# Clinical trial results:
# 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)

## Summary

| | |
|---|---|
| EudraCT number | 2019-001566-15 |
| Trial protocol | NL |
| Global end of trial date | 14 July 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 July 2021 |
| First version publication date | 16 July 2021 |
| Summary attachment (see zip file) | EIP19-NFD-501 CSR Synopsis (EIP19-NFD-501_CSR Synopsis_26Feb2021_FINAL.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | EIP19-NFD-501 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04001517 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Worldwide Clinical Trials Limited |
| Sponsor organisation address | Technology Drive, Beeston, Nottingham, United Kingdom, NG9 1LA |
| 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 Avenue, Suite 6017, Boston, United States, 02116 |
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| Scientific contact | Dr. John Alam, EIP Pharma, 1 617-669-8426, johnjalam@gmail.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| 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 | 30 June 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 June 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 July 2020 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is 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)

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.

Background therapy:

All subjects were required to be receiving cholinesterase inhibitor therapy for at least 3 months and have been on a stable dose for at least 6 weeks at the time of randomization.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 July 2019 |
| 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: 13 |
| Country: Number of subjects enrolled | United States: 78 |
| Worldwide total number of subjects | 91 |
| EEA total number of subjects | 13 |

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) | 11 |
| From 65 to 84 years | 77 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details:

Active recruitment and screening began 12Jul2019. The first subject was screened on 29Aug2019 and the first subject was enrolled on 30Sep2019. The last subject was screened 14Feb2020 and the last subject was enrolled 06Mar2020. Participating countries were the United States and Netherlands.

### Pre-assignment

Screening details:

125 subjects were screened. 33 were determined ineligible for the study therefore deemed screen failures: 12 due to not meeting MMSE inclusion criteria, 7 due to negative DaTscan, 4 withdrew consent, and 10 due to 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, investigators and site staff, CRO staff, and sponsor staff were blinded to treatment assignment until after database lock.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Neflamapimod TID |

Arm description:

40 mg capsules administered orally TID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg

| | |
|---|---|
| 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 3 neflamapimod 40 mg capsules per day (TID), given orally within 30 minutes following a meal or snack (i.e., morning, mid-day and evening meals). Doses were given at least 3 hours apart at approximately the same time each day for 16 weeks.

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

Arm description:

40 mg capsules administered orally BID with food for 16 weeks; subjects followed the BID regimen if Screening weight was <80 kg

| | |
|---|---|
| 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 2 neflamapimod 40 mg capsules per day (BID), given orally within 30 minutes following a meal or snack (i.e., morning and evening meals). Doses were given at least 3 hours apart at approximately the same time each day for 16 weeks.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

40 mg matching placebo capsules administered orally TID or BID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg and the BID regimen if Screening weight was <80 kg

| | |
|---|---|
| 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:

For TID, subjects received 3 neflamapimod matching placebo capsules per day (TID), given orally within 30 minutes following a meal or snack (i.e., morning, mid-day and evening meals). For BID, subjects received 2 neflamapimod matching placebo capsules per day (BID), given orally within 30 minutes following a meal or snack (i.e., morning and evening meals). Doses were given at least 3 hours apart at approximately the same time each day for 16 weeks.

| **Number of subjects in period 1** | Neflamapimod TID | Neflamapimod BID | Placebo |
|---|---|---|---|
| Started | 20 | 26 | 45 |
| Completed | 20 | 20 | 41 |
| Not completed | 0 | 6 | 4 |
| Adverse event, serious fatal | - | - | 1 |
| Consent withdrawn by subject | - | 3 | 1 |
| Physician decision | - | - | 1 |
| Adverse event, non-fatal | - | 3 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Neflamapimod TID |
| Reporting group description: | |
| 40 mg capsules administered orally TID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg | |
| Reporting group title | Neflamapimod BID |
| Reporting group description: | |
| 40 mg capsules administered orally BID with food for 16 weeks; subjects followed the BID regimen if Screening weight was <80 kg | |
| Reporting group title | Placebo |
| Reporting group description: | |
| 40 mg matching placebo capsules administered orally TID or BID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg and the BID regimen if Screening weight was <80 kg | |

| Reporting group values | Neflamapimod TID | Neflamapimod BID | Placebo |
|---|---|---|---|
| Number of subjects | 20 | 26 | 45 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 2 | 2 | 7 |
| From 65-84 years | 18 | 23 | 36 |
| 85 years and over | 0 | 1 | 2 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 72.2 | 74.5 | 72.1 |
| full range (min-max) | 59 to 84 | 63 to 85 | 62 to 87 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 7 | 6 |
| Male | 19 | 19 | 39 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 91 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 11 | | |
| From 65-84 years | 77 | | |
| 85 years and over | 3 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 14 | | |
| Male | 77 | | |

## End points

### End points reporting groups

| Reporting group title | Neflamapimod TID |
|---|---|
| Reporting group description: | |
| 40 mg capsules administered orally TID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg | |
| Reporting group title | Neflamapimod BID |
| Reporting group description: | |
| 40 mg capsules administered orally BID with food for 16 weeks; subjects followed the BID regimen if Screening weight was <80 kg | |
| Reporting group title | Placebo |
| Reporting group description: | |
| 40 mg matching placebo capsules administered orally TID or BID with food for 16 weeks; subjects followed the TID regimen if Screening weight was ≥80 kg and the BID regimen if Screening weight was <80 kg | |

### Primary: NTB (Neuropsychological Test Battery)

| End point title | NTB (Neuropsychological Test Battery) |
|---|---|
| End point description: | |
| Change from Baseline to Week 16 in the composite score of a study-specific Cogstate Neuropsychological Test Battery (NTB), including assessments of attention, executive function, and visuospatial function in neflamapimod treated-subjects as compared to the placebo-treated subjects, as analyzed using the Mixed Model Repeated Measures (MMRM) analysis method. The following six tests will be included in the composite: (1) Cogstate Detection test (DET), (2) Cogstate Identification test (IDN), (3) Cogstate One Card Learning test (OCL), (4) Cogstate One Back test (ONB), (5) Letter Fluency Test, (6) Category Fluency Test (CFT). Each score on the individual tests will be converted to a z-score, and then a total z-score will be calculated, in which each test is weighted equally. The change in total z-score in neflamapimod vs. placebo-recipients will be analyzed. As the analysis is based on z-scores, there is no minimum or maximum value. | |
| End point type | Primary |
| End point timeframe: | |
| 16 weeks | |

| End point values | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 20 | 37 | |
| Units: Z-Score by Time on Study | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 0.06 (± 0.17) | 0.02 (± 0.15) | 0.05 (± 0.11) | |
| Week 4 | 0.17 (± 0.14) | -0.08 (± 0.18) | -0.05 (± 0.13) | |
| Week 8 | 0.28 (± 0.16) | -0.12 (± 0.18) | 0.05 (± 0.17) | |
| Week 16 | 0.21 (± 0.18) | -0.08 (± 0.21) | -0.03 (± 0.14) | |

## Statistical analyses

| Statistical analysis title | Linear Mixed Effects (LME) |
|---|---|

Statistical analysis description:

This was an exploratory trial and no explicit a priori hypothesis was established and contained in the protocol. As such, no formal power calculations were conducted. The primary objective of the study was to evaluate the effects of neflamapimod on cognition, and accordingly the primary endpoint was change in combined z-score of the six tests in the NTB, analyzed by Linear Mixed Effects (LME) model for repeated measures.

| | |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.049 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.175 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.001 |
| upper limit | 0.345 |

Notes:

[1] - Change from baseline analyzed by linear mixed effects model for repeated measures. Comparison of all NFMD vs. Placebo was not significant. p=0.015 (cohen's D effect size=0.52) for NFMD 40mg TID vs. combined other groups; p=0.049 (effect size=0.47) for NFMD 40mg TID vs. placebo.

[2] - Comparison of NFMD 40mg TID vs. placebo is reported. Comparison of all NFMD vs. Placebo was not significant. p=0.015 (cohen's D effect size=0.52) for NFMD 40mg TID vs. combined other groups .

## Secondary: Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB)

| End point title | Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) |
|---|---|

End point description:

Change in Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) score based on semi-quantitative scoring of each domain (box) evaluating cognitive impairment in milder and more progressive forms of dementia, in neflamapimod-treated subjects compared to placebo-recipients. The domain (box) scores will be calculated for a Sum of Boxes score. Secondary efficacy endpoints will utilize the same analysis method and model as the primary endpoint.

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

End point timeframe:

16 weeks

| End point values | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 37 | |
| Units: Change from Baseline by Time on Study | | | | |
| arithmetic mean (standard error) | | | | |
| Week 8 | 0.11 (± 0.2) | 0.19 (± 0.3) | 0.76 (± 0.25) | |
| Week 16 | 0.34 (± 0.2) | 0.34 (± 0.18) | 0.86 (± 0.32) | |

## Statistical analyses

| Statistical analysis title | Linear Mixed Effects (LME) |
|---|---|

Statistical analysis description:

Due to Covid19 restrictions on clinical research CDR-SB evaluations were conducted remotely (i.e., via telephone or video conference, with the subject and informant at home rather than in person at the clinical site). However, within the study at home visits resulted in significantly better scores (~0.8 points lower, p=0.02). As the baseline visits were all conducted onsite, and at home CDR-SB visits has not been validated, the change analysis reported includes only data from onsite visits.

| | |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.17 [3] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.34 |
| upper limit | 0.24 |

Notes:

[3] - p=0.028 for combined combined NFMD vs. placebo.

## Secondary: Mini-Mental State Examination (MMSE)

| End point title | Mini-Mental State Examination (MMSE) |
|---|---|

End point description:

Change in Mini-Mental State Examination (MMSE) with respect to orientation, memory, concentration, language, and praxis (scores ranging from 0 to 30 with lower scores indicating greater cognitive impairment), in neflamapimod-treated subjects compared to placebo-recipients. Secondary efficacy endpoints will utilize the same analysis method and model as the primary endpoint.

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

End point timeframe:

16 weeks

| End point values | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 21 | 41 | |
| Units: Change from Baseline by Time on Study | | | | |
| arithmetic mean (standard error) | | | | |
| Week 8 | 0.11 (± 0.74) | 0.08 (± 0.64) | -0.59 (± 0.38) | |
| Week 16 | -0.85 (± 0.49) | -1.75 (± 0.67) | -0.53 (± 0.49) | |

## Statistical analyses

| Statistical analysis title | Linear Mixed Effects (LME) |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 82 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.2 [4] |
| Method | Mixed models analysis |

Notes:

[4] - There were no significant differences between treatment groups.

## Secondary: Neuropsychiatric Inventory (NPI-10)

| | |
|---|---|
| End point title | Neuropsychiatric Inventory (NPI-10) |

End point description:

Change in Neuropsychiatric Inventory (NPI-10) domains, specifically depression (dysphoria), anxiety, hallucinations, and agitation/aggression, in neflamapimod-treated subjects compared to placebo-recipients. Responses indicating subject has a problem with a particular sub-domain lead to questions of the caregiver rating the frequency of the symptoms on a 4-point scale, severity on a 3-point scale, and the distress the symptoms cause them on a 5-point scale. Secondary efficacy endpoints will utilize the same analysis method and model as the primary endpoint.

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

End point timeframe:

16 weeks

| End point values | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 19 | 20 | 37 | |
| Units: Total Score by Time on Study | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 11.3 (± 2.8) | 10.5 (± 1.9) | 10.9 (± 1.5) | |
| Week 4 | 9.2 (± 2.2) | 10 (± 2.2) | 8.9 (± 1.5) | |
| Week 8 | 7.3 (± 1.9) | 8.9 (± 1.8) | 9.2 (± 1.6) | |
| Week 16 | 7.6 (± 2.0) | 10.9 (± 2.4) | 11.0 (± 1.9) | |

### Statistical analyses

| Statistical analysis title | Linear Mixed Effects (LME) |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |
| Number of subjects included in analysis | 76 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | > 0.2 [5] |
| Method | Mixed models analysis |

Notes:

[5] - There were no significant differences between the treatment groups for total NPI-10 score. For hallucinations there was a significant treatment effect (p=0.019,LME for repeated measures) for NFMD 40mg TID vs. placebo. p=0.05 for all NFMD vs. placebo.

## Secondary: Timed Up and Go (TUG)

| | |
|---|---|
| End point title | Timed Up and Go (TUG) |

End point description:

Change in Timed Up and Go Test (TUG) to assess mobility (score of >15 seconds indicates subject has increased risk of falls) in neflamapimod-treated subjects compared to placebo-recipients. Secondary efficacy endpoints will utilize the same analysis method and model as the primary endpoint.

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

End point timeframe:

16 weeks

| **End point values** | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 37 | |
| Units: Change from Baseline by Time on Study | | | | |
| arithmetic mean (standard error) | | | | |
| Week 8 | -0.2 (± 0.5) | 1.0 (± 0.9) | 0.4 (± 0.4) | |
| Week 16 | -1.4 (± 1.0) | 1.3 (± 0.7) | 1.5 (± 0.9) | |

## Statistical analyses

| **Statistical analysis title** | Linear Mixed Effects (LME) |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | other[6] |
| P-value | = 0.28 [7] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | -2.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.84 |
| upper limit | -0.28 |

Notes:

[6] - Change from baseline analyzed by linear mixed effects model for repeated measures. In the comparison of the combined NFMD groups vs. placebo, there was significant reduction in the time required to complete the TUG test (i.e. improvement) with neflamapimod treatment (p=0.04, difference of -1.36 sec, 95% CI -0.04 to -2.69). A significant difference favoring neflamapimod treatment was also noted for the comparison of NFMD TID vs. placebo (p=0.028, difference of –2.56 sec, 95% CI -0.28 to -4.84).

[7] - Comparison of NFMD 40mg TID vs. placebo is reported. For the comparison of the combined NFMD groups vs. placebo, p=0.044.

## Secondary: International Shopping List Test (ISLT)

| End point title | International Shopping List Test (ISLT) |
|---|---|

End point description:

Change in International Shopping List Test (ISLT) immediate and delayed recall and recognition will be used to assess episodic memory in neflamapimod-treated subjects compared to placebo-recipients. Secondary efficacy endpoints will utilize the same analysis method as the primary endpoint.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| 16 weeks | |

| **End point values** | Neflamapimod TID | Neflamapimod BID | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 41 | |
| Units: ISLT immediate recall score | | | | |
| arithmetic mean (standard error) | | | | |
| Change from Baseline to Week 4 | 0.29 (± 1.08) | -1.24 (± 0.61) | 0.11 (± 0.54) | |
| Change from Baseline to Week 8 | 2.11 (± 1.66) | -0.75 (± 1.37) | 0.41 (± 0.65) | |
| Change from Baseline to Week 16 | 0.30 (± 1.04) | 0.11 (± 0.99) | -0.15 (± 0.46) | |

## Statistical analyses

| **Statistical analysis title** | Linear Mixed Effects (LME) |
|---|---|
| Comparison groups | Neflamapimod TID v Neflamapimod BID v Placebo |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | > 0.2 [8] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.27 |
| upper limit | 1.91 |

Notes:

[8] - No significant treatment group differences were identified.

## 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.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Neflamapimod TID |
| Reporting group description: - | |
| Reporting group title | Neflamapimod BID |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Serious adverse events | Neflamapimod TID | Neflamapimod BID | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 3 / 26 (11.54%) | 4 / 45 (8.89%) |
| number of deaths (all causes) | 0 | 2 | 0 |
| number of deaths resulting from adverse events | 0 | 2 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Diagnosis of brain tumor | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 26 (3.85%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 26 (3.85%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| New brain lesions of unclear etiology | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 26 (3.85%) | 0 / 45 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Intraparenchymal hemorrhage | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 26 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Blood and lymphatic system disorders | | | |
| Internal bleeding | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 26 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Gastrointestinal disorders | | | |
| Hematochezia | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 26 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma exacerbation | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 26 (0.00%) | 1 / 45 (2.22%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Neflamapimod TID | Neflamapimod BID | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 8 / 26 (30.77%) | 17 / 45 (37.78%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 5 / 26 (19.23%) | 4 / 45 (8.89%) |
| occurrences (all) | 1 | 5 | 5 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 1 / 26 (3.85%) | 2 / 45 (4.44%) |
| occurrences (all) | 3 | 1 | 3 |
| Tremor | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 26 (0.00%) | 3 / 45 (6.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 3 / 20 (15.00%) | 0 / 26 (0.00%) | 5 / 45 (11.11%) |
| occurrences (all) | 3 | 0 | 5 |
| Nausea | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 2 / 26 (7.69%) | 3 / 45 (6.67%) |
| occurrences (all) | 1 | 2 | 3 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported