# Clinical trial results:
# Randomised, double-blind, placebo-controlled, complete 3-way cross-over phase IIa trial to investigate safety and efficacy of two THN102 doses in subjects with excessive daytime sleepiness associated with Parkinson's disease

## Summary

| | |
|---|---|
| EudraCT number | 2017-004475-31 |
| Trial protocol | HU CZ |
| Global end of trial date | 20 December 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 07 July 2021 |
| First version publication date | 07 July 2021 |
| Summary attachment (see zip file) | THN102-202 clinical study report synopsis (THN102-202_CTR Synopsis_final 1.0_20200723.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | THN102-202 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03624920 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Theranexus |
| Sponsor organisation address | 86 route de Paris, Orsay, France, 91400 |
| Public contact | Damien Bouvier, Theranexus S.A., 0033 146548524, damien.bouvier@theranexus.com |
| Scientific contact | Damien Bouvier, Theranexus S.A., 0033 146548524, damien.bouvier@theranexus.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 | 18 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 December 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety profile of THN102 (modafinil/flecainide combination) at two doses (200 mg/18 mg and 200 mg/2 mg) versus placebo in subjects with excessive daytime sleepiness associated with Parkinson's disease (PD).

Protection of trial subjects:

All subjects were closely monitored during the trial. Subjects who discontinued trial participation prematurely were asked to come to the site for an early discontinuation and follow-up visits to exclude the possibility of an adverse event (AE) being the cause and otherwise to assess if the AE had any potential relationship to the trial medication. Serious adverse events (SAEs) were to be followed-up until resolution or until no further improvement could be expected, and follow-up information was to be recorded by the investigators. SAEs detected after the last subject's visit, were to be collected if in the investigator's opinion, they were related either to the investigational medicinal product (IMP) or to the trial procedure.
Subjects with electrocardiogram (ECG) signs of left ventricular hypertrophy had to be withdrawn from further participation in the trial and were to be referred to a cardiologist for further examination.
Subjects who answered "yes" to point 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS), were to be withdrawn from the trial and sent for psychiatric consultation. Subjects with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 times the upper limit of normal (ULN), or ALT and AST ≥ 3 times the ULN together with bilirubin ≥ 2 times the ULN were to be withdrawn from the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 July 2018 |
| 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 | Czechia: 25 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Germany: 19 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Country: Number of subjects enrolled | United States: 5 |
| Worldwide total number of subjects | 77 |
| EEA total number of subjects | 72 |

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) | 36 |
| From 65 to 84 years | 41 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

105 patients were screened and 77 were randomized and 75 were exposed to study medication

### Pre-assignment

Screening details:

Randomised, double-blind, placebo-controlled, complete 3-way cross-over trial in subjects aged 18 to 80 years with excessive daytime sleepiness associated with Parkinson's disease. The study consisted of a screening period, followed by three 2-week treatment periods separated by washout periods of 1 to 2 weeks each, and 1-week follow-up.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 77 |
| Number of subjects completed | 75[1] |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | Protocol deviation: 1 |

Notes:

[1] - The number of subjects reported to be in the pre-assignment period is not consistent with the number starting period 1. It is expected that the number completing the pre-assignment period are also present in the arms in period 1.
Justification: Crossover design

### 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:

Modafinil 100 mg capsules and modafinil placebo capsules as well as flecainide 1 mg or 9 mg capsules and matching placebo capsules were identical in size and appearance, as well as colour of modafinil and respective placebo (orange), and flecainide and respective placebo (white). The packaging and labelling did not allow for any distinction between them.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | THN102 Placebo |

Arm description:

Dosage A

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | THN102 placebo |
| Investigational medicinal product code | dose A |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

In this trial, all subjects received the same doses of IMP (modafinil/flecainide 200 mg/2 mg, 200 mg/18 mg and matching placebo). IMP (2 capsules modafinil or placebo plus 2 capsules flecainide or placebo; 4 capsules in total) were to be administered in the morning. The IMP was to be swallowed before meal with 150 mL tap water at 8:00 h (± 1 h). The interval of 24 h between the 2 intakes should be followed. Subjects aged above 65 years were asked to take half a dose of IMP (2 capsules) during the first 3 days

of each treatment period, followed by the full IMP dose since the fourth treatment day.

| **Arm title** | THN102 200/2 |
|---|---|
| Arm description:<br>Dosage B | |
| Arm type | Experimental |
| Investigational medicinal product name | THN102 200/2 |
| Investigational medicinal product code | Dosage B |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

In this trial, all subjects received the same doses of IMP (modafinil/flecainide 200 mg/2 mg, 200 mg/18 mg and matching placebo). IMP (2 capsules modafinil or placebo plus 2 capsules flecainide or placebo; 4 capsules in total) were to be administered in the morning. The IMP was to be swallowed before meal with 150 mL tap water at 8:00 h (± 1 h). The interval of 24 h between the 2 intakes should be followed. Subjects aged above 65 years were asked to take half a dose of IMP (2 capsules) during the first 3 days of each treatment period, followed by the full IMP dose since the fourth treatment day.

| **Arm title** | THN102 200/18 |
|---|---|
| Arm description:<br>Dosage C | |
| Arm type | Experimental |
| Investigational medicinal product name | THN102 200/18 |
| Investigational medicinal product code | dosage C |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

In this trial, all subjects received the same doses of IMP (modafinil/flecainide 200 mg/2 mg, 200 mg/18 mg and matching placebo). IMP (2 capsules modafinil or placebo plus 2 capsules flecainide or placebo; 4 capsules in total) were to be administered in the morning. The IMP was to be swallowed before meal with 150 mL tap water at 8:00 h (± 1 h). The interval of 24 h between the 2 intakes should be followed. Subjects aged above 65 years were asked to take half a dose of IMP (2 capsules) during the first 3 days of each treatment period, followed by the full IMP dose since the fourth treatment day.

| **Number of subjects in period 1** | THN102 Placebo | THN102 200/2 | THN102 200/18 |
|---|---|---|---|
| Started | 68 | 72 | 73 |
| Completed | 68 | 68 | 68 |
| Not completed | 0 | 4 | 5 |
| Adverse event, non-fatal | - | 3 | 3 |
| Protocol deviation | - | 1 | 2 |

## Baseline characteristics

| Reporting groups[1] | |
|---|---|
| Reporting group title | overall trial |
| Reporting group description: - | |

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: among the 77 patients randomized 2 left the study before any IMP intake. These 2 patients have been exluded from the safety set.

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 75 | 75 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 35 | 35 | |
| From 65-84 years | 40 | 40 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.5 | | |
| standard deviation | ± 9.35 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 50 | 50 | |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The Full Analysis Set (FAS) includes all randomised subjects with an evaluable ESS score at the end of at least one treatment period. Evaluability of treatment periods is described in Section 5.6. The efficacy analyses will be conducted on the FAS.

| | |
|---|---|
| Subject analysis set title | SAFETY SET |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The Safety Set (SS) includes all subjects with at least one IMP administration.

| Reporting group values | Full analysis set | SAFETY SET | |
|---|---|---|---|
| Number of subjects | 72 | 75 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 34 | 35 | |
| From 65-84 years | 38 | 40 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.3 | 63.5 | |
| standard deviation | ± 9.43 | ± 9.35 | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 24 | 25 | |
| Male | 48 | 50 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | THN102 Placebo |
| Reporting group description: | |
| Dosage A | |
| Reporting group title | THN102 200/2 |
| Reporting group description: | |
| Dosage B | |
| Reporting group title | THN102 200/18 |
| Reporting group description: | |
| Dosage C | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The Full Analysis Set (FAS) includes all randomised subjects with an evaluable ESS score at the end of at least one treatment period. Evaluability of treatment periods is described in Section 5.6. The efficacy analyses will be conducted on the FAS. | |
| Subject analysis set title | SAFETY SET |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The Safety Set (SS) includes all subjects with at least one IMP administration. | |

### Primary: Epworth Sleeping Scale (ESS)

| | |
|---|---|
| End point title | Epworth Sleeping Scale (ESS) |
| End point description: | |
| Range of the scale : 0 to 24. A low score indicates a good outcome. Results shown are corresponding to a change from baseline of the ESS score. | |
| End point type | Primary |
| End point timeframe: | |
| 2 weeks | |

| End point values | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 69 | 71 | |
| Units: ESS score | | | | |
| least squares mean (standard error) | -2.4 (± 3.65) | -3.9 (± 4.87) | -3.1 (± 4.12) | |

### Statistical analyses

| Statistical analysis title | THN102 200/2 vs THN102 placebo A ESS Score |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/2 v THN102 Placebo |
| Number of subjects included in analysis | 137 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.012 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3994 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.4861 |
| upper limit | -0.3128 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5492 |

Notes:

[1] - Analysis of Epworth Sleepiness Scale Score

[2] - Estimates are based on the mixed linear regression model with the fixed effects of treatment, period, treatment by period interaction, sequence, baseline score, and the random effect of subjects within sequences.

| **Statistical analysis title** | THN102 200/18 vs THN102 placebo A ESS score |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 Placebo |
| Number of subjects included in analysis | 139 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.1769 [4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.7427 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.8249 |
| upper limit | 0.3394 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.547 |

Notes:

[3] - Analysis of Epworth Sleepiness Scale Score

[4] - Estimates are based on the mixed linear regression model with the fixed effects of treatment, period, treatment by period interaction, sequence, baseline score, and the random effect of subjects within sequences.

| **Statistical analysis title** | THN102 200/18 vs THN102 200/2 A ESS score |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 139 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[5] |
| P-value | = 0.2303 [6] |
| Method | mixed linear regression model |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.6567 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4212 |
| upper limit | 1.7346 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.5449 |

Notes:

[5] - Analysis of Epworth Sleepiness Scale Score

[6] - Estimates are based on the mixed linear regression model with the fixed effects of treatment, period, treatment by period interaction, sequence, baseline score, and the random effect of subjects within sequences.

## Secondary: Psychomotor Vigilance Test (PVT) : Reaction Time (Miliseconds) Change From Baseline

| | |
|---|---|
| End point title | Psychomotor Vigilance Test (PVT) : Reaction Time (Miliseconds) Change From Baseline |

End point description:

PVT measures reaction time in milliseconds. The results below are corresponding to the reaction time change from baseline

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

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

End point timeframe:

2 weeks

| End point values | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 67 | 67 | |
| Units: miliseconds | | | | |
| least squares mean (standard error) | -16.69 (± 84.983) | -24.92 (± 81.279) | -18.89 (± 78.450) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: ESS Responder rate

| | |
|---|---|
| End point title | ESS Responder rate |

End point description:

ESS score responder rate, defined as the proportion of subjects with at least 25% ESS improvement from baseline, at the end of each treatment period

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

End point timeframe:

2 weeks

| **End point values** | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 70 | 72 | |
| Units: count of participant | | | | |
| number (not applicable) | 68 | 69 | 71 | |

**Statistical analyses**

| **Statistical analysis title** | ESS Responder rate THN102 200/2 vs placebo |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – absence of residual somnolence and ESS responder status at each key visit – were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| Comparison groups | THN102 Placebo v THN102 200/2 |
|---|---|
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1209 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.9766 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8342 |
| upper limit | 4.6835 |

| **Statistical analysis title** | ESS Responder rate THN102 200/18 vs placebo |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – absence of residual somnolence and ESS responder status at each key visit – were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| Comparison groups | THN102 200/18 v THN102 Placebo |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3534 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.4985 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6357 |
| upper limit | 3.5323 |

| **Statistical analysis title** | THN102 200/18 vs 200/2 |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – absence of residual somnolence and ESS responder status at each key visit – were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 200/2 |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4971 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.7581 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3397 |
| upper limit | 1.6919 |

## Secondary: ESS Patients in remission

| End point title | ESS Patients in remission |
|---|---|

End point description:

Number of patients in remission (=without residual sleepiness), i.e. ESS < 11 at the end of each treatment period

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

End point timeframe:

2 weeks

| End point values | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 70 | 72 | |
| Units: count of participant | | | | |
| number (not applicable) | 68 | 69 | 71 | |

## Statistical analyses

| Statistical analysis title | ESS remission THN102 200/2 vs Placebo |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – Number of patients in remission (=without residual sleepiness), i.e. ESS < 11 at the end of each treatment period– were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/2 v THN102 Placebo |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05332 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.0831 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9842 |
| upper limit | 9.6577 |

| Statistical analysis title | ESS remission THN102 200/18 vs Placebo |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – Number of patients in remission (=without residual sleepiness), i.e. ESS < 11 at the end of each treatment period– were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 Placebo |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.102 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.619 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8246 |
| upper limit | 8.3182 |

| **Statistical analysis title** | ESS remission THN102 200/18 vs 200/2 |
|---|---|

Statistical analysis description:

Categorical efficacy endpoints – Number of patients in remission (=without residual sleepiness), i.e. ESS < 11 at the end of each treatment period– were analysed using a generalised linear mixed regression model (GLMM), with the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 200/2 |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7177 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.8495 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.3493 |
| upper limit | 2.0657 |

## Secondary: MoCA score analysis

| End point title | MoCA score analysis |
|---|---|

End point description:

MoCA score reflects the cognitive capacities of a person. Range of the total score of 10 test items: 0 to 30 points. A high score indicates good cognitive functioning. A score of 26 and above is considered normal.

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

End point timeframe:

2 weeks

| **End point values** | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 70 | 72 | |
| Units: score on a scale | | | | |
| number (not applicable) | 68 | 69 | 70 | |

## Statistical analyses

| **Statistical analysis title** | MoCA THN102 200/2 vs Placebo |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/2 v THN102 Placebo |
| Number of subjects included in analysis | 138 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3815 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.1913 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.6223 |
| upper limit | 0.2397 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2178 |

| **Statistical analysis title** | MoCA THN102 200/18 vs Placebo |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 Placebo |
| Number of subjects included in analysis | 140 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3566 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.2012 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.229 |
| upper limit | 0.6313 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2174 |

| **Statistical analysis title** | MoCA THN102 200/18 vs 200/2 |
|---|---|

Statistical analysis description:

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - were analysed using a mixed linear regression model, which included the treatment, period, treatment by period interaction, sequence, and baseline scores as fixed effects, and the subject nested within sequence as a random effect.

| | |
|---|---|
| Comparison groups | THN102 200/18 v THN102 200/2 |
| Number of subjects included in analysis | 142 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0722 |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3924 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.0359 |
| upper limit | 0.8208 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2165 |

## Secondary: MoCA score

| | |
|---|---|
| End point title | MoCA score |

End point description:

MoCA score reflects the cognitive capacities of a person. Range of the total score of 10 test items: 0 to 30 points. A high score indicates good cognitive functioning. A score of 26 and above is considered normal.

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

End point timeframe:

2 weeks

| End point values | THN102 Placebo | THN102 200/2 | THN102 200/18 | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 70 | 72 | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | 28 (± 2.02) | 27.8 (± 2.47) | 28.2 (± 1.78) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| AE collection through study duration, starts with screening until follow up visit (last phone call), a total of 13 weeks. | |
| Adverse event reporting additional description: | |
| Number of participants with spontaneously reported treatment-related adverse events | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

| Reporting groups | |
|---|---|
| Reporting group title | THN102 placebo |
| Reporting group description: | |
| Dosage A | |
| Reporting group title | THN102 200/2 |
| Reporting group description: | |
| Dosage B | |
| Reporting group title | THN102 200/9 |
| Reporting group description: | |
| dosage C | |

| Serious adverse events | THN102 placebo | THN102 200/2 | THN102 200/9 |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 72 (0.00%) | 1 / 73 (1.37%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 72 (0.00%) | 1 / 73 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | THN102 placebo | THN102 200/2 | THN102 200/9 |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 68 (4.41%) | 10 / 72 (13.89%) | 22 / 73 (30.14%) |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Headache | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 2 / 72 (2.78%) | 4 / 73 (5.48%) |
| occurrences (all) | 0 | 2 | 4 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 68 (2.94%) | 0 / 72 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 2 | 0 | 2 |
| Chest pain | | | |
| subjects affected / exposed | 1 / 68 (1.47%) | 2 / 72 (2.78%) | 1 / 73 (1.37%) |
| occurrences (all) | 1 | 2 | 2 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 2 / 72 (2.78%) | 3 / 73 (4.11%) |
| occurrences (all) | 0 | 2 | 3 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 72 (0.00%) | 3 / 73 (4.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 72 (1.39%) | 2 / 73 (2.74%) |
| occurrences (all) | 0 | 1 | 2 |
| Confusional state | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 72 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 0 | 0 | 2 |
| Nightmare | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 0 / 72 (0.00%) | 2 / 73 (2.74%) |
| occurrences (all) | 0 | 0 | 2 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 2 / 72 (2.78%) | 0 / 73 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 68 (0.00%) | 1 / 72 (1.39%) | 3 / 73 (4.11%) |
| occurrences (all) | 0 | 1 | 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