflamapimod treatment utilizing a central Interactive Web Response System (IWRS). Study drug for the entire 24-week period will then be sent on a per subject basis to the site. Randomization will be stratified by 1) background AD-specific therapy (cholinesterase inhibitor or memantine versus no cholinesterase inhibitor or memantine); and 2) CDR-Global Score of 0.5 versus 1.0.

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 may 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and the Medical Monitor and/or Sponsor as soon as possible, preferably by telephone and then in writing, regarding the necessity of code breaking. When possible, the Medical Monitor should be contacted to discuss reasons for breaking the blind.

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 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.

At study entry, any subject taking a drug for AD (e.g., donepezil or other cholinesterase inhibitors or memantine) must have been on a stable dose for at least 2 months (refer to Section 4). Furthermore, the dose must remain unchanged during the study, unless required for management of AEs.

While drug-drug interaction studies have not been conducted, in vitro testing indicates that neflamapimod is metabolized by oxidation in the liver by the 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 in could impact neflamapimod metabolism in subjects who have an underlying CYP2C19 genotypic variant that impacts activity of that CYP2C19. Subjects will be tested for CYP2C19 genotype at baseline to assess any differences in neflamapimod levels and effect (see Section 6.2.5).

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.
- Any anti-tumor necrosis factor-alpha therapy.
- Typical and atypical antipsychotics.

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

Strong Inhibitors ≥5-fold increase in AUC or >80% decrease in CL	Moderate inhibitors ≥2 but <5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors ≥1.25 but <2-fold increase in AUC or 20-50% decrease in CL
boceprevir cobicstat 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

Table 5-2: CYP3A4 Inducers

Strong Inducers ≥80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	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:

- Inclusion criterion #1 (Section 4.1) and Exclusion criteria #12 and #13 (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) are not eligible for the study. 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: complete abstinence, vasectomy, or barrier method of contraception.

Pregnancy of a female partner of a male subject (and, although unlikely, in a female subject) 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. In the unlikely event 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. Activity Restrictions

The Investigator is to advise subjects to take measures to minimize exposure to ultraviolet light during study participation through 2 weeks after the last study drug dose.

5.10. 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.

Patients will be provided with identification cards on which they will record the date and time of study drug administration prior to each scheduled study center visit.

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 / Visit Number / Study Day									
	Screening[a]		Treatment Period							
	1[a]	2[a]	3	4	5	6	7	8	ET Visit[c]	Follow-Up Visit[d]
Assessment	**Within 42 days of D1**		**1[b]**	**21 (±3)**	**42 (±3)**	**84 (±5)**	**126 (±5)**	**168 (±5)**	**Within 3 days after last dose**	**14 (±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	X	X	X	X	X	X	X	X	X	X
C-SSRS	X		X	X	X	X	X	X	X	
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X
Adverse events recording[h]	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[i]	X		X	X	X	X	X		X	X
Coagulation studies[i]	X					X				X
12-lead electrocardiogram[j]	X							X	X	
MMSE[k]	X		X			X				X
CT/MRI[l]		X								
HVLT-R and WMS[k]			X		X	X		X	X	
CDR	X					X		X	X	
Lumbar puncture[m]		X						X[n]	X[n,o]	
Dispense study drug[p]			X	X	X	X	X			
Pharmacokinetic sampling[q]				X	X	X				
CYP2C19 genotyping and optional ApoE4 testing[r]			X							
Final study drug reconciliation								X	X	

CDR: Clinical Dementia Rating Scale; C-SSRS: Columbia-Suicide Rating Scale; CT: Computed tomography; D=day; HVLT-R: Hopkins Verbal Learning Test – Revised; MMSE: Mini-Mental State Examination; MRI: Magnetic resonance imaging; WMS: Wechsler Memory Scale.

Note: Telephone contacts will be conducted to determine subject status and assess compliance between Days 42 and 84 (Visits 5 and 6); Days 84 to 126 (Visits 6 and 7); and Days 126 and 168 (Visits 7 and 8).

a. Two Screening visits are planned to allow most screening procedures to be completed and reviewed during the first visit before lumbar puncture is performed at Visit 2. All screening assessments should be conducted within 42 days of Day 1.
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 clinical site 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 6.2.9 for details regarding physical examination.
h. Definitions and procedures for documenting and reporting AEs serious adverse events (SAEs) are provided in Section 7.
i. Details of clinical laboratory sampling for chemistry, hematology, and coagulation studies are discussed in Section 6.2.11.
j. Details of 12-lead ECG assessment are discussed in Section 6.2.10.
k. Refer to the following sections for details of cognitive assessments Section 6.2.6 (MMSE, CDR), and Section 6.2.7 (NTB – HVLT-R/WMS.
l. MRI/CT results should be available and reviewed before lumbar puncture is performed.
m. Perform lumbar puncture (LP) only after subject has been deemed eligible based on all other inclusion/exclusion criteria, e.g. MRI, labs etc. Refer to Section 6.2.4 for details regarding LP.
n. LP is to be performed within ±2 days of the last study drug dose.
o. LP need not be performed at the ET visit for patients who discontinue prior to Visit 5 (Day 42).
p. Study drug details including packaging, storage, accountability, and dosing are presented in Section 5.
q. Refer to Section 6.2.8 for details regarding PK sampling.
r. CYP2C19 genotyping is mandatory; testing for apolipoprotein E is optional. (Apoliprotein E results may be disclosed to subject at the end of the study.)

6.2. Study Assessments

6.2.1. Baseline and Disease Characteristics

Details regarding AD history will be collected during Screening, as specified in the eCRF.

6.2.2. Columbia-Suicide Severity Rating Scale

The C-SSRS is a clinician-administered instrument that assesses suicidal ideation and behavior (Posner, 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.

6.2.3. Computed Tomography/Magnetic Resonance Imaging

The subject must have had MRI or CT scan within 2 years of Screening, with findings negative for evidence of other neurodegenerative or other brain disease that could account for their cognitive symptoms. If MRI or CT has not been performed within 2 years before Screening and/or results are not available, MRI or CT scan must be performed as part of Screening to exclude other disease. MRI/CT results should be available and reviewed before Screening lumbar puncture is performed (see Section 6.2.4).

6.2.4. Lumbar Puncture

LP will be performed at Screening Visit 2 and at the End-of-Treatment (Day 168 or Early Termination visit in subjects who discontinue treatment early). The End-of Treatment LP is to be performed within

±2 days after the last study drug dose. There is no need to perform the LP for subjects who discontinue prior to Visit 5 (Day 42).

Kits for collection of CSF samples will be provided. CSF levels of total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, and neurofilament light chain will be determined by enzyme-linked immunosorbent assay at a designated central laboratory.

6.2.5. Genotyping and Apolipoprotein E4 Testing

A blood sample will be collected from all subjects at Visit 3 (Day 1) for CYP2C19 genotyping; such testing is mandatory. The CYP2C19 gene encodes for a drug metabolizing enzyme that accounts for approximately half the metabolism of neflamapimod. (The other is the CYP3A4 enzyme). As there are known polymorphisms in CYP2C19, particularly in Asian populations, that reduce the function of this enzyme, the PK profiles in individual subjects may be impacted CYP2C19 genotype (Fricke-Galindo et al, 2016). PK profiles will be obtained in all subjects and correlated against CYP2C19 genotype (see Section 6.2.8 and Section 8.4). An aliquot of blood from this sample may also be used for measurement of apolipoprotein E4; such testing is optional. Results will be available to study sites and may be discussed with the subjects only after the clinical study report has been completed.

6.2.6. Mini-Mental State Examination/CDR

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.

The 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 (MCI), and is an approved regulatory endpoint recognized by the FDA. The CDR interview is to be conducted with the subject and Caregiver by an experienced and certified clinician. The CDR yields both a global and an SB score. The global CDR rating, along with the memory box score, will be used to determine a subject's eligibility for inclusion. In addition, the CDR-SB score will utilized to evaluate cognitive and functional changes from baseline to Visit 6 and Visit 8.

Standardized MMSE (Version 2.0) and CDR will be conducted by the Investigator or designee.

6.2.7. Episodic Memory Tests - HVLT-R and WMS

The HVLT-R is a verbal learning and memory test, with 6 validated alternate forms. Each form contains 12 nouns, 4 words each from 1 of 3 semantic categories (e.g., precious gems, articles of clothing, vegetables), to be learned, and repeated back to the evaluator over the course of 3 learning trials. Approximately 20–25 minutes later, a delayed recall trial and a recognition trial are completed. The delayed recall requires free recall of any words remembered. The recognition trial is composed of 24 words, including the 12 target words and 12 false-positives, 6 semantically related, and 6 semantically unrelated. The 3 learning trials are combined to calculate a total recall score; the delayed recall trial creates the delayed recall score.

For WMS, Logical Memory I & II & II-(Recognition), VPA I & II & II-(Recognition), and Visual Reproduction I & II & II-(Recognition) will be applied.

The HVLT-R and WMS tests **must** be performed sequentially within the day; with the HVLT-R to be conducted first and completed (including delayed recall component), prior to commencing WMS test.

6.2.8. Pharmacokinetic Sampling

On Day 21, the subject must not take their morning dose of study drug; instead, the morning dose of the study drug will be administered with a meal or snack in the clinic, and blood samples will be collected for PK (drug concentration) testing immediately prior to and 2.5 hours after study drug administration (i.e., at predicted time point for peak drug concentration after dose administration). On Day 42 and Day 84, blood samples will also be collected for PK sample concurrently with clinical laboratory test sampling during the time of their visit to the clinic. Subjects should take their morning dose of study drug at home with a meal or snack on Day 42 and 84 on their regular schedule and record the time of their morning dose. Day 42 and Day 84 PK samples will be collected together with the safety laboratory samples at the clinic, the time of the PK sampling must be recorded.

Refer to the Laboratory Manual for details regarding PK sample collection, processing, and shipment.

6.2.9. 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.

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).

6.2.10. 12-Lead Electrocardiogram

A 12-lead ECG will be performed using validated machinery available locally to each clinical site. Each report will be reviewed by the Investigator for qualified sub-investigator and assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant. Abnormal, clinically significant findings that represent a worsening from Baseline will be recorded as an AE.

6.2.11. Clinical Laboratory Assessments

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

Kits for clinical laboratory assessments will be provided by and samples will be analyzed at a designated central laboratory. Additional details are provided in the Laboratory Manual.

Table 6-2 Clinical Laboratory Analytes

Serum Chemistry

- Albumin
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)
- Glucose
- Blood urea nitrogen
- Calcium
- Bicarbonate
- 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 (PT)
- Partial thromboplastin time (PTT)
- 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).

6.2.12. 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 assent)
- Subject lacks ability to provide continued informed consent (or assent) and/or sound judgement as to whether to continue in the study
- Subject develops active 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.

Subjects who withdraw from the study treatment and/or study for a reason prior to Day 21 will be replaced.

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.

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

AEs occurring from when the subject signs the informed consent form (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, (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

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 as outlined below and also to the IRB/IEC according to its standard operating procedures.

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 Worldwide Clinical Trials.

SAE Reporting:

E-mail: drugsafety@worldwide.com

Telephone: +44 (0)115 922 0960

All information about SAEs will be collected and reported via the SAE form and sent by e-mail message or facsimile (contact information will be contained in the investigator site file). The Investigator should send the initial report within 24 hours of becoming aware of the SAE. At minimum, the initial report should include the following information:

- Event
- Study code
- Subject number, initials, and date of birth
- Investigational product
- Reporter name and contact information

In the case of a "minimum report" (one that solely comprises the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and for reported deaths, the Investigator should supply Worldwide Clinical Trials and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. The Sponsor or its designee will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs that are ongoing at the Follow-up visit should be followed until resolved.

8. DATA MANAGEMENT AND STATISTICAL ANALYSIS

8.1. Data Management and Quality Assurance Considerations

This study will employ eCRFs. 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 institution 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 recorded by the person updating eCRF data 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 these 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 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

Up to 76 subjects per treatment arm provides 90% power to detect ES of 0.53 and 80% power to detect ES of 0.46. This level of ES is the minimum amount considered clinically relevant treatment effect and is less than the effect size seen in the Phase 2a studies; therefore, provides a statistical buffer to achieve a positive outcome, if the magnitude of treatment effect by chance is lower in the present study.

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 post-dose HVLT-R assessment.

8.4. Pharmacokinetics (PK)

Trough and maximum concentrations (C_{Trough} and C_{max}, respectively) will be evaluated on Day 21 (i.e.; at steady-state) for each subject and descriptive statistics for the neflamapimod treatment group will be presented. In addition area under the time concentration curve (AUC) will be derived utilizing population PK methods utilizing drug concentration data from Day 21 as well the sparse sampling on Days 42 and 84. C_{Trough}, C_{max} and AUC will be correlated to CYP2C19 genotype status. In addition, a PK/PD model for neflamapimod and effects on HVLT-R, WMS, CDR-SB, and/or CSF biomarkers will be developed *post hoc* based on the available data.

8.5. Efficacy

8.5.1. Primary Efficacy Variables

The primary efficacy variable is:

- Combined change in z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients.

To obtain a single statistic, the total recall and delayed recall scores will be converted to z-scores and the combined change in z-scores will be compared for the two treatment groups. Specific statistical analyses for efficacy variables will be identified in a prospective Statistical Analysis Plan.

8.5.2. Secondary Efficacy Variables

The secondary efficacy variables are:

- Change from Baseline to Week 24 in recall and recognition of the WMS, CDR-SB, MMSE, and CSF biomarkers (total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, neurofilament light chains) comparing neflamapimod-treated subjects with placebo-recipients.

8.6. 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.

8.7. Interim Analysis

No interim analysis is planned. Only pharmacokinetic data will be monitored by an independent clinical pharmacologist on an every 3-month basis without any reference to other study data or subject identification, with the exception of baseline demographics (age, weight, race) and CYP2C19 genotype.

9. STUDY MANAGEMENT

9.1. Ethics and Consent

9.1.1. Regulations and Guidelines

The study will be performed in accordance with this protocol, US Investigational New Drug Application regulations (21 CFR 312) or local national laws (as applicable) and ICH guidelines for Good Clinical Practice. These guidelines are on file at Worldwide Clinical Trials.

9.1.2. Institutional Review Boards/Independent Ethics Committees

Conduct of the study must be approved by an appropriately constituted IRB or 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 IRB/IEC authorization has been received by the Sponsor or its designee.

9.1.3. Informed Consent

For each study subject, a written ICF will be obtained before 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) appointed guardian 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 IRB/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 30 weeks, including 24 weeks of treatment. Once the subjects have ended his 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 Food and Drug Administration (FDA) 1572 or other country-specific regulatory forms, the Investigator acknowledges that he/she has received a copy of the investigator's brochure 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 CRF 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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