CLINICAL STUDY SYNOPSIS

Neflamapimod

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)

Protocol Number:	EIP19-NFD-401
Name of Test Drug:	Neflamapimod
Indication:	Huntington's Disease
Phase:	2a
Methodology:	Double-blind, placebo-controlled crossover study
IND Number:	125198
EudraCT Number:	2018-004840-51
Clinicaltrials.gov ID:	NCT03980938
Date of Report:	15 October 2021
Sponsor:	EIP Pharma, Inc. 120 St. James Avenue, Suite #6017 Boston, MA 02116 USA
Responsible Medical Officer:	John J. Alam, MD 120 St. James Avenue, Suite #6017 Boston, MA 02116, USA Telephone: +1 617-863-3751 E-mail: jalam@eippharma.com
GCP Statement:	This study was performed in accordance with Good Clinical Practices (GCP), including the archiving of essential documents.

2. SYNOPSIS

Name of Company:	Name of Finished Product:	Name of Active Ingredient:
EIP Pharma	Neflamapimod	Neflamapimod

TITLE OF STUDY:

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)

PROTOCOL NUMBER:

EIP19-NFD-401

INVESTIGATOR AND STUDY CENTER:

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PUBLICATION (REFERENCE):

None

STUDY PERIOD:

First Patient, First Visit: 31 July 2019

Last Patient, Last Visit: 15 October 2020

PHASE OF DEVELOPMENT:

2a

OBJECTIVE:

The primary objective was to evaluate the effects of administration of neflamapimod on hippocampal function, as assessed in the virtual Morris Water Maze (MWM).

The secondary objectives were to:

- Evaluate the effects of neflamapimod on the Cambridge Neuropsychological Test Automated Battery (CANTAB) paired associates learning task.
- Evaluate effects of neflamapimod on a larger battery of parameters in the CANTAB.
- Evaluate tolerability and safety of neflamapimod in subjects with HD.

METHODOLOGY:

This was a Phase 2a, single center, 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 entered the Screening phase of the study.

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

Once eligibility was confirmed and before the first dose of study drug, subjects were randomly assigned on a 1:1 basis to placebo or neflamapimod treatment during the first treatment period (i.e., 8 subjects

planned to receive neflamapimod and 8 planned to receive placebo during the first treatment period). Study center and Sponsor personnel, with the exception of those involved in study drug supply and the unblinded statistician, as well as subjects were blinded to the treatment assignment.

Dosing started on Day 1 following completion of all baseline procedures, which included virtual MWM and CANTAB tests.

During the treatment period, subjects were to 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 were to be repeated.

All subjects were to 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 were to return to the clinic and after repeating the virtual MWM and CANTAB, resume blinded treatment; all subjects who received placebo capsules during the first treatment period were to receive neflamapimod and those who received neflamapimod were to 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 were to be repeated.

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

Due to the coronavirus disease 2019 (COVID-19) pandemic all clinical research in the United Kingdom was halted in March 2020. Accordingly, any ongoing treatment was discontinued immediately and this study was interrupted at that time. At the time the study was interrupted, two subjects were in Treatment Period 1. All other subjects who remained in the study were halted either during the washout period or within 2 weeks of starting Treatment Period 2, with the exception of 1 subject who completed Treatment Period 2 remotely.

Sponsor ultimately elected to terminate the study on 15 October 2020 both due to the ongoing COVID-19 pandemic as well as new data from a completed study that indicated the dosing regimen (40 mg, twice daily) was unlikely to demonstrate efficacy.

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

A total of 16 subjects were planned to be enrolled.

A total of 15 subjects were enrolled, of whom 8 were randomly assigned to Sequence 1 (placebo/neflamapimod) and 7 were assigned to Sequence 2 (neflamapimod/placebo).

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Subjects who met all of the following inclusion criteria were eligible to participate in this study:

1. Men and women age 30 to 70 years, inclusive.
2. Willing and able to provide informed consent.
3. 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 (PAL) Total Adjusted Error Score of >16.
4. Normal or corrected eyesight and auditory abilities, sufficient to perform all aspects of the cognitive and functional assessments.

5. No history of learning difficulties that may have interfered with the subject's ability to complete the cognitive tests.

EXCLUSION:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. A profile of impairment that was 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 have compromised 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 or alanine aminotransferase >1.5 × the upper limit of normal (ULN), total bilirubin >1.5 × ULN, and/or International Normalized Ratio >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 was longer, before enrollment in this study.
11. History of previous neurosurgery to the brain.
12. Female subjects who were pregnant or breast-feeding.
13. Male subjects with female partners of child-bearing potential who were unwilling or unable to adhere to contraception requirements specified in the protocol.
14. Female subjects who had not reached menopause or have not had a hysterectomy or bilateral oophorectomy/salpingo-oophorectomy and were not willing or unable to adhere to contraceptive requirements specified in the protocol.

15. Required concomitant use of cytochrome P450 3A4 inhibitors or anti-tumor necrosis factor-alpha therapies during study participation.
16. Known allergy to any ingredient of the study drug or placebo.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Neflamapimod 40 mg capsule(s) or matching placebo capsules were administered orally, twice daily (BID) with a meal or snack in 2 treatment periods of 10 weeks each. Doses were to 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 received matched (by size and color) capsules that contain 40 mg neflamapimod or placebo, respectively.

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

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

The batch numbers of neflamapimod and placebo used in this study were M10546 and M10201, respectively.

DURATION OF STUDY:

Subjects were screened for study eligibility within 21 days before Baseline (Week 0). Subjects who were determined to be eligible were enrolled in the study and participated in two 10-week treatment periods, with each period separated by 8 to 12 weeks). After completion of the second treatment period, subjects were to attend an End-of-Treatment visit within 3 days after the last study drug dose and then a Final Study visit 2 weeks after the last study drug dose.

The duration of subject participation was up to 37 weeks.

One subject completed the study; the remaining 14 subjects had study treatment permanently discontinued in March 2020 due to the COVID-19 pandemic until the study closure by the Sponsor in October 2020. Thus, the duration of active study participation for the majority of subjects was from 4 to 27 weeks.

CRITERIA FOR EVALUATION:

The efficacy variables were:

- 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.

Safety evaluations included documentation of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), and clinical laboratory (hematology and clinical chemistry) tests.

STATISTICAL METHODS:

Data were tabulated by treatment group by study period. On-treatment data were assessed descriptively as both observed values and as changes from baseline. When tabulated, data were presented using

descriptive statistics. Most continuous data were summarized with the following descriptive statistics unless otherwise noted: number of observations, mean, standard deviation, median, minimum, and maximum; interquartile ranges were provided as appropriate. Categorical data were summarized with frequencies and percentages.

Missing data were not imputed. Statistical tests conducted were two-sided at a level of 0.05. No adjustment for multiplicity were made. Paired t-tests were used to test the difference between treatments if the target metric was normally distributed (symmetrical distributed at the minimal), otherwise, the nonparametric approach, Wilcoxon signed rank test, was used.

For many variables, both absolute and percent change from pre-treatment assessments were to be performed, if data permitted.

Data collected and captured in the case report form were included in data listings sorted by treatment, patient, study period and time point, or as appropriate.

RESULTS

Due to the COVID-19 pandemic all clinical research in the UK was halted in March 2020. The study was interrupted at that time and any ongoing treatment was discontinued immediately. At the time the study was interrupted, two subjects were in Treatment Period 1. All other subjects who remained in the study were halted either during the washout period or within 2 weeks of starting Treatment Period 2, with the exception of 1 subject who completed Treatment Period 2 remotely.

Sponsor ultimately elected to terminate the study on 15 October 2020 both due to the ongoing COVID-19 pandemic as well as new data from a completed study that indicated the dosing regimen (40 mg, twice daily) was unlikely to demonstrate efficacy.

A total of 15 subjects were enrolled, of whom 8 were randomly assigned to receive placebo in Treatment Period 1 and neflamapimod in Treatment Period 2 (Sequence 1) and 7 were assigned to receive neflamapimod in Treatment Period 1 placebo in Treatment Period 2 (Sequence 2).

Note that only 1 subject completed the study (i.e. completed both periods of the crossover), and 13 subjects completed Treatment Period 1.

Efficacy:

Efficacy results are not presented in detail within the text of this abbreviated clinical study report. However, tabular summaries and graphical presentations of efficacy data are presented in Section 14.2.

As only one subject completed both periods of the crossover, the only efficacy analyses compared outcomes in subjects receiving neflamapimod (N=7) during Treatment period 1 to those receiving placebo during that period (N=8); i.e., an inter-subject group comparison, rather than the within-subject comparison for which the study was powered. No significant (i.e., $p<0.05$) differences between neflamapimod and placebo were seen with regard to change from baseline in any component of the MWM; UHDRS; or the CANTAB components of PAL; Motor Screening Test (MOT); or Pattern Recognition Memory (PRM). Statistically significant differences between neflamapimod and placebo were seen with regard to change from baseline in the CANTAB components of the One Touch Stockings of Cambridge (OTS) ; increase in latency to correct errors in neflamapimod vs. placebo) and Spatial Span (SS; increase in forward span length in neflamapimod vs. placebo); however, the results are inconsistent, as those in the OTS reflect apparent worsening, while those in the SS reflects apparent improvement in cognitive function.

Safety:

A total of 60% (9/15) of subjects, 63% (5/8) and 57% (4/7) of subjects in Treatment Sequence 1 (placebo/neflamapimod) and Sequence 2 (neflamapimod/placebo), respectively, experienced a total of 11 TEAEs. The only TEAE reported for >1 subject was common cold (3 subjects; 20.0%). Other TEAEs reported, each in 1 subject, included abdominal pain, diarrhea, headache, nausea, sinusitis, skin sores, increased anxiety, and urinary tract infection.

All TEAEs were mild in intensity and non-serious.

Two (13%) subjects experienced a TEAE considered by the Investigator to be study drug-related, including 1 case each of abdominal pain and nausea, with both of these events occurring during placebo treatment. The case of abdominal pain, which was rated by the subject as 1/10 in severity, was ongoing at last follow-up.

Review of descriptive statistics revealed no clinically meaningful changes from baseline in any hematology or clinical chemistry parameter.

CONCLUSIONS:

Neflamapimod was well tolerated in this study in patients with HD, with no new safety signal identified.