Theranexus S.A.

CLINICAL TRIAL REPORT

SYNOPSIS

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

Product Name	THN102 (modafinil, flecainide)
Indication	Excessive daytime sleepiness in subjects with Parkinson's disease
Protocol Number	THN102-202
EudraCT Number	2017-004475-31
Report Version	Final 1.0
Phase	IIa (proof-of-concept)
Date First Subject Entered	12-JUL-2018
Date Last Subject Completed	18-DEC-2019
Coordinating / Principal Investigator	Jean-Cristophe Corvol, MD; PhD Coordinating investigator Centre d'Investigation Clinique Neuroscience (CIC1422) Bâtiment ICM Hôpital La Pitié-Salpêtrière 47-83 Boulevard de l'Hôpital 75651 Paris Cedex 13, France
Name of Sponsor Signatory	Dr. Werner Rein Theranexus S.A. 86, rue de Paris F-91400 Orsay, France E-mail: werner.rein@theranexus.fr
Report Issue Date	23-JUL-2020

Title of trial:

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

Trial number: THN102-202

EudraCT number: 2017-004475-31

IND No.: 137871

Sponsor details:

Name: Theranexus S.A.

Address: 86, rue de Paris
F-91400 Orsay, France

Phone: +33 6 80 02 67 79

www.theranexus.com

Investigators:

The trial was conducted at 29 sites: 26 sites in 4 European countries (7 sites in the Czech Republic, 6 sites in France, 8 sites in Germany and 5 sites in Hungary) and 3 sites in the USA.

Coordinating Investigator:

Jean-Cristophe Corvol, MD, PhD, Paris, France.

Publication (reference):

None.

Studied period (years):

date of first enrolment: 12-JUL-2018
date of last subject completed: 18-DEC-2019

Phase of development: IIa (proof-of-concept)

Background and rationale:

Excessive daytime sleepiness (EDS) occurs in 20-50% of Parkinson's disease (PD) patients, it appears to be linked to multiple causes, among them disease severity and duration as well as dopamine agonist dosing. Currently there is no drug treatment approved for EDS in PD. Modafinil is a wake-promoting drug approved for the treatment of EDS in narcolepsy (Europe and US), obstructive sleep apnoea and shift work disorder (US only, both). Theranexus has recently demonstrated that flecainide – a class Ic antiarrhythmic compound – can significantly modify at very low dose the basic pharmacological profile of modafinil by enhancing modafinil activity on wakefulness and cognition. The mode of action of this combination called THN102 is under investigation. This proof-of-concept, phase IIa trial with THN102 should collect a sufficient body of information to assess the safety and efficacy profile of THN102 versus placebo in PD subjects suffering from EDS.

Objectives:

Primary:

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

Secondary:

1. To quantify the efficacy of THN102 versus placebo in improving sleepiness.
2. To quantify the efficacy of THN102 versus placebo in improving
    a. attention, vigilance
    b. cognition
3. To determine the dose response profile of THN102 versus placebo on efficacy parameters.
4. To determine the plasma levels of modafinil and flecainide at steady state.

Methods:

This was a prospective, multicentre, randomised, double-blind, placebo-controlled, complete 3-way cross-over trial in subjects aged 18 to 75 (enroled up to 27-FEB-2019) - 80 years (those enroled since 27-FEB-2019) with excessive daytime sleepiness associated with Parkinson's disease. The study consisted of 1-2 weeks screening period, followed by three 2-week treatment periods separated by washout periods of 1 to 2 weeks each, and 1-week follow-up. The subjects were randomised double-blind (1:1:1:1:1:1) to one of the prespecified treatment sequences, including THN102 (modafinil/flecainide) 200 mg/2 mg, THN102 200 mg/18 mg and placebo.

Number of subjects (planned and analysed):

planned: 60 randomised	screened: 105	randomised: 77
withdrawn: 10	completed: 67	analysed (safety): 75
analysed (efficacy): 72	analysed (PK): 70	

Diagnosis and main criteria for inclusion and exclusion:

Males and females 18 to 75 years (enroled up to 27-FEB-2019) or 18 to 80 years (those enroled since 27-FEB-2019) old, body mass index (BMI) >18 kg/m^2 and < 30 kg/m^2 (up to 27-FEB-2019 for all countries and since 12-APR-2019 for France only) or >18 kg/m^2 and < 35 kg/m^2 (from 27-FEB-2019 to 12-APR-2019 for France and since 27-FEB-2019 for all other countries) with excessive daytime sleepiness associated with PD and Epworth Sleepiness Scale (ESS) score ≥ 14 were eligible for the trial. Subjects with any other cause of EDS, psychiatric and neurological disorders (other than Parkinson's disease), cardiovascular disorders, impulse control disorder, dementia or Montreal Cognitive Assessment (MoCA) < 23, current suicidal risk, hepatic or renal impairment were not eligible for the trial.

Paediatric regulatory details: Not applicable

Measures of protection of subjects taken:

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.

Test products, dose and mode of administration, batch number:

Modafinil capsules (100 mg).

Flecainide capsules (1 mg, 9 mg).

Oral administration of 2 modafinil over-encapsulated tablets and 2 flecainide capsules, once daily in the morning at 08:00 h (± 1:00 h). A 24-hour (± 1:00 h) interval between 2 consecutive doses was required. Subjects aged above 65 years had to take 1 modafinil and 1 flecainide capsule (100 mg modafinil/1 mg flecainide or 100 mg modafinil/9 mg flecainide) on the first 3 days of each treatment period.

The total daily dose was 200 mg modafinil/2 mg flecainide or 200 mg modafinil/18 mg flecainide.

Batch numbers: ES107 (flecainide 1 mg), ES109 (flecainide 9 mg);
MM1073B.2DP.1MA.1PIL18 (modafinil)

Duration of treatment:

Total treatment duration was 8-10 weeks (including two 1-2-week washout periods in between without treatment), the net treatment duration was 6 weeks.

Reference therapy, dose and mode of administration, batch number:

THN102 placebo combination drug constituted of modafinil over-encapsulated placebo tablets and flecainide placebo capsules matching the test products. Daily dosages: modafinil 0 mg and flecainide 0 mg.

Batch numbers: ES106 (flecainide placebo); 779/04.2PB.1PIL18 (modafinil placebo)

Endpoints:

Safety:

1. Adverse events
2. Safety laboratory
3. Vital signs change
4. Electrocardiogram assessments
5. Columbia-Suicide Severity Rating Scale (C-SSRS)
6. Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
7. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)

Efficacy:

Key efficacy endpoint

8. Mean ESS score change from baseline at the end of each treatment period

Secondary efficacy endpoints

9. 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
10. Absence of residual somnolence, i.e. ESS < 11 at the end of each treatment period
11. Psychomotor Vigilance Test (PVT) variables change from baseline at the end of each treatment period
12. MoCA score change from baseline at the end of each treatment period
13. Actimetry change (inactivity) from baseline at the end of each treatment period
14. Number and duration of diurnal involuntary sleep attacks (subject diaries) change from baseline at the end of each treatment period
15. Episodes of somnolence (subject diaries) change from baseline at the end of each treatment period

Statistical methods:

For the sample size planning ESS was considered to be the key efficacy endpoint. Solid information on the expected difference between placebo and THN102 dose and the associated intrasubject variance were not available. Using results reported in Adler et al., 2003 as a rough orientation an effect size of 0.40 may constitute a conservative estimation for the comparison of the high THN102 dose with placebo. A sample size of 54 subjects was assumed to have a power of 82% to detect this effect size based on a paired t-test with a 0.05 two-sided significance level. To account for drop outs 60 subjects were planned to be randomised.

The safety data were analysed on the safety set (SS). The safety data were summarised using summary statistics and frequency tabulations.

Efficacy analyses were performed on the full analysis set (FAS) and for some parameters (ESS, PVT, cognition and actimetry) were repeated on the per protocol (PP) set.

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.

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.

Treatment least-square means and mean differences were reported with their standard errors and 95% confidence intervals (CIs). The treatment least-squares means of the log-odds were reported as well as their standard errors and 95% CIs. The odds ratios between each treatment were displayed with 95% CIs.

The pharmacokinetic analysis was performed on the pharmacokinetic (PK) analysis set. The concentrations of modafinil and flecainide at each visit were summarised using the geometric mean, geometric standard deviation, and geometric coefficient of variation in addition to the default summary statistics.

SUMMARY OF RESULTS

SUBJECT DISPOSITION:

A total of 77 (100.0%) subjects were randomised to six sequence groups and 75 (97.4%) subjects of them received the IMP and were allocated to the safety set. Of these, 68 subjects received Placebo, 72 subjects Test 200/2 and 73 subjects Test 200/18. The total number of subjects analysed in the FAS was 72 (93.5%). All these subjects were included in the PP set. Of 75 subjects in the SS, 67 (89.3%) subjects completed the trial as scheduled.

Most safety set (SS) subjects were of white race (98.7%). Male subjects prevailed in this study and comprised 66.7%; the percentages of male subjects ranged between 42.9% (BCA group) and 83.3% (BAC group) in the sequence groups. The subjects' age ranged from 38 to 80 years and the mean (SD) age was 63.5 (9.35) years. Regarding the sequence groups, the mean (SD) age ranged between 58.3 (10.18) years (ACB group) and 66.8 (9.60) years (BAC group).

Most of the subjects were assessed as Hoehn & Yahr Stage of 2 (45.3%), 2.5 (21.3%) and 3 (20.0%).

The most common ongoing medical history findings by preferred term included hypertension (33.3%), depression (21.3%), hypercholesterolaemia and constipation (10.7%, each), and deep brain stimulation (8.0%).

All subjects (SS) used at least one anti-Parkinson drug. The most commonly used concomitant anti-Parkinson medications by substance name overall were benserazide hydrochloride/levodopa (37.3%), carbidopa/levodopa (33.3%) and pramipexole dihydrochloride (29.3%). The most commonly used other concomitant medications overall were acetylsalicylic acid (16.0%), ibuprofen and domperidone (9.3%, each), and pantoprazole and paracetamol (8.0%, each). For each used concomitant medication, including anti-Parkinson medication, the percentages of subjects were similar during each treatment.

The compliance to IMP based on electronic case report form (eCRF) data was high, a total of 97.3% of subjects in the SS had a compliance between 80% and 120% with similar percentages during each treatment. The mean (SD) compliance was 101.03% (6.868). The compliance ranged from 88.9% to 142.9%.

An overall mean (SD) treatment duration of 39.0 (9.60) days and a median duration of 42.0 days was reported. Total treatment duration ranges between one day and 48 days were observed. In each treatment period, median treatment durations of 14 days were reported in total and under each treatment except for treatment with Test 200/18 with a median of 13.5 days during Treatment Period 3.

SAFETY RESULTS:

The primary objective of the trial was to assess the safety profile of THN102 at 2 doses (200 mg/2 mg and 200 mg/18 mg) versus placebo in subjects with excessive daytime sleepiness associated with PD.

The safety analyses included adverse events, safety laboratory, vital signs change, ECG assessments, Columbia-Suicide Severity Rating Scale (C-SSRS), Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS).

Overall, 44 subjects (58.7%) experienced 109 treatment emergent adverse events (TEAEs) during the trial. The overall frequency of adverse events was higher following each test

treatment compared to Placebo treatment: 23 subjects (31.9%) during Test 200/2 and 29 subjects (39.7%) during Test 200/18 treatment *vs* 19 subjects (27.9%) during Placebo treatment.

The most frequent TEAEs during the Test 200/18 treatment were headache (4 subjects, 5.5%), followed by nausea, nasopharyngitis and dry mouth (3 subjects, 4.1%; each). The most frequent TEAEs during Test 200/2 treatment, each reported for 2 subjects (2.8%) were headache, nausea, chest pain and muscle spasms. During Placebo treatment, the only TEAE reported for 2 subjects was fatigue, all other TEAEs were reported only for one subject each.

In line with the overall frequency of TEAEs, the highest proportion of subjects with TEAEs assessed by the investigator as being related to IMP was observed for the Test 200/18 treatment (18 subjects, 24.7%), and the lowest for the Placebo treatment (5 subjects, 7.4%). Overall, the most common TEAE considered related to IMP was nausea, reported for 3 subjects (4.1%) during the Test 200/18 treatment and 2 subjects (2.8%) during the Test 200/2 treatment. No such TEAEs were reported during the Placebo treatment.

The vast majority of TEAEs were mild to moderate in intensity. Overall, one subject after start of the Test 200/2 treatment experienced tachycardia, palpitations and chest discomfort TEAEs, which were assessed as being of severe intensity.

No deaths occurred during the trial. The incidence of treatment emergent SAEs was low: One subject treated with Test 200/18 experienced 2 contusion treatment emergent serious adverse events (TESAEs), which were assessed as not related to IMP.

The overall frequency of TEAEs leading to premature trial termination was low and was similar during both test treatments (Test 200/2: 3 subjects [4.2%]; Test 200/18: 3 subjects [4.1%]) whereas no withdrawals due to TEAEs were reported during the Placebo treatment period.

No relevant treatment differences were observed for any of the laboratory variables investigated. Changes from normal at baseline to clinically significant abnormal values of haematology parameters at endpoint were reported for 3 subjects, one treated with Placebo and 2 with Test 200/18. No changes from normal or not clinically significant abnormal at baseline to clinically significant abnormal at endpoint were reported for any biochemistry variable. Based on urinalysis results, such change was reported for one subject with leucocytes detected in urine during Test 200/2 treatment.

Overall, TEAEs related to blood pressure or heart rate changes were reported for 5 subjects: one experienced blood pressure fluctuation while treated with Test 200/2 followed by hypertension while treated with Test 200/18; 2 subjects treated with Test 200/2 (hypertension and tachycardia) and 2 with Test 200/18 (blood pressure fluctuation, orthostatic hypotension). No TEAEs based on blood pressure or heart rate changes were reported during the Placebo treatment period.

No changes from normal at baseline to clinically significant abnormal ECG findings at endpoint were reported. Based on ECG findings, TEAEs were reported for 3 subjects: left ventricular hypertrophy (Placebo treatment), electrocardiogram abnormal (Test 200/2 treatment; finding: 3 atrial premature contractions: unifocal) and ECG signs of myocardial infarction (reported: suspicion of old anteroseptal myocardial according to ECG; Test 200/18 treatment). All these TEAEs were considered to be mild and not related to IMP.

No suicidal ideation or behaviour were reported by the safety set subjects during the trial based on Columbia-Suicide Severity Rating Scale.

The total MDS-UPDRS score decreased from baseline at endpoint, showing improvement following all treatments, with slightly higher median decrease of -3.0 points after both test

treatments compared to -2.5 points after exposure to Placebo. Improvements following all 3 treatments were observed for non-motor aspects of experiences of daily living (Part I) and motor signs of PD (Part III). Minimal mean changes (decrease) and median change of 0.0 points from baseline at endpoint after all treatments were noted for motor aspects of experiences of daily living (Part II). In contrary to other parts, mean scores of the Part IV assessing complications of PD therapy slightly increased from baseline at endpoint following all 3 treatments. The most pronounced mean [SD] change was observed following the Test 200/18 treatment (+0.6 [1.71] points) and the lowest following the Test 200/2 treatment (+0.2 [1.74] points). Median change of Part IV scores at endpoint was 0.0 points after all treatments.

No relevant changes from baseline were detected following each treatment either for the total QUIP-RS score or for the subscale scores as well as impulse control disorder (ICD) scores (median change from baseline at endpoint was 0.0 points for all treatments).

EFFICACY RESULTS:

The key efficacy endpoint in this trial were changes in mean ESS score at the end of each treatment period as compared to baseline. Secondary efficacy endpoints comprised the ESS responder rate, absence of residual somnolence (remission), PVT variable changes from baseline (reaction time, lapses, errors of commission, total errors), MoCA score changes from baseline, actimetry changes from baseline, the number and duration of diurnal involuntary sleep attacks as compared to baseline and changes from baseline regarding somnolence episodes as reported in the diary. In addition, summary statistics on serum concentrations of modafinil and flecainide were provided. All efficacy endpoints in this CTR were evaluated pooled by treatment.

In most of the subjects **ESS scores** decreased during treatment or at least remained almost the same as compared to baseline while increase of ESS scores was only observed in a few subjects. The most remarkable mean [SD] change from baseline overall could be observed after treatment with Test 200/2 (-3.9 [3.65] points absolute; -23.55 [28.600]% relative). Using a mixed linear regression model for statistical analysis, a statistically significant difference between treatments could be demonstrated when comparing Test 200/2 *vs* Placebo (p-value = 0.012) while no statistically significant differences could be observed when comparing Test 200/18 *vs* Placebo or Test 200/2.

The highest **responder rate** at the corresponding endpoint visit was observed after treatment with Test 200/2 (40.6%). However, statistical analysis of the responder rate revealed no statistically significant differences between treatments.

The highest proportion of subjects without **residual somnolence** at the corresponding endpoint visit was observed after treatment with Test 200/2 (27.5%) Statistical analysis showed that Test 200/2 just failed to reach significance *vs* Placebo (p-value = 0.0532), no significant differences in proportion of subjects with absence of residual somnolence could be found for Test 200/18 *vs* Placebo or *vs* Test 200/2 (p-value = 0.102).

For most subjects, no remarkable changes from baseline or only minor decreases were observed regarding **PVT mean response time**. The greatest overall mean [SD] absolute decrease from baseline at the corresponding endpoint visit was observed after treatment with Test 200/2 (-24.92 [81.279] ms). Statistical analysis revealed that changes from baseline were statistically significant for all three treatments, but no significant differences between treatments could be observed.

The greatest overall mean [SD] absolute decrease of **number of lapses** from baseline at the corresponding endpoint visit was observed after treatment with Test 200/2

(-0.63 [2.248] lapses). Similar results were observed for **total errors**. Regarding the number of **errors of commission**, the overall most remarkable mean [SD] decrease from baseline at the corresponding endpoint visit was observed after treatment with Placebo (-0.14 [0.707] errors of commission). Statistical analysis revealed no statistically significant changes from baseline or differences between treatments in any category of PVT errors.

At baseline and throughout the trial, all mean and median **MoCA scores** were above 26.0 points, showing no cognitive impairment. The mean (SD) total MoCA score slightly increased from 27.8 (1.74) points at baseline to 28.2 (2.17) points at V3B. The most pronounced mean (SD) increase of MoCA score from baseline at endpoint was observed for the Test 200/18 treatment (0.41 [1.49] points) compared to that for the Test 200/2 (0.0 [1.86] points) and for the Placebo (0.1 [1.51] points). Median change from baseline at endpoint for all treatments was 0.0 points. No statistically significant differences between any test treatment and Placebo as well as between the 2 test doses were observed. Covariate-adjusted estimates of changes from baseline were statistically significant only for Test 200/18 treatment changes at endpoint (*p*-value = 0.0267).

Analysis of **objective activity measures (actimetry)** showed that covariate-adjusted estimates of changes from baseline were statistically significant for the Test 200/18 treatment changes at endpoint for the night time immobility duration (*p*-value = 0.0141), diurnal immobility periods (*p*-value = 0.0474) and diurnal immobility duration (*p*-value = 0.0310), and for Placebo changes at endpoint for night physical activity (*p*-value = 0.0271). As the analysis of night physical activity data revealed a statistically significant treatment by period interaction (*p*-value = 0.0257), an additional analysis was performed for this parameter using only data collected during the first treatment period. No statistically significant treatment effect was found.

The median **number and duration of diurnal involuntary sleep attacks** decreased at the end of each treatment period as well as at endpoint as compared to baseline. The median number of diurnal involuntary sleep attacks decreased by -0.33 attack from baseline at endpoint of all 3 treatments.

The mean and median decrease of **somnolence episodes** from baseline was observed for all treatments at the end of each treatment period and at endpoint. The median number of somnolence episodes decreased from 1.67 episodes at baseline to 1.33 episodes at endpoint for all treatments.

The post-hoc analysis of the **duration of voluntary naps** revealed that covariate-adjusted estimates of changes from baseline were statistically significant for both test treatments (Test 200/2: *p*-value <0.0001; Test 200/18: *p*-value = 0.0012). Comparison between each pair of treatments showed statistically significant difference between the Test 200/2 and Placebo treatments (p-value = 0.0272), whereas no significant differences were observed between the Test 200/18 and Placebo or between the 2 test treatments.

For all subjects included in the PK analysis set, no flecainide was detected at all washout periods, whereas modafinil was detected after 4 to 9-day washout periods at either V1C or V2C for 4 subjects. No PK parameters based on plasma concentrations were analysed.

Overall, the Test 200/2 treatment showed statistically significant difference (improvement) *vs* Placebo for the key efficacy endpoint ESS change from baseline and results close to statistical significance for the absence of residual somnolence. Changes for Test 200/18 were greater than for Placebo but did not reach statistical significance for all ESS analyses. The other secondary efficacy endpoints did not show significant differences between the three treatment conditions,

with the exception of the diary data on duration of voluntary naps where Test 200/2 was significantly different from Placebo.

CONCLUSION:

Both THN102 doses were well tolerated in subjects with excessive daytime sleepiness associated with Parkinson's disease.

THN102 200 mg/2 mg significantly improved daytime sleepiness as measured by Epworth Sleepiness Scale compared to Placebo.

Additional trials to assess the long-term safety and efficacy of THN102 for the treatment of excessive daytime sleepiness associated with Parkinson's disease are necessary.

Date of the report:

23-JUL-2020