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 16-Week Study of the Cognitive Effects of the Oral P38 Alpha Kinase Inhibitor Neflamapimod in Dementia with Lewy Bodies (DLB)

Investigators and/or Study Centers:

Patients were enrolled in this study at 24 study centers in the United States and the Netherlands; Investigators and study centers are identified in Section 6.

Publication (reference):

Alam JJ, Gomperts SN, Dautzenberg P, Lemstra AW, Arnold SE, Prins N, et al. The p38α kinase inhibitor neflamapimod significantly improves cognition in patients with mild-to-moderate dementia with Lewy bodies (DLB) (Digital Presentation LB22). Presented at CTAD (Clinical Trials on Alzheimer's Disease) Digital Conference, 07 November, 2020.

Studied Period:	**Phase of development:**
30 September 2019 to 14 July 2020 (Date of first patient randomization to date of last patient visit)	Phase 2

Objectives:

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

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

The secondary objectives of this study were to:

- Evaluate the effects of neflamapimod on informant/caretaker evaluation of cognition and function, as assessed by the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).
- Assess the effects of neflamapimod on general cognition, as assessed by the Mini Mental State Examination (MMSE).

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- Assess the effects of neflamapimod on episodic memory, as assessed by the International Shopping List Test (ISLT).
- Assess the effects of neflamapimod on select domains of the 10-item Neuropsychiatric Inventory (NPI-10), including depression (dysphoria), anxiety, hallucinations, and agitation/aggression.
- Evaluate the effects of neflamapimod on motor function as assessed by the Timed Up and Go Test (TUG).
- Evaluate the effects of neflamapimod on quantitative electroencephalography (EEG) parameters.

Methodology:

Study EIP19-NFD-501 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, proof-of-principle study of neflamapimod 40 mg or matching placebo administered twice daily (BID) or three times daily (TID) depending on weight, with subjects weighing <80 kg receiving capsules BID and those weighing ≥80 kg receiving capsules TID. Dosing occurred for 16 weeks in subjects aged ≥55 years with mild-to-moderate (MMSE 15-28) probable DLB by consensus criteria including a positive DaTscan™, who were concurrently receiving cholinesterase inhibitor therapy. If the DaTscan was negative, but the subject had historical polysomnography (PSG)-verified REM sleep behavioral disorder (RBD), this also qualified as probable DLB.

Following completion of informed consent procedures, subjects entered the Screening phase of the study. One to two Screening visits were planned, during which safety screening measures were undertaken, practice NTBs were performed, and the required diagnosis and cognitive impairment was confirmed. All screening assessments were to be conducted within 21 days of Day 1 (first dose of study drug), the extension to 35 days was allowed if a DaTscan™ was required to determine study eligibility.

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 14, 28, 56, 84, and 112. Due to the COVID-19 global pandemic, some of these visits were permitted to be held remotely due to local restrictions to travel and in-clinic visits. Furthermore, visits, including the Week 16 visit, may have been conducted outside the protocol-specified visit windows.

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

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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):

A total of 80 subjects were planned to be enrolled.

A total of 91 subjects were randomized (i.e., enrolled) and assigned to either placebo (45 subjects; 18 to the BID regimen and 27 to the TID regimen) or to neflamapimod (46 subjects; 26 to the BID regimen and 20 to the TID regimen).

Diagnosis and Main Criteria for Inclusion:

Men and women aged ≥55 years with probable DLB and identified cognitive deficits, according to current consensus criteria, specifically one core clinical feature and a positive DaTscan; an MMSE score of 15-28, inclusive; and who were receiving cholinesterase inhibitor therapy (having received such therapy for greater than 3 months and on a stable dose for at least 6 weeks at the time of randomization) during Screening were eligible. (If the subject had a negative DaTscan, but had historical PSG-verified RBD, the subject would have qualified.)

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 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) for BID and 24 capsules for TID (i.e., 1-week supply of study, with three extra capsules). The blister cards were kitted, with 2 blister cards per kit.

The batch number of neflamapimod used in this study was M10546.

Subjects assigned to neflamapimod received 40 mg capsule orally, BID or TID with food for 16 weeks. Subjects followed the BID regimen if weighing <80 kg or the TID regimen if weighing ≥80 kg. Doses were taken within 30 minutes following a meal or snack (i.e., morning, mid-day (TID only), and evening meals) at least 3 hours apart and at approximately the same times each day throughout the study.

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

Subjects assigned to placebo received placebo capsules orally, BID or TID with a meal or snack for 16 weeks. Doses were taken within 30 minutes following a meal or snack (i.e., morning, mid-day (TID only), and evening meals) at least 3 hours apart and at approximately the same times each day throughout the study.

Duration of Treatment:

Subjects received neflamapimod or matching placebo for 16 weeks.

Criteria for Evaluation:

Efficacy:

Clinical and biomarker assessments included the NTB comprised of the DET; IDN; OCL; ONB, Letter Fluency Test, and CFT; Columbia-Suicide Severity Rating Scale (C-SSRS); quantitative electroencephalography (qEEG); CDR-SB; MMSE; ISLT; NPI-10; and TUG.

Pharmacokinetics:

Sparse blood samples for PK (drug concentration) were scheduled to be collected at Days 14, 28, and 56; the actual sample collection time on the designated visit days was per study center / subject convenience. The actual sample collection date and time relative to the most recent study drug dose was documented.

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 S-PLUS (Version 8.2), R (Version 3.6.3 or higher) or SAS (Version 9.3 or higher).

The data were presented in standard individual subject data listings. The listings included subject identification number, demographics, and treatment. In data summaries, descriptive statistics (n, arithmetic mean, standard deviation [SD], median, lower and upper quartiles, minimum and maximum values) were presented for continuous variables. Counts and percentages were presented for categorical variables.

Data were tabulated by treatment group by study period, with data listings provided for all data captured in the electronic case report form (eCRF), including laboratory data. On-treatment data was 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

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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.

The original intent in the protocol was to evaluate the effect of neflamapimod treatment on the efficacy endpoints as one dose group. However, during the course of this study, the results of the Phase 2b study in Alzheimer's disease (EIP-VX17-745-304) indicated that a 40mg BID dose regimen of neflamapimod was unlikely to be efficacious. As a result, the analytic approach taken in the current study was to consider that there were 4 treatment groups within the study: placebo BID, placebo TID, neflamapimod BID and neflamapimod TID.

The primary endpoint was a study specific NTB (Attentional/Executive/Visuospatial Composite) score, which consisted of the DET, IDN, OCL, ONB accuracy, CFT and LFT. The primary efficacy analysis used a Mixed Model for Repeated Measures (MMRM) analysis method with change from baseline of Attentional/Executive/Visuospatial Composite as the dependent variable. There was a fixed effect on treatment that may have been extended to other covariates (i.e. baseline composite score, study visit, patient characteristics). The interaction term (i.e., scheduled visit by treatment) was considered. The random effect factor was subject.

Due to the various scales among different tests and the need to have equal weights for deriving composite score metrics. Performance on each the tests were standardized relative to baseline data from all randomized subjects (i.e., the score was converted to a z-score by subtracting the study sample's mean at baseline from the score and dividing by the standard deviation (SD) of the study sample's baseline).

The primary endpoint composite z-score was calculated as the average of the z-scores from the component of the six individual tests in the composite (DET, IDN, OCL, ONB accuracy, CFT and LFT). For any given subject and timepoint, 4 of the 6 tests had to have been successfully completed to have a composite z-score calculated and included for that datapoint in the analysis.

For the purposes of facilitating further understanding of the drug effects two exploratory composite endpoints that were made up of the tests in NTB were calculated and evaluated: an Attention Composite that consisted of the DET and IDN tests, and the other an Executive Function composite consisting of ONB, CFT and LFT tests.

The primary efficacy analysis used a Mixed Model for Repeated Measures (MMRM) analysis method with change from baseline of Attentional/Executive/Visuospatial Composite as the dependent variable. There was a fixed effect on treatment that may have been extended to other covariates (i.e. baseline composite score, study visit, patient characteristics). The interaction term (i.e., scheduled visit by treatment) was considered. The random effect factor was subject.

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The COVID-19 pandemic had an impact on data collection in this study. For the primary endpoint, a total of 15 subjects either did not have an on-treatment NTB assessment or did not have a primary composite score during the treatment period due to incomplete primary endpoint data. In order to evaluate the impact of patients who completed treatment but did not have a NTB assessment at one or more timepoints, in secondary sensitivity analyses, imputation technique was used in the mITT efficacy population to accommodate deviations occurring due to COVID-19 illness and/or COVID-19 control measures. The first was an analysis of covariance analysis and the second was a trend analysis at for placebo vs. BID patients vs. TID patients using the Jonckere-Terpstra (J-T) test. Single and multiple imputation approaches were used (i.e., the last observation was carried forward (LOCF)).

The analyses results following the imputation approaches were summarized to assess sensitivity of the estimates of treatment effect.

Descriptive statistics of the observed values and change from baseline were presented by treatment group and visit.

Disposition and Demographics:

A total of 91 subjects were randomized (i.e., enrolled) and assigned to either placebo (45 subjects; 18 to the BID regimen and 27 to the TID regimen) or to neflamapimod (46 subjects; 26 to the BID regimen and 20 to the TID regimen). Of the 91 subjects enrolled, all 91 received at least 1 dose of study drug and were accordingly included in the Safety population. A total of 81 of 91 subjects completed 16 weeks on study. For the primary endpoint, 76 patients completed at least 1 post-baseline NTB evaluation and were accordingly included in the prospectively-defined efficacy (i.e., modified intent-to-treat) population.

Consistent with more than two-thirds of individuals with DLB being male, the study predominantly enrolled male subjects. In terms of disease characteristics, the lower weight subjects who were dosed BID had more slightly advanced disease with a numerically higher mean CDR scores, and lower MMSE and lower ISLT. Importantly, within the BID groups or the TID groups the subjects were well balanced in terms of these characteristics in placebo versus neflamapimod recipients.

Summary of Efficacy:

This study demonstrated a positive treatment effect on the primary endpoint in patients receiving 40 mg neflamapimod TID, with significant, clinically-relevant effect size improvements in cognition in the subjects receiving 40 mg neflamapimod TID compared to those receiving either placebo or neflamapimod BID, as assessed using an NTB composed of 6 specific cognitive tests designed to assess attention, executive function, and visuospatial function. In the primary analysis, treatment with neflamapimod TID was a statistically significant positive factor (p=0.015), associated with a mean increase (i.e., improvement) of 0.20950 (95% CI 0.0411, 0.3779) in the primary composite z-score versus the other groups in the study, with an effect size (Cohen's D) of 0.52. Baseline primary composite score was another important covariate. The positive effect on the NTB was evident at Week 4 and

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maintained throughout the 16-week study period. In a secondary analysis in which missing data were imputed utilizing last-observation-carried forward (LOCF), neflamapimod TID was also associated with statistically significant improvement (p=0.009) relative to the three other groups (placebo BID, placebo TID, neflamapimod TID) and an effect size of 0.60.

Multiple sensitivity analyses (with or without imputation of any missing data by LOCF) support the primary analysis, as they also demonstrated significantly improved outcome on the NTB in (1) the comparison of neflamapimod TID subjects compared to all placebo subjects (i.e., combined placebo BID and placebo TID) and (2) the comparison neflamapimod TID subjects compared to placebo TID subjects. The effect size in these analyses ranged from 0.47 to 0.56.

In addition, the Jonckeere-Tersptra (J-T) test was used to explore any upward dose-dependent trend in the change from baseline in the primary composite at each visit for placebo versus neflamapimod BID versus neflamapimod TID; an analysis in which there was a statistically significant positive effect observed at Week 4 (p = 0.041, J-T test).

Analyses of secondary endpoints (TUG, NPI-10, CDR-SB) were supportive and suggested that the effect of neflamapimod administered TID on cognition leads to a clinically meaningful impact on function.

- With regard to the TUG, Linear Mixed Effects (LME) analysis of the on-treatment results demonstrated significant improvement in neflamapimod TID recipients compared to all placebo recipients (p=0.03, effect size = 0.50). From Baseline to Week 16, the mean time required to complete the tests decreased (i.e., improved) by 1.4 (±1.0) seconds in the neflamapimod TID group and increased (i.e., worsened) by 1.5 (±0.9) seconds amongst placebo recipients. In addition, at Week 16, improvement in TUG scores in neflamapimod TID > neflamapimod BID > placebo was evident (p< 0.1, J-T test).
- With regard to the NPI-10, on-treatment results demonstrated favorable trends in neflamapimod TID recipients with improvement (reduction in score) compared to placebo recipients, with numerically greater mean improvement from baseline at each study visit in the neflamapimod recipients. However, differences between treatment groups were not statistically significant. Within the NPI sub-categories, hallucination scores were reported on at least one occasion in 36 patients. Within that group, an improvement on hallucination severity was seen in neflamapimod TID versus neflamapimod BID and placebo; J-T statistic improvement in neflamapimod TID > neflamapimod BID > placebo, p< 0.1 at each of Week 4, 8 and 16).
- With regard to the CDR-SB, J-T trend analysis of improvement in neflamapimod TID > neflamapimod BID > placebo demonstrated positive trends at both Week 8 (p=0.07) and Week 16 (p=0.19). CDR-SB is a test that best measures differences in progression of the disease. In this 16-week study, patients in the placebo group did not measurably progress. When restricted to CDR-SB assessments conducted onsite, the J-T trend analysis of improvement in

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neflamapimod TID > neflamapimod BID > placebo demonstrated more robust trends at both Week 8 (p=0.04) and Week 16 (p=0.12). The improvement relative to placebo in CDR-SB scores with neflamapimod treatment were driven mostly by differences in the functional domains, particularly Community Affairs (J-T p-value = 0.067) and Personal Care, both at Week 8. Minor trends were also noted in the LME/MMRM analysis favoring NFMD TID compared to either combined placebo (p=0.18) or placebo TID (p=0.08).

Due to the impact of COVID-19 restrictions, a very limited number of subjects had both a baseline and Week 16 EEG assessments and as a result no inference could be made regarding effects of neflamapimod treatment on EEG parameters.

Summary of Pharmacokinetics:

Due to the nature of PK study design (i.e., sparse sampling), the steady state concentration (Css) was derived for each subject by calculating the median of all available concentrations for that subject. Including all subjects, the neflamapimod TID group (median Css=9.15) had a 27.4% higher median Css than the neflamapimod BID group (median Css=7.18). The differences were greater in the mITT population for the primary endpoint, where the median Css was 10.2 ng/mL in the neflamapimod TID group and 6.76 ng/mL in the neflamapimod BID group.

Summary of Safety:

Overall, neflamapimod was well tolerated in this study. The incidence of TEAEs was similar among neflamapimod- and placebo-treated patients, with 67% (31/46) and 69% (31/45) of patients in each group reporting at least 1 TEAE. Review of the incidence of TEAEs by regimen revealed a higher incidence with the TID versus BID regimen in the neflamapimod group (75% [15/20] versus 62% [16/26], respectively); the incidence of TEAEs with the TID and BID regimens were more similar in the placebo group (70% [19/27] versus 67% [12/18]).

The only TEAEs occurring at an incidence >5% among either neflamapimod- or placebo-treated patients were fall (13% [6/46] versus 9% [4/45]); headache (9% [4/46] versus 4% [2/45]); diarrhea (7% [3/46] versus 11% [5/45]); nausea (7% [3/46] versus 7% [3/45]); and tremor (0% versus 7% [3/45]). When evaluated by dose regimen among neflamapimod-treated patients, the incidence (3 of 20, 15% for each) of diarrhea and headache were higher among those who received neflamapimod TID than those who received neflamapimod BID (0 of 26, 0% for diarrhea; 1 of 26, 3%) whereas the incidence of fall was higher among those who received neflamapimod BID (5/26, 19%) than among those who received neflamapimod TID (1/20, 5%).

Most individual TEAEs (preferred terms) that were considered by the Investigator to be at least possibly related to study drug were experienced by 1 patient only. The only treatment-related TEAEs reported for >1 neflamapimod-treated patient, with the corresponding incidence among placebo-treated patients, were nausea (4% [2/46] versus 2% [1/45]) and headache (9% [4/46] versus 2% [1/45]).

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Two placebo-treated patients experienced a TEAE with an outcome of death. No TEAEs with an outcome of death were reported among neflamapimod-treated patients. Overall, 4 subjects, 3 in the neflamapimod group (of whom all received neflamapimod BID) and 1 in the placebo group, were withdrawn because of a non-fatal TEAE. Among neflamapimod-treated subjects, the TEAE leading to withdrawal was considered by the Investigator to be study drug-related for 1 subject (somnolence) in the neflamapimod BID group; for the remaining 2 subjects, the event was considered unrelated.

Seven patients overall, 3 (7%) of 46 neflamapimod-treated patients and 4 (9%) of 45 placebo-treated patients, experienced an SAE. All SAEs were considered by the Investigator to be unrelated to study drug.

Hematology, clinical chemistry, vital sign, and ECG parameters showed that changes from baseline were generally small and similar in the neflamapimod and placebo groups.

No neflamapimod-treated subjects had aspartate aminotransferase and alanine aminotransferase elevations >3×the upper limit of normal.

Conclusions:

This study demonstrated a treatment effect on the primary endpoint at a dose level of 40 mg TID, with significant, clinically relevant effect size improvements in cognition in subjects receiving 40 mg neflamapimod TID compared to those receiving either placebo or neflamapimod BID, as assessed using an NTB composed of 6 specific cognitive tests) designed to assess attention, executive function, and visuospatial function. The positive effect on the NTB was evident at Week 4 and maintained throughout the 16-week study period. Multiple sensitivity analyses (with or without imputation of any missing data by LOCF) support the primary analysis, as they also demonstrated significantly improved outcome on the NTB in (1) the comparison of neflamapimod TID subjects compared to all placebo subjects (i.e., combined placebo BID and placebo TID) and (2) the comparison neflamapimod TID subjects compared to placebo TID subjects. Analyses of secondary endpoints (Timed Up and Go Test, NPI-10, CDR-SB) are supportive and suggest that the effect of neflamapimod administered TID on cognition leads to a clinically meaningful impact on function.

Neflamapimod was very well tolerated and no new safety signals were identified.

The combined efficacy and safety results support progressing neflamapimod to confirmatory clinical studies as a treatment for patients with DLB to improve cognition.

Date of the Report: 26 February 2021