# EU Clinical Trials Register

## Clinical trial results:
## 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

### Summary

| EudraCT number | 2017-004388-11 |
|---|---|
| Trial protocol | GB DK NL CZ |
| Global end of trial date | 17 July 2019 |

### Results information

| Result version number | v1 (current) |
|---|---|
| This version publication date | 24 July 2020 |
| First version publication date | 24 July 2020 |
| Summary attachment (see zip file) | EIP-VX17-745-304 Synopsis (EIP-VX17-745-304 Synopsis_Final_2020 Jan 27.pdf) |

### Trial information

#### Trial identification

| Sponsor protocol code | EIP-VX17-745-304 |
|---|---|

#### Additional study identifiers

| ISRCTN number | - |
|---|---|
| ClinicalTrials.gov id (NCT number) | NCT03402659 |
| WHO universal trial number (UTN) | - |

Notes:

#### Sponsors

| Sponsor organisation name | EIP Pharma |
|---|---|
| Sponsor organisation address | 120 St James Ave, The Yard, Suite 6017, Boston, United States, 02116 |
| Public contact | Project Management, Worldwide Clinical Trials Limited, +44 1159567711, |
| Scientific contact | Project Management, Worldwide Clinical Trials Limited, +44 1159567711, |
| Sponsor organisation name | EIP Pharma |
| Sponsor organisation address | 120 St James Ave, The Yard, Suite 6017, Boston, United States, 02116 |
| Public contact | Jennifer Conway, Clinical Development , EIP Pharma 120 St James Ave, The Yard, Suite 6017 Boston, MA 02116, jconway@eippharma.com |
| Scientific contact | John Alam, MD CEO and Founder, EIP Pharma 120 St James Ave, The Yard, Suite 6017 Boston, MA 02116, 617 744-4400, jalam@eippharma.com |

Notes:

#### Paediatric regulatory details

| Is trial part of an agreed paediatric | No |
|---|---|

| investigation plan (PIP) | |
|---|---|
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| Analysis stage | Final |
|---|---|
| Date of interim/final analysis | 17 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 July 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

No trial-related activities were performed until the subject had been consented and given an opportunity to ask questions and discuss the study with family/caregiver. Numbing agents were used, as necessary, for the lumbar puncture/CSF draw. Phone calls were implemented between visits that were 6 weeks apart to check in with the subject.

Background therapy: -

Evidence for comparator: -

| Actual start date of recruitment | 22 December 2017 |
|---|---|
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

## Subjects enrolled per country

| Country: Number of subjects enrolled | Netherlands: 20 |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 52 |
| Country: Number of subjects enrolled | Czech Republic: 9 |
| Country: Number of subjects enrolled | Denmark: 7 |
| Country: Number of subjects enrolled | United States: 73 |
| Worldwide total number of subjects | 161 |
| EEA total number of subjects | 88 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 23 |
| From 65 to 84 years | 136 |
| 85 years and over | 2 |

# Subject disposition

## Recruitment

Recruitment details:

Recruitment Period:  22 December 2017 to 11 January 2019
Participating countries:  United States, United Kingdom, Netherlands, Czech Republic, Denmark

## Pre-assignment

Screening details:

477 subjects were screened, of which 13 were re-screened.
316 subjects were determined ineligible for the study.  119 subjects did not meet CSF criteria, 79 subjects did not meet MMSE criteria, 44 subjects were unable to provide consent, 40 subjects withdrew consent, 34 were for other exclusionary reasons.

## Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

All subjects, caregivers, site staff, CRO staff (e.g. monitors, PMs, regulatory, data management) and sponsor staff were blinded to the treatment assignment until after database lock.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Placebo Arm |

Arm description:

Arm of trial including the 83 subjects that were randomly assigned (1:1) to take placebo

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Matching Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received neflamapimod matching 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.

| | |
|---|---|
| **Arm title** | Neflamapimod Arm |

Arm description:

Arm of trial including the 78 subjects that were randomly assigned (1:1) to take neflamapimod (active study drug).

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | neflamapimod |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received neflamapimod 40 mg 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.

| Number of subjects in period 1 | Placebo Arm | Neflamapimod Arm |
|---|---|---|
| Started | 83 | 78 |
| Completed | 78 | 73 |
| Not completed | 5 | 5 |
|    Consent withdrawn by subject | 3 | 3 |
|    Adverse event, non-fatal | 2 | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 161 | 161 | |
| Age categorical | | | |
| 161 subjects were enrolled between the ages of 56-85 years at Screening | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 23 | 23 | |
| From 65-84 years | 136 | 136 | |
| 85 years and over | 2 | 2 | |
| Age continuous | | | |
| 161 subjects were enrolled between the ages of 56-85 years at Screening | | | |
| Units: years | | | |
| arithmetic mean | 71.8 | | |
| standard deviation | ± 6.84 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 80 | 80 | |
| Male | 81 | 81 | |

## End points

### End points reporting groups

| Reporting group title | Placebo Arm |
|---|---|
| Reporting group description: | |
| Arm of trial including the 83 subjects that were randomly assigned (1:1) to take placebo | |
| Reporting group title | Neflamapimod Arm |
| Reporting group description: | |
| Arm of trial including the 78 subjects that were randomly assigned (1:1) to take neflamapimod (active study drug). | |

### Primary: HVLT-R

| End point title | HVLT-R |
|---|---|
| End point description: | |
| Combined change in z-scores of total recall and delayed recall on the HVLT-R (Hopkins Verbal Learning Test - Revised) in neflamapimod-treated subjects compared to placebo-recipients. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline (Day 1) to End of Treatment (Week 24) | |

| End point values | Placebo Arm | Neflamapimod Arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72 | 71 | | |
| Units: Z-score | 72 | 71 | | |

| Attachments (see zip file) | MMRM Change from Baseline (HVLT-R)/Table_14_02_03_03.rtf |
|---|---|

### Statistical analyses

| Statistical analysis title | MMRM Analysis - HVLT-R |
|---|---|
| Statistical analysis description: | |
| The primary endpoint was analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD-specific therapy, 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) are provided for treatment group differences and estimated endpoint values by visit. | |
| Comparison groups | Neflamapimod Arm v Placebo Arm |
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.564 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.06 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.06098 |
| upper limit | 0.14777 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | HVLT-R - PK/PD Analysis |
|---|---|

Statistical analysis description:

In addition to the primary analysis, a pre-specified PK/PD analysis was conducted in which the change in the primary endpoint from baseline to Week 24 was assessed by plasma trough drug concentration (Ctrough) at Day 21 (i.e. at steady-state).   Neflamapimood-treated subjects with Ctrough > 4 ng/mL tended to show less decline in the primary endpoint than either placebo-recipients or neflamapimod-treated subjects with Ctrough < 4 ng/mL.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 143 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| P-value | = 0.06 |
| Method | Mixed models analysis |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard deviation |

Notes:

[1] - The proportion of subjects with >1 SD decline in the primary endpoint in the placebo group was 15.4% (12 of 78) versus 0% (0 of 23) in neflamapimod subjects with Ctrough > 4 ng/mL (two-sided p-value=0.06 vs. placebo)

## Secondary: WMS

| End point title | WMS |
|---|---|

End point description:

Change in WMS (Wechsler Memory Scale) immediate and delayed recall composites in neflamapimod-treated subjects compared to placebo-recipients.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) to End of Treatment (Week 24)

| **End point values** | Placebo Arm | Neflamapimod Arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 77 | 71 | | |
| Units: composite score | 77 | 71 | | |

| Attachments (see zip file) | MMRM Change from Baseline (WMS)/Table_14_02_02_03.rtf |
|---|---|

## Statistical analyses

| Statistical analysis title | MMRM Analysis - WMS |
|---|---|

Statistical analysis description:

WMS scores were analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD-specific therapy, 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) are provided for treatment group differences and estimated endpoint values by visit.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.823 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.6 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -6 |
|     upper limit | 4.8 |
| Variability estimate | Standard error of the mean |

| Statistical analysis title | WMS - PK/PD Analysis |
|---|---|

Statistical analysis description:

In pre-specified PK/PD analyses, in subjects on background AD therapy, neflamapimod subjects with Ctrough levels > 4 ng/mL demonstrated a significant improvement in WMS Immediate and Delayed Recall composite scores, relative to placebo
recipients at both week 12 (p=0.018) and at Week 24 (p=0.046).

| Comparison groups | Neflamapimod Arm v Placebo Arm |
|---|---|
| Number of subjects included in analysis | 148 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.046 |
| Method | Mixed models analysis |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
| Variability estimate | Standard deviation |

## Secondary: CDR-SB

| End point title | CDR-SB |
|---|---|

End point description:

Change in CDR-SB (CDR Sum of Boxes) in neflamapimod-treated subjects compared to placebo-recipients.

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Baseline (Day 1) to End of Treatment (Week 24) | |

| **End point values** | Placebo Arm | Neflamapimod Arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 78 | 74 | | |
| Units: score | 78 | 74 | | |

| **Attachments (see zip file)** | MMRM Change from Baseline (CDR-SB)/Table_14_02_02_05.rtf |
|---|---|

### Statistical analyses

| **Statistical analysis title** | MMRM Analysis - CDR-SB |
|---|---|

Statistical analysis description:

CDR-SB scores were analyzed using Mixed Model for Repeated Measures (MMRM) with fixed effects for treatment, background AD-specific therapy, 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) are provided for treatment group differences and estimated endpoint values by visit.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.806 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.1 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -0.4 |
|     upper limit | 0.6 |
| Variability estimate | Standard error of the mean |

### Secondary: MMSE

| End point title | MMSE |
|---|---|
| End point description: | |
| Change in MMSE (Mini-Mental State Exam) in neflamapimod-treated subjects compared to placebo-recipients. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1) to Follow-up Visit (2 weeks after last dose) | |

| End point values | Placebo Arm | Neflamapimod Arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 79 | 70 | | |
| Units: score | 79 | 70 | | |

| Attachments (see zip file) | ANCOVA Change from Baseline (MMSE)/Table_14_02_02_07. |
|---|---|

## Statistical analyses

| Statistical analysis title | ANCOVA - MMSE |
|---|---|

Statistical analysis description:

Changes MMSE scores were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 149 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.489 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.3 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -1 |
|     upper limit | 0.5 |
| Variability estimate | Standard error of the mean |

## Secondary: CSF Biomarkers

| End point title | CSF Biomarkers |
|---|---|

End point description:

Change in CSF biomarkers (total tau, p-tau181, $A\beta$1-40, $A\beta$1-42, neurogranin, neurofilament light chain) in neflamapimod-treated subjects compared to placebo-recipients.

| End point type | Secondary |
|---|---|

End point timeframe:

Baseline (Day 1) to End of Treatment (Week 24)

| End point values | Placebo Arm | Neflamapimod Arm | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 68 | 62 | | |
| Units: value | 68 | 62 | | |

| | |
|---|---|
| **Attachments (see zip file)** | ANCOVA Change from Baseline (t-tau) |
| | ANCOVA Change from Baseline (p-tau) |
| | ANCOVA Change from Baseline (AB1-40) |
| | ANCOVA Change from Baseline (AB1-42) |
| | ANCOVA Change from Baseline (neurogranin) |
| | ANCOVA Change from Baseline (NFL)/Table_14_02_02_08_07. |
| | ANCOVA Change from Baseline (p-tau/AB ratio) |

## Statistical analyses

| **Statistical analysis title** | ANCOVA t-tau |
|---|---|

Statistical analysis description:

Changes in Total Tau (t-tau) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.031 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -18.8 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | -35.8 |
|     upper limit | -1.8 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | ANCOVA p-tau181 |
|---|---|

Statistical analysis description:

Changes in Phospho-Tau (p-tau181) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|

| Number of subjects included in analysis | 130 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.012 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.6 |
| upper limit | -0.5 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | ANCOVA AB1-40 |
|---|---|

Statistical analysis description:

Changes in Amyloid beta (AB1-40) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.709 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -117.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -738.9 |
| upper limit | 504.2 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | ANCOVA AB1-42 |
|---|---|

Statistical analysis description:

Changes in Amyloid beta (AB1-42) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|

| Number of subjects included in analysis | 130 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.192 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -52.7 |
| upper limit | 10.7 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | ANCOVA Neurogranin |
|---|---|

Statistical analysis description:

Changes in Neurogranin were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.068 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -43.6 |
| upper limit | 1.6 |
| Variability estimate | Standard error of the mean |

| **Statistical analysis title** | ANCOVA NFL |
|---|---|

Statistical analysis description:

Changes in Neurofilament Light Chain (NFL) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|

| Number of subjects included in analysis | 130 |
|---|---|
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.156 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -110.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -262.7 |
| upper limit | 42.4 |
| Variability estimate | Standard error of the mean |

| Statistical analysis title | ANCOVA p-tau/AB1-42 |
|---|---|

Statistical analysis description:

Changes in the ratio of Phospho-Tau/Amyloid Beta (p-tau181/AB1-42) were compared using an ANCOVA with treatment group, background AD-specific therapy, CDR-Global Score as main effects and the baseline assessment as the covariate. The results of the ANCOVA are summarized using the treatment groups' least square means, the difference between the treatment groups' least square means, the 95% confidence interval for the treatment group difference and the p-value.

| Comparison groups | Placebo Arm v Neflamapimod Arm |
|---|---|
| Number of subjects included in analysis | 130 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.59 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0 |
| Variability estimate | Standard error of the mean |

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

AEs occurring from when the subject signed the ICF until the last study event were collected. Any AEs occurring before the start of treatment (i.e., before the first dose of the investigational product) were recorded in the medical history.

Adverse event reporting additional description:

Any sign, symptom, or disease present before starting the treatment period were only considered AEs if they worsen after starting the treatment period.

| Assessment type | Systematic |
|---|---|

## Dictionary used

| Dictionary name | MedDRA |
|---|---|
| Dictionary version | 20.1 |

## Reporting groups

| Reporting group title | Neflamapimod |
|---|---|

Reporting group description:

This reporting group includes subjects who were randomized to the neflamapimod group.  Adverse Events are only reported for incidence of 5% or higher.

| Serious adverse events | Neflamapimod | | |
|---|---|---|---|
| **Total subjects affected by serious adverse events** | | | |
| subjects affected / exposed | 2 / 78 (2.56%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Multiple Myeloma | Additional description:  Multiple Myeloma occurred in one subject.  It was not considered related to neflamapimod. | | |
| subjects affected / exposed | 1 / 78 (1.28%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalemia | Additional description:  One SAE of Hypokalemia was reported.  It was considered not related to neflamapimod. | | |
| subjects affected / exposed | 1 / 78 (1.28%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Neflamapimod | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
|     subjects affected / exposed | 18 / 78 (23.08%) | | |
| Injury, poisoning and procedural complications | | | |
|    Fall | Additional description: The incidence of fall in the neflamapimod group was 6%. The incidence of fall in the placebo group was 4% | | |
|      subjects affected / exposed | 5 / 78 (6.41%) | | |
|      occurrences (all) | 5 | | |
| Nervous system disorders | | | |
|    Headache | Additional description: The incidence of headache in the neflamapimod group was 6%. The incidence of headache in the placebo group was 4%. | | |
|      subjects affected / exposed | 5 / 78 (6.41%) | | |
|      occurrences (all) | 6 | | |
| Gastrointestinal disorders | | | |
|    Diarrhea | Additional description: The incidence of diarrhea in the neflamapimod group was 5%. The incidence of diarrhea in the placebo group was 2%. | | |
|      subjects affected / exposed | 4 / 78 (5.13%) | | |
|      occurrences (all) | 4 | | |
| Infections and infestations | | | |
|    Upper respiratory tract infection | Additional description: The incidence of upper respiratory tract infection in the neflamapimod group was 5%. The incidence of upper respiratory tract infection in the placebo group was 8%. | | |
|      subjects affected / exposed | 4 / 78 (5.13%) | | |
|      occurrences (all) | 4 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 28 September 2018 | Amendment 2 was issued on 27 August, 2018. Changes made by the country-specific amendments were harmonized in this version. Notable changes made by Amendment 2 included:<br>•	It was clarified that the CDR-SB (rather than the CDR) would be employed.<br>•	With regard to CSF biomarkers, measurement of neurogranin was added.<br>•	Telephone contacts were to be conducted to determine subject status and assess compliance between Days 42 and 84 (Visits 5 and 6); Days 84 to 126 (Visits 6 and 7); and Days 126 and 168 (Visits 7 and 8).<br>•	The neflamapimod administration procedures relative to meals were clarified.<br>In addition, editorial and administrative changes were made by Amendment 2. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

 None reported