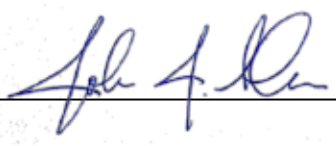
EIP PHARMA, INC

CLINICAL STUDY PROTOCOL

Title	A Double-Blind, Placebo-Controlled Two-Period 10-Week Treatment Within-Subject Crossover Study Of Cognitive Effects Of Neflamapimod in Early-Stage Huntington Disease (HD)
Investigational Product	Neflamapimod
Development Phase	2a
EIP Study Number	EIP19-NFD-401
IND Number	125198
EudraCT Number	2018-004840-51
Date (Version)	30 July, 2019 (Version 3.0)
Sponsor Address	EIP Pharma, Inc. 201 Broadway, Suite 201 Cambridge MA 02139 USA

CONFIDENTIAL

SPONSOR PROTOCOL APPROVAL PAGE



Signature

John J. Alam

Sponsor Responsible Person

President and CEO

Title

31 July 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:
Address:
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Date

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SYNOPSIS

Title	A Double-Blind, Placebo-Controlled Two-Period 10-Week Treatment Within-Subject Crossover Study of Cognitive Effects of Neflamapimod in Early-Stage Huntington Disease (HD)
Study Phase	2a
Study center:	Single centre study in the United Kingdom.
Study Objectives	• The primary objective is to evaluate the effects of administration of neflamapimod on hippocampal function, as assessed in the virtual Morris Water Maze (MWM). The secondary objectives are: • To evaluate the effects of neflamapimod on the Cambridge Neuropsychological Test Automated Battery (CANTAB) paired associates learning task. • To evaluate effects of neflamapimod on a larger battery of parameters in the CANTAB. • To evaluate tolerability and safety of neflamapimod in subjects with HD.
Study Endpoints	Primary efficacy endpoints: • Latency during the learning phase of virtual MWM (hidden platform training) during the neflamapimod-treatment period compared to that during the placebo-administration period. Secondary endpoints: • Percent of time spent in the correct quadrant during MWM probe test during the neflamapimod-treatment period compared to that during the placebo-administration period. • Number of overall errors in the CANTAB paired associates learning task during the neflamapimod-treatment period compared to that during the placebo-administration period. • Safety as determined by the number of related adverse events and general tolerability reported during the neflamapimod treatment period compared to the placebo administration period. In addition, exploratory analyses of the full set of parameters in the CANTAB will be conducted.
Number of Subjects	A total of 16 subjects are planned to be enrolled.

Subject Population	Subjects aged 30 to 70 years with genetically confirmed Stage 1 HD and identified cognitive deficits.
Inclusion Criteria:	1. Men and women age 30 to 70 years, inclusive. 2. Willing and able to provide informed consent. 3. Must have genetically confirmed HD and identified cognitive deficits: a. Stage 1, as defined by Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) score ≥9, and, b. CANTAB Paired Associate Learning Total Adjusted Error Score of >16. 4. Normal or corrected eye sight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments. 5. No history of learning difficulties that may interfere with the subject's ability to complete the cognitive tests.
Exclusion criteria	1. A profile of impairment that is not consistent with HD. 2. Diagnosis of any other ongoing central nervous system condition other than HD, including, but not limited to, vascular dementia, dementia with Lewy bodies, and Parkinson's disease. 3. 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. 4. Ongoing 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. 5. Diagnosis of alcohol or drug abuse within the previous 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. Anemia with a hemoglobin ≤10 g/dL, clinically significant thyroid function abnormality, electrolyte abnormalities.
8. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.
9. Known human immunodeficiency virus; or active hepatitis B or hepatitis C virus infection; evidence of active or latent tuberculosis.
10. Subject 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.
11. History of previous neurosurgery to the brain.
12. Female subjects who are pregnant or breast-feeding.
13. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements specified in the protocol (see Section 5.8).
14. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy and are not willing or unable to adhere to contraceptive requirements specified in the protocol (see Section 5.8).
15. Requires concomitant use of cytochrome P450 (CYP) 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation.
16. Known allergy to any ingredient of the trial medication or placebo.

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 2a, single centre, randomized, double-blind, placebo-controlled, 2-period within-subject crossover proof-of-principle study of neflamapimod 40 mg or matching placebo administered twice daily for 10 weeks in subjects with Stage 1 HD.

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

One screening visit is planned within 21 days before baseline (Day 1), during which time safety screening measures and initial assessments, including CANTAB will be undertaken and subject eligibility will be confirmed.

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 treatment during the first treatment period (i.e., 8 subjects will receive neflamapimod and 8 will receive placebo during the first treatment period). Investigators and subjects will be blinded to the treatment assignment.

Dosing will start on Day 1 following completion of all baseline procedures, which will include virtual Morris Water Maze (MWM) and CANTAB tests.

During the treatment period, subjects will return to the clinic every 2 to 4 weeks.

At Weeks 4 and 10 of the first treatment period, the virtual MWM and CANTAB tests will be repeated.

All subjects will return for a safety visit 2 weeks after stopping drug in the first treatment period.

After at least 8 weeks (and up to 12 weeks) after completion of the first treatment period, subjects will return to the clinic and after repeating virtual MWM and CANTAB, will resume blinded treatment; all subjects who received placebo capsules during the first treatment period will receive neflamapimod, while those who received neflamapimod will receive placebo capsules during this second treatment period.

At the end of Weeks 4 and 10 of the second treatment period, the virtual MWM and CANTAB tests will be repeated.

A Final Study Visit will be conducted 2 weeks after completion of the second treatment period.

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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
ASK1	Apoptosis signal-regulating kinase 1
AST	Aspartate aminotransferase
AUC	Area under the time concentration curve
BID	bis in die (twice a day)
CANTAB	Cambridge Neuropsychological Test Automated Battery
CL	Clearance
CNS	Central Nervous System
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic Case report form
FDA	Food and Drug Administration
$GABA_A$	γ-aminobutyric acid type A
HD	Huntington's Disease
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug
LFT	Liver function test
MAP	Mitogen-activated protein
MAP2K6	p38 MAP-Kinase 6
MedDRA	Medical Dictionary for Regulatory Activities
MKP-1	Mitogen-activated protein kinase phosphatase 1
MOT	Motor Screening Task

Abbreviation	Definition
mTOR	Mammalian target of rapamycin
MWM	Morris-Water-Maze
OTS	One Touch Stockings of Cambridge
p38α	Mitogen-activated protein kinase 14
PAL	Paired Associated Learning
PRM	Pattern Recognition Memory
RA	Rheumatoid arthritis
RTI	Reaction Time
SAE	Serious adverse event
SS	Spacial Span
TFC	Total Functional Capacity
UHDRS	Unified Huntington's Disease Rating Scale
ULN	Upper limit of normal

1. INTRODUCTION

1.1. Scientific Rationale

This is a double-blind, placebo-controlled 2-period 10-week treatment within-subject crossover study of neflamapimod in early-stage Huntington disease (HD). The primary objective is to determine whether neflamapimod can reverse hippocampal dysfunction in patients with early-stage HD, as assessed by the virtual Morris Water Maze test (MWM) for evaluating spatial learning and selected tests on the Cambridge Neuropsychological Test Automated Battery (CANTAB).

While HD is defined as a movement disorder, cognitive deficits precede motor deficits and recently, impairment in hippocampus-dependent cognitive function was defined as one of the earliest manifestation of HD (Begeti et al, 2016). These results of Begeti et al confirm prior studies in multiple animal models that demonstrated dysregulation of hippocampal synaptic dysfunction (Milnerwood & Raymond, 2010; Smith et al, 2014; Giralt et al, 2012). Further synaptic dysfunction and neurodegeneration has been, in transgenic models directly linked to the toxicity of mutant huntingtin (HTT) synapses (Xu et al, 2013; Valencia et al, 2013; Sepers & Raymond, 2014). From a mechanistic standpoint, the synaptic toxicity appears to be a result of defects in protein trafficking/degradation as correction through increasing endosomal trafficking via overexpression of Rab11 (Steinert et al, 2011), while increasing autophagy by increasing mammalian target of rapamycin (mTOR) activity (Lee et al, 2015), reverses synaptic dysfunction and ameliorates behavioral/motor deficits. In addition, synaptic dysfunction has been linked to disruption of γ-aminobutyric acid type A ($GABA_A$) receptor trafficking (Yuen et al, 2012).

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 Alzheimer's disease (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 alpha 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 MAPKα has been recognized as a leading therapeutic target to improve hippocampal 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).

In the HD context, p38 activation has been demonstrated in the transgenic YAC128 mouse model of disease (Dau et al 2014; Gladding et al, 2014) and been implicated in vitro in expanded-polyglutamine mediated cytotoxicity (Tsirigotis et al, 2008). In addition, overexpression of mitogen-activated protein kinase phosphatase 1 (MKP-1), which reduces the activity of p38 and other mitogen-activated protein (MAP) kinase pathways, is neuroprotective in a lentivirus model of HD (Taylor et al, 2013). In humans, p38α has been implicated as genetic loci of two upstream activators of p38α, apoptosis signal-regulating

kinase 1 (ASK1) and p38 MAP-Kinase 6 (MAP2K6), which have been identified as a genetic modifier of the age of onset in HD (Arning et al, 2008).

Regarding neflamapimod in preclinical and early phase studies, it has been shown to reverse spatial learning deficits, as assessed in the MWM 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), which are known to be dependent on proper hippocampal function (Gold & Budson, 2008). 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 HD.

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 an 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 impaired 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 Alzheimer's disease.

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 hippocampal neurons, including impaired autophagy and endolysosomal dysfunction (.Alam & Scheper, 2016.). The proteostasis defect-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 non-clinically and clinically in AD and also in earlier studies in rheumatoid arthritis (RA) and the risks to date are well documented. In long-term (9- and 12-month) toxicity studies in the dog, pathological evidence of toxicity was evident in the liver and CNS (predominantly axonal damage in the spinal cord). The findings are discussed in detail in the investigator brochure, but there were only minimal to equivocal findings evident at blood drug concentrations ten-fold higher than those achieved in humans with the 40 mg twice-daily (BID) dose to be utilized in the planned clinical study (n.b: the no-adverse-effect level was two-fold higher on a plasma drug concentration basis). In the recent AD clinical studies, neflamapimod was well tolerated, with 24 of 25 subjects completing their scheduled dosing period. 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 AD studies were mild somnolence reported in 5 patients, and self-limiting mild diarrhoea reported in 4 patients. There was also one event of moderate diarrhoea, which was considered not related, as the event did not recur during the 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. Increases in liver transaminases have been identified as the dose-limiting clinical toxicity in prior clinical studies. This was seen in 10% to 15% of patients with RA in a prior study at a dose of 250 mg BID for 3 months; a dose level at which the plasma drug concentrations were 4- to 5-fold higher than in the previous or planned AD studies.

There is an ongoing double-blinded randomized study in early AD. The study is designed to treat 152 patients with either neflamapimod 40 mg or placebo BID. The study is ongoing and blinded. There has been one reported unrelated serious adverse event (SAE) of hypokalemia. The drug was interrupted but re-started. There has been one report of liver transaminase increases to >3 times the upper limit of normal. Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were increased to slightly >3 times the upper limit of normal, and there was no associated increase in bilirubin. The patient had no other illness or symptoms, history of moderate alcohol intake, and the transaminase levels began to resolve during continued study drug administration. Study drug is currently interrupted, and the subject's treatment assignment has not been unblinded. Otherwise in this study the majority of events have been mild to moderate and unrelated.

Given the potential benefits to patients with early HD, the safety margin relative to animal toxicity findings, and the prior clinical experience at substantially higher dose levels, the benefit/risk profile is favourable for the planned study at the 40 mg BID dose level.

2. OBJECTIVES

2.1. Primary Objective

The primary objective is:

- To evaluate the effects of administration of neflamapimod on hippocampal function, as assessed in the virtual MWM.

2.2. Secondary Objectives

The secondary objectives are:

- To evaluate the effects of neflamapimod on the CANTAB paired associates learning task.
- To evaluate effects of neflamapimod on a larger battery of parameters in the CANTAB.
- To evaluate tolerability and safety of neflamapimod in subjects with HD.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is a Phase 2a, single centre, randomized, double-blind, placebo- controlled, two-period within-subject crossover proof-of-principle study of neflamapimod 40 mg or matching placebo administered BID for 10 weeks in subjects with Stage 1 HD.

At least 8 weeks (and up to 12 weeks) after completion of the first treatment period, subjects will return to the clinic and after repeating virtual MWM and CANTAB, will resume blinded treatment; all subjects who received placebo capsules during the first treatment period will receive neflamapimod, while those who received neflamapimod will receive placebo capsules during this second treatment period.

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. One screening visit is planned within 21 days before baseline (Day 1), during which safety screening measures and assessments, including CANTAB, will be undertaken and subject eligibility will be confirmed.

3.1.2. Treatment Period

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 treatment during the first treatment period (i.e., 8 subjects will receive neflamapimod and 8 will receive placebo during the first treatment period); refer to Section 5.4 for details regarding assignment to treatment group. Investigators and subjects will be blinded to the treatment assignment.

Dosing will start on Day 1 following completion of all baseline procedures, which will include virtual MWM and CANTAB tests.

At Weeks 4 and 10 of the first treatment period, the virtual MWM and CANTAB tests will be repeated.

All subjects will return for a safety visit 2 weeks after stopping drug in the first treatment period.

At least 8 weeks (and up to 12 weeks) after completion of the first treatment period, subjects will return to the clinic and after repeating virtual MWM and CANTAB, will resume blinded treatment; all subjects who received placebo capsules during the first treatment period will receive neflamapimod, while those who received neflamapimod will receive placebo capsules during this second treatment period.

At the end of Weeks 4 and 10 of the second treatment period, the virtual MWM and CANTAB tests will be repeated.

A Final Study Visit will be conducted 2 weeks after completion of the second treatment period.

3.1.3. 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 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

Given the inter-subject variability in the level of cognitive dysfunction in Huntington's disease, a cross-over design, in which each subject will serve as his or her own control, would provide significantly more statistical power to detect treatment differences than a parallel group design. In addition, given that any beneficial effects of neflamapimod would be through improvement of synaptic function (i.e. a functional effect) any potential effects would be expected to wash-out relatively rapidly (i.e. within a small number of weeks).

As a secondary objective, the impact of neflamapimod on slowing the decline in cognitive function in subjects with HD will be assessed using the CANTAB, a method commonly employed in clinical studies (Smith et al, 2013). In particular, the effect of neflamapimod on the CANTAB paired associates learning task as well as on the MWM test, tests known to rely on hippocampal integrity (Begeti, 2016), will be assessed.

3.2.1. Rationale for Dose Selection

3.2.1.1. Efficacy Considerations

The 40 mg BID regimen was chosen based on pharmacokinetic-pharmacodynamic modeling (plasma drug concentration response) correlations, which indicated a plasma drug concentration dependency on the effects on episodic memory that argues against going to lower doses and only modest further increases in efficacy with utilizing a 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 pharmacokinetic-pharmacodynamic 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 chronic toxicology findings in the dog.

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 of neflamapimod administration, and 16 completing 12 weeks of 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 cerebrospinal fluid 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 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 is currently being tested in an ongoing, blinded Phase 2b study of 152 mild AD patients. One unrelated SAE has been reported to date and the majority of events have been mild to moderate AEs and unrelated to study drug. One event of liver transaminase increase to >3 times the upper limit of normal has been reported. The patient had no other illness or symptoms, had a history of moderate alcohol intake, and the transaminase levels began to resolve during continued study drug administration. Study drug is currently interrupted, and the subject's treatment assignment has not been unblinded.

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 30 to 70 years, inclusive.
2. Willing and able to provide informed consent.
3. Must have genetically confirmed HD and identified cognitive deficits:
   a. Stage 1, as defined by Unified Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) score ≥9, and
   b. CANTAB Paired Associate Learning Total Adjusted Error Score of >16.
4. Normal or corrected eye sight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments.
5. No history of learning difficulties that may interfere with the subject's ability to complete the cognitive tests.

4.2. Exclusion Criteria

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

1. A profile of impairment that is not consistent with HD.
2. Diagnosis of any other ongoing CNS condition other than HD, including, but not limited to, vascular dementia, dementia with Lewy bodies, and Parkinson's disease.
3. 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.
4. Ongoing 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.
5. Diagnosis of alcohol or drug abuse within the previous 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 a MAP kinase inhibitor and/or assessment of drug safety and efficacy.
7. Anemia with a hemoglobin ≤10 g/dL, clinically significant thyroid function abnormality, electrolyte abnormalities.
8. AST or ALT >1.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio (INR) >1.5.

9. Known human immunodeficiency virus; or active hepatitis B or hepatitis C virus infection; evidence active or latent tuberculosis.
10. Subject 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.
11. History of previous neurosurgery to the brain.
12. Female subjects who are pregnant or breast-feeding.
13. Male subjects with female partners of child-bearing potential who are unwilling or unable to adhere to contraception requirements specified in the protocol (see Section 5.8).
14. Female subjects who have not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy and are not willing or unable to adhere to contraceptive requirements specified in the protocol (see Section 5.8).
15. Requires concomitant use of cytochrome P450 (CYP) 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation (see Section 5.7).
16. Known allergy to any ingredient of the trial medication or placebo.

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 6.2.10).

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.

Up to four subjects who withdraw from the study treatment and/or study prior to completing study assessments at Week 4 of the second treatment period may be replaced.

5. TREATMENTS ADMINISTERED

Neflamapimod 40 mg capsule(s) or matching placebo capsules will be administered orally, BID with a meal or snack in 2 treatment periods of 10 weeks each. 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 in each treatment period will be administered at the study centre.

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 an individual subject basis.

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 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 and are deemed eligible, they will be randomized in a blinded manner to receive either a) neflamapimod for 10 weeks followed by placebo for 10 weeks or b) placebo for 10 weeks followed by neflamapimod for 10 weeks utilizing a manually generated random code.

5.5. Study Blinding and Breaking the Blind

Subjects and site personnel associated with study conduct will be blinded to treatment assignment. Treatment codes will be provided in sealed envelopes to the site and will be stored by the pharmacist or designee.

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), as 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, 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 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.
- Live vaccines, with the exception of influenza during study participation and through 3 months after the last study drug dose.
- Any anti-tumor necrosis factor-alpha therapy.

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 are Prohibited)

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 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

Table 5-2: CYP3A4 Inducers (to be Used with Caution)

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

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 #13 and #14 (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 every four weeks during the 1st and 2nd treatment periods and must use a barrier method of contraception in addition to at least 1 of the following contraceptive methods: complete abstinence regardless of menstrual cycle timing, contraceptive (oral, transdermal, injectable, or implantable), or intrauterine device.

Male subjects with female partners of child-bearing potential must use a barrier method of contraception in addition to 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 Voisin Consulting Life Sciences 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. 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.

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

	Screening[a]	Treatment Period 1				Washout (8 to 12 weeks)	Treatment Period 2				ET Visit[c]	Final Study Visit[d]
Evaluation	**Within 21 days of D1**	**W0[b]**	**W4 (±4 d)**	**W8 (±4 d)**	**W10 (±2 d)**	**2 wks (±3 d) of last dose in Period 1**	**W0[b]**	**W4 (±4 d)**	**W8 (±4 d)**	**W10 (±2 d)**	**Within 3 d after last dose**	**2 wks (±3 d) of last dose**
Informed Consent	X[e]											
Medical history review	X											
Pregnancy testing	X[f]	X	X	X			X	X	X			X
Physical examination[g]	X				X		X			X	X	X
C-SSRS	X				X		X			X		
Hospital Anxiety and Depression Scale	X		X		X		X	X		X		
UHDRS	X				X		X			X		
CANTAB	X	X	X		X		X	X		X	X	
MWM	X	X	X		X		X	X		X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events recording[h]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and chemistry[i]	X	X	X	X		X	X	X	X			X
12-lead electrocardiogram[j]	X											

	Screening[a]	Treatment Period 1				Washout (8 to 12 weeks)	Treatment Period 2				ET Visit[c]	Final Study Visit[d]
Evaluation	**Within 21 days of D1**	**W0[b]**	**W4 (±4 d)**	**W8 (±4 d)**	**W10 (±2 d)**	**2 wks (±3 d) of last dose in Period 1**	**W0[b]**	**W4 (±4 d)**	**W8 (±4 d)**	**W10 (±2 d)**	**Within 3 d after last dose**	**2 wks (±3 d) of last dose**
Dispense study drug[k]		X	X	X			X	X	X			
Final study drug reconciliation					X					X	X	

CANTAB= Cambridge Neuropsychological Test Automated Battery; C-SSRS: Columbia-Suicide Rating Scale; D=Day; ET = End-of-Treatment; MWM=Morris Water Maze; UHDRS= Unified Huntington's Disease Rating Scale; W=Week.

Note: Telephone contacts will be conducted to determine subject status and assess compliance between W0 and W4 and between W4 and W8 of each Treatment Period.

a. All screening assessments should be conducted within 21 days of Day 1.
b. At Week 0 of each treatment period, 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 2 weeks (±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 of child-bearing potential or who have reached menopause in the previous year must have a serum or urine pregnancy test performed during Screening, W0, every 4 weeks during the 1st and 2nd treatment periods, and at the Follow-up Visit; subjects with positive results are not eligible for study participation.
g. Refer to Section 6.2.7 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 and hematology, are discussed in Section 6.2.9.
j. Details of 12-lead ECG assessment are discussed in Section 6.2.8.
k. Study drug details including packaging, storage, accountability, and dosing are presented in Section 5.

6.2. Study Assessments

6.2.1. Baseline and Disease Characteristics

Details regarding HD 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 et al, 2011). The "Baseline" version of the instrument will be administered to subjects during Screening and before beginning the second treatment period, and the "Since Last Visit" version will be used at all other time points specified in Table 6-1.

6.2.3. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is a 14-item self-assessment scale designed to determine the degree of anxiety and depression a patient is experiencing (Zigmond, Snaith, 1983). Each item on the questionnaire is scored from 0-3; thus total scores range from 0 and 21 for either anxiety or depression. The Hospital Anxiety and Depression Scale is to be completed at the time points specified in Table 6-1.

6.2.4. Unified Huntington's Disease Rating Scale

The UHDRS was developed as a clinical rating scale to assess 4 domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity (Huntington Study Group, 1996).

- The **motor section** of the UHDRS assesses motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability. A demonstration of the techniques of the motor exam and examples of each grade of abnormality are provided on the accompanying videotape. The total motor impairment scores is the sum of all the individual motor ratings, with higher scores indicating more severe motor impairment than lower scores.
- **Cognitive operations** are assessed by a phonetic verbal fluency test, Symbol Digit Modalities Test, and the Stroop Interference Test. The Stroop Test results are reported as the raw number of correct answers given in a 45-second period. Results for the other tests are reported as the raw number of correct responses. Higher scores indicate better cognitive performance.
- The **behavioral assessment** measures the frequency and severity of symptoms related to affect, thought content and coping styles. The total behavior score is the sum of all responses; however, this score may have less usefulness than the individual subscale scores for mood, behavior, psychosis, and obsessiveness which are created by summing the responses to the corresponding questions. The evaluator is also requested to provide a clinical impression as to whether the patient, at the time of the evaluation, has clinical evidence of confusion, dementia, or depression and whether the patient requires antidepressant therapy, according to preset definitions in the examination guidelines. Higher scores on the behavior assessments indicate more severe disturbance than lower scores.
- The **functional assessments** include the HDFCS, the Independence scale, and a checklist of common daily tasks. For the latter items, the investigator indicates if the patient could perform the task. The checklist is summed by giving a score of 1 to all "yes" replies. The HDFCS is

reported as the total functional capacity (TFC) score. The independence scale is rated from 0 to 100, with higher scores on the function scales indicating better functioning than lower scores.

The UHDRS is to be administered at the time points specified in Table 6-1.

6.2.5. CANTAB

The CANTAB battery was developed for the assessment of cognitive deficits in humans with neurodegenerative diseases or brain damage. It consists of a series of interrelated computerized tests of memory, attention, and executive function, administered via a touch-sensitive screen (Fray and Robbins, 1996). Specifically, CANTAB tests include:

- Motor Screening Task: 2 minutes
- Reaction Time : 3 minutes
- Paired Associates Learning: 8 minutes
- One Touch Stockings of Cambridge: 10 minutes
- Spatial Span: 5 minutes
- Pattern Recognition Memory: 4 minutes

The CANTAB is to be administered at the time points specified in Table 6-1.

CANTAB Motor Screening Task (MOT):

The MOT serves as a general introduction to the CANTAB battery and provides a general assessment of whether sensorimotor deficits or lack of comprehension, will limit the collection of valid data from the participant. Coloured crosses are presented in different locations on the screen, one at a time. The participant must select the cross on the screen as quickly and accurately as possible.

CANTAB Reaction Time (RTI):

RTI provides an assessment of motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity. The participant must select and hold a button at the bottom of the screen. Circles are presented above (one for the simple mode, and five for the five-choice mode.) In each case, a yellow dot will appear in one of the circles, and the participant must react as soon as possible, releasing the button at the bottom of the screen, and selecting the circle in which the dot appeared.

CANTAB Paired Associate Learning (PAL):

During the PAL, participants are required to remember the locations of a number of different objects which are hidden inside boxes on the computer screen. This task requires the participant to learn to pair two items in memory - in this case the type of object and the location of the object. When one of the paired features is revealed (in this case the object), the participant is asked to remember its associate (the location it is hidden in). This type of learning is essential in everyday life, for example when learning new words. When you learn a new word, not only do you learn the word itself, but you have to pair this with the meaning it represents.

CANTAB Spatial Span (SS):

SS tests spatial memory span by measuring ability to memorise the order in which an increasing number of white boxes change colour. The spatial span task relies on visuospatial working memory; the component of working memory that allows you to temporarily hold and manipulate information about places. Many everyday activities involve visuospatial working memory, including finding your way around your environment, judging the position of other motorists while you are driving and searching for your keys. According to one very influential cognitive model of working memory (Badderly & Hitch, 1974) visuospatial working memory depends on a specialised sub-component of the working memory system. This is referred to as the "visuospatial sketchpad" and is thought to have a visual "cache", responsible for storing visual form and colour information, and an "inner scribe" which deals with spatial and movement information. This task places significant demands on the inner scribe.

CANTAB One Touch Stockings of Cambridge (OTS):

Executive functions are a set of cognitive skills that help us to regulate the other mental processes that are necessary to complete everyday activities. They allow us to produce complex goal directed thoughts and behaviours such as planning future events, carrying out tasks with multiple stages and overcoming habitual responses. Executive functions provide us with the ability to dynamically adjust and regulate behaviour on the basis of internal representations and external feedback. The OTS measures the executive functions of spatial planning and working memory ability. The patient is shown two displays containing three coloured balls, presented so they can be perceived as stacks of coloured balls in stockings. In each trial, the patient must imagine moving the balls in the lower display to copy the pattern shown in the upper, and calculate how many 'moves' this would take. Planning ability is indexed by the number of problems solved at the first attempt at each level of difficulty. The OTS will be used in this study to determine whether performance on the sociality experiments has any relationship to deficits in executive function in HD.

CANTAB Pattern Recognition Memory (PRM)

The PRM is a test of visual recognition memory and is linked to hippocampal function (Owen et al, 1995). In the encoding phase, participants are shown a series of abstract line drawings presented one at a time in the centre of a blank screen. They are instructed to remember the patterns. During the recognition phase, two abstract line drawings are presented on the screen, side by side and participants are asked to identify the one they have previously been shown. Visual recognition memory is indexed by the percentage of patterns correctly distinguished from novel distractors.

6.2.6. Morris Water Maze Test

The MWM test is used to assess hippocampal-dependent spatial learning and memory (Morris, 1984). A virtual-reality version of MWM test is to be administered at the time points specified in Table 6-1.

This task is a human analogue of the classic MWM task commonly used in rodent studies. Patients were told to navigate through a virtual 3-dimensional pool presented on the screen using a joystick. The goal of the test is to find and remember the location of a hidden platform, using visual cues placed on the walls. Patients have a first-person view point with a field of view comparable to the human eye.

6.2.7. Physical Examination and Vital Signs

Physical examination will include a review of all body systems and measurement of weight, per each Investigator's 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).

6.2.8. 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.

6.2.9. 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.

All samples will be analyzed locally.

Table 6-2 Clinical Laboratory Analytes

Serum Chemistry

- Albumin
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)
- Glucose
- Calcium
- Total cholesterol
- Triglycerides
- Creatinine
- Gamma-glutamyl transferase
- Lactate dehydrogenase
- Phosphate
- Potassium
- Sodium
-

Hematology

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

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).

6.2.10. 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 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.

Up to four subjects who withdraw from the study treatment and/or study for a reason prior to completing study assessments at Week 4 of the second treatment period may 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.
- Causality 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).

Causality

Each AE will be assessed as to its relationship to the investigational product, based on the following criteria. The causality assessment of an AE to the investigational product will be rated as follows by the investigator:

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 at least a reasonable possibility of a causal relationship between the AE and the investigational product. This means that there are facts (evidence) or arguments to suggest a causal relationship.

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 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 Voisin Consulting Life Sciences.

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.

Any study-related AEs that are ongoing at the Follow-up visit should be followed until resolved.

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 Voisin Consulting Life Sciences outlined below and also to the 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 Voisin Consulting Life Sciences.

SAE Reporting:

E-mail: eipsafety@voisinconsulting.com

All information about SAEs will be collected and reported via the SAE form and sent by e-mail message automatically through the eCRF or manually in case the system is down. 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 Voisin Consulting Life Sciences and the IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

If an SAE form is used, the original SAE form should be signed and 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 in 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 on the eCRF pages, 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 a 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). Further details for the planned statistical analyses will be presented in a separate statistical analysis plan to be finalized prior to the end of enrollment.

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

No formal sample size calculation was performed. A sample size of 16 subjects is considered appropriate for determination of the preliminary safety and tolerability of neflamapimod in this subject population.

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 postdose assessment on the CANTAB battery and/or MWM.

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 efficacy variables are:

- Latency during the learning phase of virtual MWM (hidden platform training) during the neflamapimod-treatment period compared to that during the placebo-administration period.
- Percent of time spent in the correct quadrant during MWM probe test during the neflamapimod-treatment period compared to that during the placebo-administration period.
- Number of overall errors in the CANTAB paired associates learning task during the neflamapimod-treatment period compared to that during the placebo-administration period.

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), European Directive 2001/20/EC, 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, 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 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 1.5 years, until the last visit of the last subject (including the follow-up visit). The planned subject participation is approximately 35 weeks, including 20 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 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, central/remote eCRF review, 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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