2. STUDY SYNOPSIS

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
EIP Pharma, Inc.	Neflamapimod	Neflamapimod

Title of Study:

A Double-Blind, Placebo-Controlled Proof-of-Concept Study of a Selective p38 MAP Kinase Alpha Inhibitor, Neflamapimod, Administered for 24 Weeks in Subjects with Mild Alzheimer's Disease

Investigators and/or Study Centers:

Patients were enrolled in this study at 38 study centers in the US, United Kingdom (UK), the Netherlands, Denmark, and the Czech Republic; Investigators and study centers are identified in Section 6.

Publication (reference):

None.

Studied Period:	**Phase of development:**
22 February 2018 to 17 June 2019 (Date of first patient randomization to date of last patient visit)	Phase 2

Objectives:

The primary objective of this study was:

- To evaluate the effect of administration of neflamapimod (VX-745) for 24-weeks on immediate and delayed recall aspects of episodic memory, as assessed by the Hopkins Verbal Learning Test – Revised (HVLT-R) in subjects with mild Alzheimer's disease (AD).

The secondary objectives of this study were:

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

Methodology:

Study EIP-VX17-745-304 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-concept study of neflamapimod 40 mg or matching placebo administered twice daily for 24 weeks in subjects aged 55 to 85 years with CSF biomarker-confirmed AD; with global CDR score of

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EIP Pharma, Inc.	Neflamapimod	Neflamapimod

0.5 or 1.0, with CDR memory sub-score of at least 0.5, and MMSE scores between 20 and 28, inclusive.

Following completion of informed consent procedures, subjects entered a Screening phase of the study. Two screening visits were planned to allow most screening procedures to be completed and reviewed during the first visit before lumbar puncture to collect CSF to be performed on Screening Visit 2. All screening assessments were to be conducted within 42 days of Day 1 (first dose of study drug).

After eligibility was confirmed and before the first dose of study drug, subjects were randomly assigned to receive neflamapimod or placebo.

Dosing started on Day 1, following completion of all Baseline procedures. During the treatment period, subjects attended study center visits on Days 21, 42, 84, 126, and 168. Telephone contacts were conducted to determine subject status and assess compliance between Days 42 and 84 (Visits 5 and 6); Days 84 to 126 (Visits 6 and 7); and Days 126 and 168 (Visits 7 and 8).

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

Subjects who prematurely discontinued study drug for any reason were asked to return to the clinical site for an Early Termination visit within 3 days following the last study drug dose; if it was determined that the subject was to discontinue study drug while at the study center for a scheduled visit, then the Early Termination visit was to be conducted at that time. These subjects were asked to return to the clinical site for a Follow-up Visit 14 (±3) days following the last study drug dose. Every effort was made to ensure a subject returned for this visit.

Number of Subjects (Planned and Analyzed):

Approximately 152 subjects (76 subjects per dose group) were planned to be enrolled.

A total of 161 subjects were randomized, 83 to the placebo group and 78 to the neflamapimod 40 mg twice daily (BID) group.

Diagnosis and Main Criteria for Inclusion:

Subjects aged 55 to 85 years with CSF biomarker confirmed AD, with a CDR global score of 0.5 or 1.0, a CDR memory subscore of at least 0.5, and MMSE scores between 20 and 28, inclusive, were planned to be enrolled.

Test Product, Dose and Mode of Administration, Batch Number(s):

Neflamapimod is a highly selective, blood-brain-barrier penetrant inhibitor of p38 mitogen-activated protein kinase (MAPK), an intracellular protein kinase involved in transducing extracellular signals (e.g., stress) into a cellular response (e.g., inflammation).

Neflamapimod was supplied as opaque, capsule containing 40 mg of neflamapimod. In addition to 40 mg of neflamapimod, each capsule contained 339 mg of lactose monohydrate, 14.01 mg of

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carmellose sodium, 2.1 mg of magnesium stearate and 18.33 mg of povidone K30.

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

Subjects assigned to neflamapimod received neflamapimod 40 mg capsule(s) orally, BID with a meal or snack for 24 weeks. Doses were 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.

The batch number of neflamapimod used in this study was M10200.

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

Subjects assigned to placebo received placebo capsules orally, BID with a meal or snack for 24 weeks. Doses were 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.

The batch number of placebo used in this study was M10201.

Duration of Treatment:

Subjects received neflamapimod or matching placebo for 24 weeks.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the combined change in Z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients. The secondary efficacy variables were change from Baseline to Week 24 in recall and recognition of the WMS, CDR-SB, MMSE, and CSF biomarkers (total tau, p-tau$_{181}$, Aβ_{1-40}, Aβ_{1-42}, neurogranin, neurofilament light chains) comparing neflamapimod-treated subjects with placebo-recipients.

Pharmacokinetics, Genotyping, and Apolipoprotein E Testing:

On Day 21, the morning dose of the study drug was administered with a meal or snack at the study center, and blood samples were collected for pharmacokinetics (PK) (drug concentration) testing immediately prior to and 2.5 hours after study drug administration (i.e., at predicted time point for peak drug concentration after dose administration). Blood samples also were collected for PK on Day 42 and Day 84. Subjects were to take their morning dose of study drug at home with a meal or snack on Day 42 and 84 on their regular schedule and record the time of their morning dose.

A blood sample was collected from all subjects at Visit 3 (Day 1) for CYP2C19 genotyping; such testing was mandatory. An aliquot of blood from this sample may also have been used for measurement of apolipoprotein E4 (apoE4); such testing was optional.

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
EIP Pharma, Inc.	Neflamapimod	Neflamapimod

Safety:

Safety assessments included documentation of adverse events (AEs), including serious adverse events (SAEs), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests (hematology, clinical chemistry, and coagulation studies).

Statistical Methods:

All data listings, summaries, figures, and statistical analyses were generated using SAS version 9.4. Summaries were presented by treatment group or overall.

Continuous variables were summarized by the number of non-missing observations, mean, median, standard deviation, and minimum and maximum. For all tabulations of changes from baseline data, the lower and upper 95% confidence limits for the mean for the individual treatments were given. Categorical variables were summarized by presenting the frequency and percent. Percentages were based on the number of non-missing observations or the subject population unless otherwise specified. For each variable, all categories were shown. Zero frequencies (but not the percent) within a category were presented.

All efficacy analyses were based on the Evaluable Efficacy Population by randomized treatment regardless of the treatment actually received. Descriptive statistics by treatment group and visit were reported for all efficacy endpoints. All statistical tests were performed using a two-tailed 5% overall significance level, unless otherwise stated. All comparisons between treatments were reported with 95% confidence intervals for the difference.

The primary efficacy endpoint was the combined change in Z-scores of total recall and delayed recall on the HVLT-R in neflamapimod-treated subjects compared to placebo-recipients at Week 24. The primary endpoint was analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD-specific therapy (cholinesterase inhibitor or memantine versus no cholinesterase inhibitor or memantine), CDR-Global Score of 0.5 versus 1.0, scheduled visit (nominal) and scheduled visit by treatment interaction, random effect for subject and baseline Z-score as a covariate. Least-square means (LSM) and 2-sided 95% confidence intervals (CI) were provided for treatment group differences and estimated endpoint values by visit.

The normally-distributed assumption for the combined change in Z-scores of total recall and delayed recall on the HVLT-R were examined (at 0.05 alpha level). In case the assumption was violated, rank transformed data were applied to the MMRM model. Ranks were determined separately within each time point, based on observed data only.

Trough and maximum concentrations (C_{Trough} and C_{max}, respectively) were evaluated on Day 21 (i.e., at steady-state) for each subject. In addition, area under the time concentration curve (AUC) was derived utilizing population PK methods utilizing drug concentration data from Day 21 as well the sparse sampling on Days 42 and 84. In addition, a PK/pharmacodynamic (PD) model for neflamapimod and

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
EIP Pharma, Inc.	Neflamapimod	Neflamapimod

effects on HVLT-R, WMS, CDR-SB, and/or CSF biomarkers was developed *post hoc* based on the available data.

The incidence of treatment-emergent adverse events (AE) and serious adverse events (SAEs) the causal relationship between an AE/SAE and study drug and severity were tabulated by treatment group. Individual clinically-significant changes in clinical laboratory and electrocardiogram (ECG) parameters were listed along with median and mean and standard deviation by treatment group.

Summary and Conclusions:

Patient Characteristics at Study Entry:

A total of 161 subjects were randomized, 83 to the placebo group and 78 to the neflamapimod 40 mg BID group. Overall, the proportion of males and females was the same (each 50%). The mean age of subjects was 72 (±6.8) years, with range of 56 to 85 years. Most subjects were white (156 subjects; 97%). No significant differences were seen between treatment groups with regard to age, sex, or race. Most (138 subjects; 86%) had a high school diploma or equivalent or higher level of education.

The median duration from AD diagnosis to screening was 2.7 years (range -0.1 to 19.4 years). Overall, 97 (60%) of subjects were receiving AD treatment, with most (80 subjects; 82.4% of the 97 subjects receiving AD treatment) receiving a cholinesterase inhibitor. The duration of AD treatment to Screening was 471 days (1.3 years) (range 32 to 6017 days [16.4 years]).

Mean (±SD) CDR Global Score was 0.61 (±0.209); 125 (78%) subjects had a score of 0.5 (very mild dementia), and 36 (22%) had a score of 1 (mild dementia). Mean (±SD) MMSE score was 23.8 (±2.48) (mild impairment).

Mean (±SD) baseline CSF $A\beta_{1-42}$ was 563.9 (166.636).

One hundred fifty-five subjects had apoE results at baseline. Among these 155 subjects, based on apoE4 (rs429358), 48% (75/155) of subjects were of at least higher than normal risk (T/T or C/C), with 52% (80/155) being of lower risk. Based on apoE4 (rs7412), 95% (147/155) of subjects were of higher than normal risk, with 5% (8/155) being of lower risk. Among the 155 subjects with data, 21% (33/155) were apoE ε4/ε4 homozygotes and 52% (80/155) were ε4 heterozygotes.

Summary of Efficacy:

The primary endpoint was not met, with no significant difference from placebo with regard to change from Baseline to Week 24 in the combined Z-scores of total recall and delayed recall on the HVLT-R. Similarly, no significant difference from placebo was seen over this same time period with regard to secondary efficacy measures, including the WMS immediate and delayed recall composite scores, CDR-SB scores, or MMSE scores.

Significant improvement in the disease biomarkers CSF T-tau (p=0.031) and CSF P-tau_{181} (p=0.012)

Name of Company:	**Name of Finished Product:**	**Name of Active Ingredient:**
EIP Pharma, Inc.	Neflamapimod	Neflamapimod

were seen over the 24-week neflamapimod treatment period relative to placebo. Furthermore, a strong trend (p=0.068) towards improvement relative to placebo administration also was seen in CSF neurogranin levels in neflamapimod recipients.

Summary of Pharmacokinetics:

Pre-specified analysis of efficacy measures by C_{trough} neflamapimod levels on Day 21, with subjects separated into those with high C_{trough} levels (>75% percentile; >5.4 ng/mL) versus those with low levels (≤75% percentile; ≤5.4 ng/mL) revealed improvement from baseline in episodic memory measures (HVLT-R Total and Delayed Recall; and WMS Immediate and Delayed Recall) in those with high neflamapimod C_{trough} levels.

As was the case in the analysis for neflamapimod versus placebo overall, decreases (i.e., improvement) in T-tau and P-tau$_{181}$ were seen among neflamapimod-treated subjects regardless of C_{trough} levels on Day 21 whereas increases were seen among placebo-treated subjects.

In addition, a significant difference among those with low C_{trough} levels, those with high C_{trough} levels, and placebo was seen with regard to change from baseline to Week 24 in Aβ_{1-42}, with a greater decrease seen in subjects with high C_{trough} levels on Day 21 versus those with low C_{trough} levels and an increase seen in those treated with placebo.

Summary of Safety:

Overall, neflamapimod was well tolerated in this study, with a safety profile generally similar to that of placebo. No new safety signals with neflamapimod were identified. The only treatment-emergent adverse events (TEAEs) occurring at an incidence ≥5% in the neflamapimod group, with the corresponding incidence in the placebo group, were fall (6% and 4%); headache (6% and 4%); diarrhea (5% and 2%); and upper respiratory tract infection (5% and 8%). Most TEAEs were mild or moderate in intensity. No on-study deaths were reported. Furthermore, a low incidence of SAEs was seen in the neflamapimod group, with a low and similar incidence in the placebo group (3% and 4%, respectively), with no SAE considered to be neflamapimod-related. Similarly, a TEAE led to study drug discontinuation for a small proportion of subjects in each the neflamapimod and placebo groups (3% and 2%, respectively). No particular TEAE led to study drug discontinuation for >1 subject.

Review of change from baseline in hematology, clinical chemistry, vital sign, and ECG parameters showed that changes from baseline were generally small and similar in the neflamapimod and placebo groups. One neflamapimod-treated subject had aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) elevations >3×the upper limit of normal (ULN), which started to resolve within 1 week after cessation of treatment. The incidence (one of 78 subjects, <2%) of AST/ALT elevation to >3×ULN is substantially less than the 15% incidence of AST/ALT elevation to >3×ULN seen in a prior study of neflamapimod (Study VX00-745-102) in which the drug had been administered at a dose of 250 mg twice daily for 3 months to subjects with rheumatoid arthritis; suggesting a dose-dependency of

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EIP Pharma, Inc.	Neflamapimod	Neflamapimod
the effect of neflamapimod on liver enzyme levels.		
Conclusions: The CSF biomarker effects of neflamapimod demonstrate (1) target engagement and (2) p38α inhibition impacts the AD disease process (i.e., provides proof-of-mechanism). The CSF biomarker effects, combined with the episodic memory effects in patients with the highest blood concentrations of neflamapimod, indicate that a study of longer duration and at a higher dose of neflamapimod in patients with early-stage AD is merited and has the potential to demonstrate proof-of-concept.		
Date of the Report: 27 January 2020		