CLINICAL TRIAL PROTOCOL

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 code:	**THN102-202**
EudraCT:	**2017-004475-31**
IND No.:	**137871**
Phase:	**IIa (proof-of-concept)**
Version:	**Final 6.0**
Date:	**27 February 2019**
Product name:	**THN102 (modafinil, flecainide)**
Indication:	**Excessive daytime sleepiness in subjects with Parkinson's disease**

Sponsor's Medically Responsible Person

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Summary of Changes

Section(s)*	Change from Final Protocol Version 1.0, 11 January 2018, to Final Protocol Version 2.0, 08 March 2018	Change requested by
Title page, 14.1	The contact of the medical monitor for the USA has been added.	--
1.3.1, 3.1, 3.2, 6.1.6	The duration of the washout periods may be extended from 1 week to 2 weeks, if this is more convenient for the subject. As a consequence, the trial duration for the individual subject changes from 11 weeks to 11 – 13 weeks.	--
4.2	It has been emphasised that steroidal contraceptives must be combined with barrier methods (bold formatting in inclusion criterion no. 7).	FDA
4.3	In exclusion criterion no. 1, shift work sleep disorder has been added as a possible cause of excessive daytime sleepiness.	FDA
5.5	Information that modafinil may reduce effectiveness of steroidal contraception was added.	FDA (also requested by SÚKL)
5.5, 14.4	Instructions on concomitant medications that are CYP2D6 inhibitors, CYP3A or CYP2C19 substrates have been added. A list of concerned drugs has been provided as Appendix D.	FDA
6.1.1	UPDRS Part III will not be completed at VS1.	FDA
6.1.1, 6.2.1	It has been clarified that height has to be measured at visit VS1.	--
6.1.3, 6.1.5, 6.3.6, 8.1.1, 8.3.2, 13	UPDRS part III was replaced by MDS-UPDRS. MDS-UPDRS will be completed at VR, V1B, V2B and V3B/EDV. Statistical methods (safety) and references were updated.	FDA
6.1.3	At visit VR, three measurements of orthostatic vital signs will be performed 15-20 min apart.	FDA
6.1.3, 6.1.5	QUIP-RS will be assessed.	FDA
6.1.6	The ±1 time windows for visits V1C and V2C have been changed to -1/+7 time windows.	--
6.1.6	UPDRS Part III will not be completed at visits V1C and V2C.	FDA
	At visits V1C and V2C, three measurements of orthostatic vital signs will be performed 15-20 min apart.	FDA
6.3.3	Orthostatic vital signs (supine and standing) will be measured instead of sitting vital signs.	FDA
6.3.7, 8.1.1, 13	The QUIP-RS questionnaire has been added.	FDA
8.3.1	Procedure in case of significant treatment by period interaction has been added.	--
8.3.2	Information on vital signs' analysis has been updated, QUIP-RS and MDS-UPDRS have been added.	FDA

Section(s)*	Change from Final Protocol Version 2.0, 08 March 2018, to Final Protocol Version 3.0, 27 April 2018	Change requested by
6.1.3, 6.1.5, 6.1.6, 6.3.5	C-SSRS will be performed at all on-site visits.	FDA (also requested by SÚKL)
4.3	Exclusion criterion no. 9 has been modified to exclude subjects with hepatic or renal impairment, regardless of severity.	FDA

Section(s)*	Change from Final Protocol Version 3.0, 27 April 2018 to Final Protocol Version 4.0, 30 May 2018	Change requested by
Title page	IND number has been added.	--
4.2, 7.3	Methods of contraception have been modified.	SÚKL
4.3	Multiple system atrophy (Shy-Drager syndrome) has been added to exclusion criterion no.2.	EC of the LÄK Thüringen
4.3	Exclusion criterion no. 3 has been modified to provide a more detailed description of cardiovascular disorders.	EC of the LÄK Thüringen, SÚKL and EC Sud-Ouest et Outre Mer III, France
4.3	Exclusion criteria no. 8 and 9 have been modified by deleting "significant abnormality in physical examination or clinical laboratory results at VS1" from criterion no. 9 and adding to criterion no.8.	--
4.3, 5.5	Exclusion criterion no. 11f and the section on prior and concomitant medication have been modified. Use of efficacious medication for Parkinson's disease will be allowed if maintained at stable dosage levels.	SÚKL
	Centrally acting anti-obesity drugs and TNF-alpha inhibitors have been added as exclusion criteria nos. 11g and 11 h, and have been included as forbidden concomitant medication in Section 5.5.	--
4.3, 6.1.1, 6.2.5, 6.3.2, 13, 14.1, 14.2	Exclusion criterion no. 9 has been modified to exclude subjects with hepatic or renal impairment. New Section 6.2.5 related to calculation of glomerular filtration rate (for verification of renal impairment) has been added. Blood coagulation analysis (for verification of hepatic impairment) has been added to Sections 6.3.2, 14.1 and 14.2.	FDA
4.3, 6.3.5	Exclusion criterion no.6 will be met if the subject answers "yes" to items 4 and/or 5 of the C-SSRS only referring to the last month before VS1.	--
4.4.2	Additional criteria for subject's withdrawal from the trial have been added.	SÚKL and EC of the LÄK Thüringen
6.1.3, 6.1.5, 6.1.6, 6.5	No optional PK sampling will be done.	SÚKL
6.1.6, 6.3.4	ECG will be recorded at all on-site visits.	EC Sud-Ouest et Outre Mer III, France
6.3.5	Subjects who answer "yes" to point 4 and/or 5 of the C-SSRS will be withdrawn from the trial and sent for psychiatric consultation.	SÚKL
7.2.3	Procedures for SAE reporting have been clarified.	SÚKL
7.2.4	It has been clarified that the current version of the IB at the time of SAE reporting will be the reference for the assessment of unexpected SAEs.	SÚKL

* In addition, the changes have also been implemented in the protocol synopsis and the trial flow chart.

Note: Minor clarifications and corrections of typing errors are not listed above.

Section(s)*	Change from Final Protocol Version 4.0, 30 May 2018 to Final Protocol Version 5.0, 19 October 2018	Change requested by
Synopsis, 4.3	Exclusion criterion no. 9 has been modified to correct serum total bilirubin and prothrombin time values, based on Erratum to clinical trial protocol Final Version 4.0, 14-JUN-2018.	--
14.1	The contact details of the Medical Monitor in the US were updated.	--
Trial flow chart; 6.1.3, 6.1.5, 6.1.6, 6.4.2	If the PVT assessment schedule (10:00 h, 12:00 h, 14:00 h and 16:00 h) is too burdensome for the subject, it may be individually adapted to at least 3 assessments, with a time window of not less than 1 h between two PVT assessments. This change was implemented to relieve burden for those subjects who are not able to attend long-lasting trial visits. Its impact on the analysis of the PVT procedure should be limited as variables are analysed as a mean of the session performed at a given visit and not by timepoint.	Theranexus S.A.

Section(s)	Change from Final Protocol Version 5.0, 19 October 2018 to Final Protocol Version6.0, 27 February 2019	Change requested by
Synopsis, 4.2	Inclusion criteria no. 3 and 4 have been modified to increase the maximum age of subjects from 75 years to 80 years and the upper BMI limit from 30 kg/m^2 to 35 kg/m^2. The rationale for this change was the high pre-screening failure rate due to age and BMI restrictions. This change is considered acceptable given the exhaustive safety screening, including cognitive function (exclusion criterion no. 5) and mobility (inclusion criterion no. 2), and the exclusion of patients with cardiovascular risk factors (exclusion criterion no. 3) as well as the low dose of flecainide used in this trial.	Theranexus S.A.
1.2, 12.2, 12.3, 13	The reference was changed to the updated IB version 4.0, 24-JAN-2019 instead of the reference to the IB version 3.0, 20-OCT-2017. The references to the EMA and FDA were deleted in Section 1.2.	-

TRIAL SYNOPSIS

Sponsor: Theranexus S. A., 86, rue de Paris, F-91400 Orsay, France.
Name of active ingredients: Modafinil, flecainide.
Trial title:
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.
Protocol number: THN102-202
EudraCT number: 2017-004475-31
Coordinating investigator:
[redacted]
Investigators / trial sites: An estimated 28 sites in Europe and the USA.
Planned duration of the trial:
First subject first visit: Q2/2018
Last subject last visit: Q4/2018
Phase: IIa (proof-of-concept)
Objectives:
Primary objective:

- 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).

Secondary objectives:

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 / trial design:
This is a prospective, double-blind, randomised, controlled trial using a complete 3-way cross-over design. Subjects will attend seven on-site visits and five phone call visits.

The seven trial periods are depicted below:

Screening	Treatment I	Washout I*	Treatment II	Washout II*	Treatment III	Follow-Up
1-2 weeks No treatment	2 weeks A, B, or C	1(2) weeks No treatment	2 weeks A, B, or C	1(2) weeks No treatment	2 weeks A, B, or C	1 week No treatment

(Dose A = placebo; Dose B = THN102 200 mg/2 mg; Dose C = THN102 200 mg/18 mg.)
* Washout periods can be extended to up to 2 weeks, if this is more convenient for the subject.

At visit VR (baseline visit) the subjects will be equally randomised (1:1:1:1:1:1) double-blind to a treatment sequence containing three treatment periods (shown below).

Sequence	Treatment period I	Treatment period II	Treatment period III
1	Dose A	Dose B	Dose C
2	Dose B	Dose C	Dose A
3	Dose C	Dose A	Dose B
4	Dose A	Dose C	Dose B
5	Dose C	Dose B	Dose A
6	Dose B	Dose A	Dose C

The duration of each treatment period is 2 weeks, with a 1-week washout in between (to avoid carry-over effects) and a 1-week follow-up period after the last treatment period. Washout periods can be extended up to two weeks. THN102 will be administered orally once daily.

Number of subjects (planned): Enrolled and screened: 72, randomised and evaluable (safety): 60, evaluable (efficacy): 54.
Indication: Excessive daytime sleepiness associated with Parkinson's disease.
Inclusion criteria:
1. Subjects with a diagnosis of idiopathic Parkinson's disease as defined by the Movement Disorders Society (MDS).
2. Subjects with Hoehn and Yahr scale score ≤ 4.
3. Males or females, aged between 18 and 80 years.
4. Body mass index > 18 kg/m^2 and < 35 kg/m^2.
5. Subjects should have a complaint of daytime sleepiness impacting their quality of life and/or daytime functioning (e.g. falling asleep while reading or watching TV, while eating or talking with other people).
6. Epworth Sleepiness Scale (ESS) score ≥ 14.
7. Women of childbearing potential (not surgically sterile or < 2 years postmenopausal), must use a highly effective method of contraception, and must continue for the duration of the trial (and for 2 months after participation in the trial). Highly effective methods of contraception include hormonal contraception associated with inhibition of ovulation (combined estrogen/progestogen: oral, intravaginal, transdermal; progestogen-only: oral, implanted, and injected) **in conjunction with** a barrier method (preferably male condom). Highly effective methods further include intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that the partner is the sole sexual partner of the subject and the vasectomised partner has received medical assessment of the surgical success) and sexual abstinence, i.e. when this is in line with the preferred and usual lifestyle of the subject.
8. Subjects willing and able to follow trial procedures (including to swallow IMP capsules) and to regularly attend scheduled clinic visits as specified in the protocol, and who have signed the informed consent prior to any screening procedure.

All above-mentioned inclusion criteria will be checked at VS1.
At VR the following inclusion criteria will be re-checked: 5, 6, 7, 8.

Exclusion criteria
1. Subjects with known or with a suspected sleep apnea syndrome or who have any other cause of excessive daytime sleepiness, such as shift work sleep disorder.
2. Psychiatric and neurological disorders (other than Parkinson's disease), such as idiopathic narcolepsy, Alzheimer's disease, Huntington's Chorea, multiple sclerosis, epilepsy, psychosis, bipolar disorder, severe clinical anxiety or depression, multiple system atrophy (Shy-Drager syndrome) or other problem that in the investigator's opinion would preclude the subject's participation and completion of this trial or comprise reliable representation of subjective symptoms.
3. Cardiovascular disorders such as
   a. Uncontrolled moderate to severe hypertension
   b. ECG QTcF duration ≥ 450 ms (men) or ≥ 470 (women)
   c. ECG signs of left ventricular hypertrophy (exclusion if at least one of the three indices is abnormal):
      - Sokolow-Lyon voltage (sum of amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 ≥ 3.5 mV), or
      - Cornell voltage (S wave in V3 + R wave in aVL > 2.8 mV in men or > 2.0 mV in women), or
      - Modified Cornell (R wave in aVL > 1.1 mV)
   d. Recent (less than three months before screening visit VS1) myocardial infarction
   e. Stable or unstable angina pectoris
   f. Cardiac insufficiency
   g. Previous history of heart failure
   h. Previous history of cardiac valvular surgery
   i. Ventricular arrhythmias considered as clinically significant

   j. Atrial fibrillation unless it is stable and controlled by stable doses of amiodarone, calcium channel blocker or beta-blocker
   k. 2nd or 3rd grade atrioventricular block or chronic bifascicular block, unless an adequate pacemaker is present
   l. Sinus node dysfunction
   m. Documented Brugada syndrome
4. Subjects with current impulse control disorder.
5. Subjects showing dementia or with MoCA < 23.
6. Subjects with current suicidal risk, based on investigator's clinical judgement or with a "yes" answer to item 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at VS1, referring to the last month before screening.
7. Current or recent (within one year) history of substance abuse or dependence disorder as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-V), e. g. alcohol. Tobacco use is accepted.
8. Other active clinically significant illness, including unstable cardiovascular or malignant pathology, significant abnormality in physical examination or clinical laboratory results at VS1, which could interfere with the trial conduct or counter-indicate the trial treatments or place the subject at risk during the trial or compromise the trial participation.
9. Subjects with hepatic impairment (serum total bilirubin ≥2 mg/dL, except in patients diagnosed with Gilbert's syndrome, or prothrombin time [PT] ≥ 13.7 s (except in patients on therapeutic anti-coagulation), or serum albumin < 3.5 g/dL), or renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2, according to Kidney Disease Improving Global Outcomes (KDIGO)).
10. Known hypersensitivity to IMP (active ingredients or excipients of modafinil or flecainide capsules).
11. Subjects currently (or within 6 weeks before VS1) under one of the following medications (isolated intake up to 1 week can be accepted):
    a. Neuroleptics, anxiolytics, anticonvulsants. Benzodiazepines and benzodiazepine-like drugs are only authorised if used regularly at stable indicated doses with an evening intake as sleep promoting agents.
    b. Flecainide or other class I antiarrhythmic drugs.
    c. Psychostimulants (except caffeine if no abuse and stable consumption) such as, but not limited to, modafinil, methylphenidate, amphetamine.
    d. Antidepressants except if maintained at stable dose for at least 6 weeks before visit VS1 and anticipated to remain stable during the trial in subjects with mild or moderate unipolar depression.
    e. Antiemetic medications (except domperidone), myo-relaxing drugs and opioids.
    f. Dopaminergic medications, unless they have been used at stable doses for at least 4 weeks before screening and it is anticipated that the doses will not be changed throughout the trial. Efficacious medication for Parkinson's disease should not be discontinued for the sole purpose of the subject's enrolment into this clinical trial but must be maintained at stable dosage levels.
    g. Centrally acting anti-obesity drugs.
    h. TNF-alpha inhibitors.
12. Pregnancy or lactation. Women of childbearing potential who intend to be pregnant during the next few months.
13. Subjects protected by the law (legal guardianship).
14. Subjects participating in any other clinical trial within 60 days prior to visit VS1 in this trial or still in the protected period imposed by a previous trial.
15. Subjects working in an occupation requiring variable shift work or routine night shifts.
16. Subjects who plan to travel involving time zone changes.

All above-mentioned exclusion criteria will be checked at VS1.
At VS2 it will be checked if laboratory results, new AEs or new concomitant medication conflict with any of the exclusion criteria.
At VR the following exclusion criteria will be re-checked: 5, 11-12, 15, 16.

Duration of treatment for the individual subject:
8-10 weeks (including two 1-2-week washout periods in between without treatment),
the net treatment duration is 6 weeks.

Investigational medicinal products:
Modafinil capsules (100 mg), or matching placebo.
Flecainide capsules (1 mg, 9 mg), or matching placebo.
Oral administration of 2 modafinil and 2 flecainide capsules (i.e. 4 capsules in total), once daily in the morning at 08:00 h (± 1:00 h). A 24-hour (± 1:00 h) interval between two consecutive doses is required.

Dose	Modafinil		Flecainide		THN102
A	2 capsules (0 mg)	0 mg	2 capsules (0 mg)	0 mg	placebo
B	2 capsules (100 mg)	200 mg	2 capsules (1 mg)	2 mg	200 mg/2 mg
C	2 capsules (100 mg)	200 mg	2 capsules (9 mg)	18 mg	200 mg/18 mg

For subjects aged above 65 years:
On the first, second and third day of each treatment period, 1 modafinil and 1 flecainide capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.

Criteria for evaluation:
Safety
- Adverse events
- Safety laboratory (haematology, biochemistry, urinalysis)
- Vital signs (blood pressure, heart rate)
- 12-lead electrocardiogram (ECG)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale (MDS-UPDRS)
- Questionnaire for Impulsive-Compulsive Disorders in Parkinson’s Disease – Rating Scale (QUIP-RS)

Efficacy
- Epworth Sleepiness Scale (ESS)
- Psychomotor Vigilance Test (PVT)
- Montreal Cognitive Assessment (MoCA)
- Actimetry (inactivity evaluation)
- Subject diaries (get-up time, total time [hours] slept last night, wake-up periods during night sleep, time of drug intake, number of capsules taken, somnolence episodes, diurnal involuntary sleep attacks, voluntary naps, number of caffeinated drinks, going-to-bed time)

Pharmacokinetics
- Modafinil and flecainide concentrations in plasma

Statistical methods
Safety endpoints
1. Adverse events
2. Safety laboratory
3. Vital signs change
4. Electrocardiogram assessments
5. Columbia-Suicide Severity Rating Scale (C-SSRS)
6. MDS-UPDRS
7. QUIP-RS

Efficacy endpoints

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

Sample size justification

For the purpose of sample size planning ESS is considered to be the key efficacy endpoint. Solid information on the expected difference between placebo and THN102 dose and the associated intrasubject variance are not available. Using results reported in Adler et al. 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 will 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 will be randomised.

Analysis populations

- The Safety Set (SS) includes all subjects who have received IMP at least once.
- The Full Analysis Set (FAS) includes all randomised subjects with an evaluable ESS score at the end of at least one treatment period. The efficacy analyses will be conducted on the FAS.
- The Per Protocol (PP) set includes all subjects who have completed the trial without major protocol deviation. Major and minor violations will be defined in the SAP. The main secondary endpoints (ESS, PVT and cognition) will be analysed with the PP set to demonstrate robustness of the primary analysis.
- The pharmacokinetic (PK) analysis set will include all subjects who have received treatment as per protocol (even if the trial was not completed) and who present no major protocol deviations with an impact on PK.

Efficacy analysis

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - will be analysed using a mixed linear regression model. The model will include 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 – will be analysed using a mixed effects logistic regression model, 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 will be reported with their standard errors and 95% confidence intervals. The significance of the differences between Treatment A (THN102 Placebo), Treatment B (THN102 200/2) and Treatment C (THN102 200/18) will be assessed with a contrast t-test at the two-sided 5% level.

Supportive analysis
The same analysis will be repeated on the PP set, to assess robustness of the analysis of the variables from ESS and PVT and possibly on other efficacy results. Subgroup analyses may be performed to investigate the effect of the main demographics (age, gender) and disease characteristics (in terms of daily sleepiness extent, and cognitive impairment) on the efficacy outcomes.

The presence of a significant treatment by period interaction term in the main model may indicate a residual treatment (carryover) effect. In case of a significant treatment by period interaction, period I results will be analysed separately, and further analyses will be performed to explore the carry-over effects. The methods for evaluation of carryover effects will be defined in the SAP.

Safety analysis
Safety data will be summarised using summary statistics and frequency tabulations, as appropriate.

Pharmacokinetics

- Plasma concentrations of modafinil and flecainide at visits VR, V1B, V1C, V2B, V2C and V3B, considering time after last IMP intake.
- Concentration-time data per treatment and subject for modafinil and for flecainide. Plasma concentrations and time post IMP intake, to assess range of exposure at steady state for each treatment.

Trial flow chart

	VS1	VS2	VR	V1A	V1B	V1C	V2A	V2B	V2C	V3A	V3B/ EDV[11]	V3C
	Screening	Actigraphy	Baseline	Actigraphy	End of treatment I	End of washout I	Actigraphy	End of treatment II	End of washout II	Actigraphy	End of treatment III	Follow-up
Visit day[1]	**D-15 to D-7**	**D-5 ±1[9]**	**D-1[9]**	**D10 ±1[9]**	**D14 ±2[9]**	**D21[13] - 1/+7**	**D31 ±1[9]**	**D35 ±2[9]**	**D42[13] - 1/+7**	**D52 ±1[9]**	**D56 ±2[9]**	**D63 ±1**
On-site visit / phone call visit												
Informed consent	X											
Hand out subject card	X											
Demography (incl. height measurement)	X											
Medical history, prior medication	X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Hoehn & Yahr staging	X											
Check for eligibility	X	X	X									
Randomisation			X									
IMP dispensation			X			X			X			
IMP accountability, compliance check, collect IMP					X			X			X	
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory (blood, urine)[2]	X		X		X			X			X	
Pregnancy test (urine)[3]	X		X		X			X			X	
Vital signs[4]	X		X		X	X		X	X		X	
Weight[5]	X		X		X			X			X	
12-lead ECG (10 min supine)	X		X		X	X		X	X		X	
C-SSRS[6]	X		X		X	X		X	X		X	
MDS-UPDRS			X		X			X			X	
QUIP-RS			X		X			X			X	
Physical examination	X		X		X			X			X	
ESS	X		X		X	X		X	X		X	

	VS1	**VS2**	**VR**	**V1A**	**V1B**	**V1C**	**V2A**	**V2B**	**V2C**	**V3A**	**V3B/ EDV[11]**	**V3C**
	Screening	Actigraphy	Baseline	Actigraphy	End of treatment I	End of washout I	Actigraphy	End of treatment II	End of washout II	Actigraphy	End of treatment III	Follow-up
Visit day[1]	**D-15 to D-7**	**D-5 ±1[9]**	**D-1[9]**	**D10 ±1[9]**	**D14 ±2[9]**	**D21[13] - 1/+7**	**D31 ±1[9]**	**D35 ±2[9]**	**D42[13] - 1/+7**	**D52 ±1[9]**	**D56 ±2[9]**	**D63 ±1**
On-site visit / phone call visit												
PVT[7], upload data			X		X	X		X	X		X	
MoCA[10]	X		X		X	X		X	X		X	
Remind subject to wear actigraphy device[9]		X		X			X			X		
Collect and charge actigraphy device			X		X			X			X	
Read out actigraphy device, upload data[9]			X		X			X			X	
Issue actigraphy device (fully charged)	X		X			X			X			
Issue subject diary[8]	X		X			X			X			
Check subject diary[8]			X		X	X		X	X		X	
Collect subject diary[8]			X			X			X		X	
PK blood samples[12]			X		X	X		X	X		X	

C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EDV = early discontinuation visit; ESS = Epworth Sleepiness Scale; IMP = investigational medicinal product; MDS-UPDRS = Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale; MoCA = Montreal Cognitive Assessment; PK = pharmacokinetics; PVT = Psychomotor Vigilance Test; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale.

1. There is no Day 0 (D0), i.e. the day after D-1 is D1. First IMP intake will be on Day 1. (On the day after V1C for treatment period II, on the day after V2C for treatment period III).
2. Safety laboratory will include haematology, biochemistry and urinalysis. At VS1 also serology and blood coagulation.
3. Urine pregnancy tests will be done in women of childbearing potential only. They may be performed more frequently to meet country-specific requirements.
4. Vital signs: Systolic and diastolic blood pressure as well as heart rate will be measured twice: after 5 minutes of supine rest and after 2 minutes in standing position (one set). At VR, V1C and V2C three sets of supine and standing vital signs will be measured 15-20 min apart.
5. Weight will be measured in street clothes without shoes.
6. At VS1 the C-SSRS Screening version will be completed. At other visits, the C-SSRS Since Last Visit version will be completed.
7. PVT will be done at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each). If this PVT assessment schedule is too burdensome for the subject, it may be individually adapted to at least 3 assessments, with a time window of not less than 1 h between two PVT assessments. Once chosen, the timeframe should remain constant during the trial for each subject.

8. The subject diary will be used continuously (i.e. also during washout periods) to record get-up time, total time (hours) slept last night, wake-up periods during night sleep, time of drug intake and number of capsules taken (except screening phase diary issued at VS1), somnolence episodes, diurnal involuntary sleep attacks, voluntary naps, number of caffeinated drinks and going-to-bed time.
9. Visits V1A and V1B should be scheduled so that 3 days of actigraphy data can be collected. (The same for VS2 and VR, V2A and V2B, as well as V3A and V3B.) Actigraphy will be assessed using an actigraphy wrist band.
10. MoCA should be performed in the morning.
11. In case of early discontinuation, the same procedures as required for V3B will be performed.
12. One PK blood sample will be taken when the subject arrives on the site. The times of blood withdrawal must be recorded.
13. Starting from Day 21, the visit day numbers are theoretical, as the washout period is flexible and can be extended to up to 14 days. The 2-week duration of the treatment period is fixed.

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LIST OF ABBREVIATIONS

AE	adverse event
ALQ	above limit of quantification (assay)
ALT	alanine aminotransferase (SGPT)
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (French Health Agency)
AST	aspartate aminotransferase (SGOT)
AUC	area under the curve i.e. area under the plasma concentration versus time curve over time periods (AUC_{0-t}, $AUC_{0-\infty}$)
BMI	body mass index = body weight (kg) / height^2 (m^2)
CA	competent authority
CNS	central nervous system
C_{max}	maximal plasma concentration after oral treatment
CMO	chief medical officer
CRO	contract research organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CTR	clinical trial report
CYP450	cytochrome P450
CV	coefficient of variation
DMP	data management plan
DSUR	development safety update report
EC	Ethics Committee
eCRF	electronic case report form
ECG	electrocardiogram
EDS	excessive daytime sleepiness
EDV	early discontinuation visit
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
hCG	human chorionic gonadotropin
IB	investigator's brochure
ICD	impulse control disorder
ICF	informed consent form
ICH	International Council for Harmonisation
IEC/IRB	independent ethics committee / institutional review board
IMP	investigational medicinal product
ISF	investigator site file
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
KDIGO	Kidney Disease Improving Outcomes
LÄK	State Chamber of Physicians, Germany
LC-MS/MS	liquid chromatography-mass spectrometry/mass spectrometry (liquid chromatography-tandem mass spectrometry)
LLOQ	lower limit of quantification (assay)
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment

PCA	Pharmacie Centrale des Armées (Central Army Pharmacy)
PD	Parkinson's disease
PK	pharmacokinetics
PP set	Per Protocol set
PT	prothrombin time
PVT	Psychomotor Vigilance Test
QRS	combination of three of the graphical deflections on an electrocardiogram
QT	duration between Q wave and T wave on the ECG (expressed in ms)
QTcF	corrected QT-interval (Fridericia's formula) in ECG (expressed in ms)
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
SmPC	summary of product characteristics
SS	Safety Set
SÚKL	State Institute for Drug Control, Czech Republic
SUSAR	suspected unexpected serious adverse reaction
THN102	Theranexus internal code for the combination modafinil and flecainide
TMF	trial master file
TNF	tumour necrosis factor
$t_{1/2}$	terminal elimination half-life
t_{max}	time to reach maximal drug concentration in biological matrix (plasma)
WBC	white blood cells
WHO	World Health Organisation

1. INTRODUCTION

1.1. Background

Parkinson's disease (PD) is one of the most common neurodegenerative disorders with an estimated prevalence of about 1% in subjects over 60 years of age. Among the non-motor symptoms of PD, sleep disorders are prominent and have a considerable negative effect on the quality of life of the patients. Excessive daytime sleepiness (EDS) occurs in 20-50% of PD patients, it appears to be linked to disease severity and duration. Current hypotheses about the etiology of EDS include neurodegenerative dopamine denervation, effects of dopaminergic drugs and nocturnal sleep disruption. [1,2] Currently there is no drug treatment approved for EDS in PD. Modafinil has been used in three small trials [3,4,5] with positive results in two of the three trials and was well tolerated. Pitolisant, an H3 inverse agonist has been tested in large scale phase III trials, however, results are not published. Phase II trials in EDS in PD subjects are ongoing with JZP-110, a norepinephrine-dopamine reuptake inhibitor and BEN-2001 (bavisant), an H3 antagonist (Source: ClinicalTrials.gov).

Modafinil, a wake promoting agent with a unique profile different from amphetamine, produces enhanced vigilance and arousal, is generally well tolerated and has been approved in the US for the treatment of daytime sleepiness in narcolepsy, [6,7,8,9]obstructive sleep apnea, and shift work disorder. In Europe the indication is limited to EDS in narcolepsy. Modafinil also has shown activity in fatigue in cancer, in neurodegenerative disorders, etc.). [10] Besides, many common situations involve short or long sleep deprivation periods or wake-sleep rhythm modifications. Sleep loss alters attention and vigilance, and reduces operational performance. Modafinil works well in sleep-deprived subjects to support vigilance, cognitive performance, coping skills, and recovery sleep. [11,12,13,14,15] Positive impact on cognition, performance, and mood was seen in healthy subjects. [16,17]

Context: Theranexus has investigated new potential drugs for treating narcolepsy and cataplexy among others. 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, preliminary data have been published. [18]

Non-clinical safety pharmacology: According to scientific advice from the French Medicines Agency (ANSM) a safety pharmacology study was conducted in alert dogs monitored by telemetry over 24 hours prior to initiation of phase I and phase II. Vital signs, body temperature, and motor activity were recorded as well as ECG to investigate impact on cardiac electrophysiology profile and potential for arrhythmias with incremental single doses of 50/3, 50/9 and 75/9 mg/kg modafinil/flecainide acetate. Concomitantly to the dose-dependent increase in heart rate and blood pressure linked to spontaneous motor activity and estimated to be elicited by modafinil pharmacological activity, the PR and the QT intervals were shortened. No significant effects on the QRS or the corrected QT (Fridericia's and van de Water's formulae) intervals were noted. No arrhythmia and no other morphology change were observed over the test periods in any dog in this model, which is considered as highly predictive for man.

First phase I trial in healthy volunteers: The safety and tolerance of THN102 was recently investigated in a 3-way cross-over, randomised, double-blind trial in 9 healthy male volunteers comparing single oral doses of THN102 (400 mg modafinil/50 mg flecainide acetate) to 400 mg modafinil/placebo and to placebo/placebo (trial THN102-101). The 50 mg dose selected for flecainide in phase I is derived of electrophysiological activity when administered alone and more than twice the maximum dose planned (18 mg) in this trial. In the phase I trial (THN102-101) body temperature as well as supine blood pressure and heart rate were increased over time in subjects with THN102 and modafinil treatment vs. subjects on placebo. No orthostatic symptoms were seen for any treatment. Safety and tolerance profile for adverse events was good and similar for THN102 and modafinil. In the 24 h Holter analysis performed by a central ECG laboratory blinded to treatment, no impact on cardiac electrophysiology was seen on QRS and QTcF (Fredericia's formula) and no indication of arrhythmia or of morphological changes were documented for

THN102 and modafinil versus placebo. A marginal PR shortening for both active treatments was seen in line with the clear positive chronotropic effect. Addition of flecainide had no impact on the pharmacokinetic profile of modafinil, and parameters measured were similar (including C_{max}, t_{max}, $t_{1/2}$, and AUC) to modafinil given alone, and flecainide had the anticipated mean terminal plasma $t_{1/2}$ (12.2 h) and median t_{max} (3 h) but a lower C_{max}, possibly due to lack of dose linearity when administering at low dose.

Second phase I trial in sleep-deprived healthy volunteers: A phase Ib trial has been terminated in Q2 2016, in 20 healthy male volunteers undergoing a 40-hour sleep deprivation protocol. This trial THN102-102 included 20 healthy male subjects, in a double-blind, randomised, incomplete-block 3-period cross-over design involving 5 treatments (n=12 per group): placebo, modafinil 100 mg, and combinations THN102 (modafinil 100 mg and 1, 3 or 9 mg flecainide as THN1, THN3 and THN9), as 3 oral doses over 18 h. THN102-treated volunteers showed a statistically significant improvement in their vigilance levels (PVT with speed as primary endpoint) versus modafinil alone without showing a linear dose effect. Secondary endpoints assessing cognition (2-back, Go-NoGo, Wisconsin Sorting Card Task) were consistent with this effect. These results reinforce the interest in THN102 for the treatment of excessive daytime sleepiness, a debilitating symptom affecting a number of patients with CNS disorders such as narcolepsy and Parkinson's disease.

Ongoing phase IIa trial in narcoleptic subjects: A phase IIa trial (Trial THN102-201, double-blind, crossover design with 3 randomised periods with 300 mg modafinil + placebo, 300 mg modafinil + 3 mg flecainide and 300 mg modafinil + 27 mg flecainide per day) is ongoing since September 2016. 48 narcoleptic subjects will be included in a prospective, 5-site, placebo-controlled trial using a complete 3-way cross-over design after a 2-week stabilisation period with modafinil and followed by 1-week washout.

Objectives of this phase IIa trial: The most appropriate flecainide dose in THN102 remains to be selected in subjects with Parkinson's disease (PD) experiencing excessive daytime sleepiness (EDS). This trial aims at assessing safety of THN102, efficacy on EDS, vigilance and cognition as well as modafinil and flecainide plasma levels at steady state.

It is assumed that THN102 treatment should improve the excessive daytime sleepiness (EDS), without changing the safety profile seen with modafinil in Parkinson's disease subjects.

1.2. Test Drugs

Extensive information on modafinil and flecainide can be found in their respective SmPCs (Summary of Product Characteristics, see investigator brochure, IB [31] Section 7 and 8). A table summarising the key features for both compounds and covering mechanism of action, safety pharmacology, pharmacokinetic profile, metabolism, dosing and most prevalent adverse events is provided in Table 1. Both compounds have been on the market for more than 20 and 30 years, respectively. At least one million patients have received modafinil for narcolepsy and other medical conditions worldwide and several millions have been treated with flecainide acetate.

A review of THN102 pharmacology profile and safety pharmacology is provided in the IB. A dedicated electrophysiology study was performed in conscious dogs under telemetry with THN102 and no change on QTcF and QRS was detected up to maximum combination given (75 mg/kg modafinil + 9 mg/kg flecainide acetate) and no occurrence of arrhythmias was observed. Blood pressure, body temperature, and activity especially at night were increased, presumably linked to the awakening effects of THN102.

Table 1: Characteristics of modafinil and of flecainide

	Modafinil	Flecainide Acetate
Indication and mechanism of action		
	• Modafinil is approved for the treatment of narcolepsy with and without cataplexy. • The mechanism of action is partly understood and involves modulation of several neurotransmitters in the brain	• Flecainide is used to prevent and treat tachyarrhythmias. • It has local anaesthetic activity and belongs to the membrane stabilising (Class 1) group of antiarrhythmic agents. • It blocks Nav1.5 sodium channel in the heart, slowing the upstroke of cardiac potential (especially on His-Purkinje system and ventricular myocardium).
Safety Pharmacology		
	• Mild increase of blood pressure, heart rate and temperature at mid and high doses (mainly at 200 and 400 mg) • Rare occurrences of ventricular arrhythmia [19] • Well tolerated	• Prolongs QT interval and widens QRS complex. • Related to systemic exposure in conscious dogs and in man [20] • Narrow therapeutic range
Pharmacokinetic Profile		
	• Oral bioavailability: 40-65% • Plasma concentrations linear and time-independent • Dose proportional between 200 to 600 mg • T_{max}: 2 to 4h (tablet) • C_{max} delayed 1h by food • C_{max}: 3.7 to 4.8µg/mL (200 mg dose) • Terminal half-life: 15 h (range 10-15h) • Impact of ethnicity and gender • Protein binding: 60% [21]	• Oral bioavailability: 95% • Plasma concentrations approximately dose dependent within therapeutic range but unclear when below • T_{max}: 1.5 to 3 h (tablet) • No food interaction • C_{max}: 200 to 1,000 ng/mL (100-300 mg) • Terminal half-life: 13 h (mean across single dose studies, range wide). • Protein binding: 40% [22,23]
Metabolism (human)		
	• Amide pathway (major) and oxidative pathway (minor) • Substrate: multiple CYP450 including CYP3A4/3A5 • Metabolised by liver • ≤5% intact drug excreted in urine [24] No anticipated interaction with Flecainide metabolism (different CYP450 pathway) 200 to 400 mg/day (in narcolepsy) Registration: 1992 (France), 2003 (USA)	• Substrate: CYP2D6 (mainly) and 1A2 • Metabolised by liver • ~30% intact drug in urine [25] No anticipated interaction with Modafinil metabolism (different CYP450 pathway) 100 to 300 mg/day (in tachyarrhythmia) Registration: 1983 (France)
Adverse events cited in SmPC from EMA (chronic therapy, with above posology)		
>10%	• Headache	• Dizziness, light headedness, headache • Visual disturbances
1-10%	• Nervousness, insomnia, anxiety, depression, confusion • Dizziness, somnolence, paraesthesia • Tachycardia, palpitation • Blurred vision • Abdominal pain, nausea, dry mouth, diarrhea, constipation and others • Chest pain, asthenia • Increased liver function tests	• Depression, anxiety, insomnia • Paraesthesia, ataxia, tremor, syncope… • Palpitation • Nausea, vomiting, abdominal pain and others • Dyspnea • Asthenia, fatigue, oedema

An extensive list of adverse events is presented in each SmPC, albeit from patients on chronic treatment, frequently on concomitant therapy and at a much higher dose in case of flecainide. These documents will serve as a basis to identify Suspected Unexpected Serious Adverse Reactions (SUSAR) in this trial (also see Section 7.2.2).

Very rare incidence of severe cutaneous skin reactions (such as Stevens-Johnson syndrome, DRESS syndrome or Toxic Epidermal Necrosis) may occur with modafinil. As reviewed in the SmPC the incidence in clinical trials was found to be 0.8% in children (13 withdrawn out of 1585 cases and also including serious cutaneous adverse events) and 0% in adults based on exposure of 4264 patients.

1.3. Rationale for Trial Design and Dose Selection

1.3.1. Trial design

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 Parkinson's disease subjects suffering from excessive daytime sleepiness. The sample size required for a crossover design is approximately one third of the size required in a parallel trial. To use a cross-over option is thus a viable alternative design, with a sample size of about 60 subjects in this condition. In addition, a direct comparison between THN102 doses can be performed in the same subject. The selected trial design for this pilot proof-of-concept phase IIa trial is consequently a randomised, placebo-controlled, 3-way cross-over trial design comparing two dose levels of THN102 to placebo and followed by a washout period of 1-2 weeks. It was perceived as essential to take advantage of the cross-over design for exploring two doses of THN102 and comparing their impact on safety, ESS and other efficacy endpoints. The treatment duration of 2 weeks per period appears sufficient to observe therapeutic activity as the steady state will be reached after about 3 days of drug intake. Each treatment period is followed by a one-week washout period, which can be extended up to two weeks. In addition to the key efficacy endpoint, ESS, other efficacy endpoints have been selected, such as cognitive assessments including PVT and MoCA before and after each treatment period.

A difference of 25% in ESS is considered clinically relevant. [26] Therefore responder rates will be analysed, with responders being defined as subjects with at least 25% improvement from baseline.

1.3.2. Dose selection

Based on the reported trial data with modafinil in PD subjects, a single morning dose of 200 mg was chosen, as it showed efficacy on EDS [3,5]. (Subjects aged above 65 years will be started on 100 mg during the first three days.) Trials using a higher dose (up to 400 mg) failed to show increased efficacy. [4] The flecainide doses were chosen based on preclinical pharmacological and exposure data as well as results of the phase Ib trial including healthy subjects after total sleep deprivation (THN102-102).

1.4. Risk/Benefit Ratio

1.4.1. Evaluation of risk

It is anticipated that the safety and tolerance profile of THN102 is similar to that of modafinil given alone in a PD-EDS population, with frequent occurrence of headache, gastric pain, palpitation, tachycardia, dizziness, insomnia, anxiety, confusion, and blurred vision (see Table 1).
For the treatment of tachyarrhythmias, flecainide is given at daily doses between 100 and 300 mg. In the present trial flecainide will be administered for EDS at two very low doses (2 mg, 18 mg as a single daily dose). In previous clinical studies with THN102 flecainide reached a mean (±SD) maximal concentration of 44.9±9.6 ng/mL when 50 mg were given as a single dose (study THN102-101), and of 19.5 ng/mL after 27 mg (3 doses of 9 mg over 20 hours). The C_{max} data appeared linear between flecainide doses of 3, 9, and 27 mg: 2.2±0.8 ng/mL, 6.4±2.2 ng/mL, and 19.5±4.5 ng/mL respectively. Extrapolating from steady state C_{max} of 100 mg of flecainide [25] (173±46 ng/mL), one would expect a steady state C_{max} for 18 mg/d, the maximal flecainide dose used in this trial, of about 30 ng/mL. This exposure level is well below exposure levels where cardiovascular AEs are expected for flecainide. [27] Flecainide does not trigger any significant cardiovascular effects below 100 ng/mL or even 200 ng/mL in plasma. [28,29,30]

Thus, no cardiac effect is expected at the very low flecainide concentrations associated with the prescribed doses used in this trial and flecainide is not expected to raise any safety and tolerance issue in combination with THN102. As a precautionary measure cardiovascular exclusion criterion 3 has been included.

In the two phase I trials with THN102 the adverse events' profile did not significantly differ between THN102 and modafinil. A small but significant increase in blood pressure and heart rate was noted with both THN102 (400 mg/50 mg) and modafinil (400 mg/0 mg) in trial THN102-101 with 24-hour Holter

monitoring. No impact on cardiac conduction (QT, QRS) and no arrhythmia were seen (for more details, see the IB [31]). The lists of typical adverse events reported for modafinil and for flecainide are also listed in the IB and mentioned in the information for the subject.

Risk will be minimised by regular contact between subject and investigator and by close safety monitoring.

1.4.2. Evaluation of benefit

These subjects have documented excessive daytime sleepiness (EDS) and it is expected that THN102 at one or both doses may significantly improve excessive daytime sleepiness, decreasing episodes of sleepiness and sleep attacks and may even improve night sleep in quantity and quality.

This is a proof-of-concept trial in approximately 60 PD subjects with EDS treated with THN102 at two doses (200 mg/18 mg, 200 mg/2 mg) compared to placebo under a 3-way, double-blind, cross-over trial design. The exposure is thus limited (2 weeks at each dose). This design might contribute to a better understanding of the mode of action of THN102 in the target population, to define the profile for dose response and time response and to assess recovery after washout. If successful, a phase IIb-III trial could be initiated in the future.

In summary, the risk/benefit ratio for this proof-of-concept trial is considered as satisfactory.

2. OBJECTIVES

2.1. Primary Objective

- 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).

2.2. Secondary Objectives

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.

3. TRIAL DESIGN

3.1. Overall Trial Design and Plan

This is a prospective, double-blind, randomised, controlled trial using a complete 3-way cross-over design. Subjects will attend the site for twelve visits. The seven trial periods are depicted in Table 2.

Table 2: Trial design

Screening	Treatment I	Washout I*	Treatment II	Washout II*	Treatment III	Follow-Up
1-2 weeks No treatment	2 weeks A, B, or C	1(2) weeks No treatment	2 weeks A, B, or C	1(2) weeks No treatment	2 weeks A, B, or C	1 week No treatment

(Dose A = placebo; Dose B = THN102 200 mg/2 mg; Dose C = THN102 200 mg/18 mg.)
*Washout periods can be extended to up to 2 weeks, if this is more convenient for the subject.

The trial procedures by visit are presented in the flow chart on Page 12.

At visit VR the subjects will be equally randomised (1:1:1:1:1:1) double-blind to a treatment sequence containing three periods (shown in Table 3).

Table 3: Treatment sequences

Sequence	Treatment period I	Treatment period II	Treatment period III
1	Dose A	Dose B	Dose C
2	Dose B	Dose C	Dose A
3	Dose C	Dose A	Dose B
4	Dose A	Dose C	Dose B
5	Dose C	Dose B	Dose A
6	Dose B	Dose A	Dose C

The duration of each treatment period is 2 weeks, with a 1-week washout in between (to avoid carry-over effects) and 1-week follow-up period after the last treatment period. Washout periods can be extended up to two weeks. THN102 will be administered orally once daily.

3.2. Trial Duration and Dates

The expected duration of this clinical trial is approximately 7 months. For the individual subject the trial will last 11 – 13 weeks.

First subject first visit: Q2/2018

Last subject last visit: Q4/2018

4. TRIAL POPULATION

4.1. Number of Subjects

A total of 60 Parkinson's disease subjects with excessive daytime sleepiness will be randomised. Recruitment will be competitive. Dropouts will not be replaced. The target figure is 54 subjects completing the trial as per protocol. To be eligible for inclusion into this trial, each subject must fulfill the following inclusion criteria and none of the exclusion criteria at visit VS1. For the sample size calculation refer to Section 8.5.

4.2. Inclusion Criteria

1. Subjects with a diagnosis of idiopathic Parkinson's disease as defined by the Movement Disorders Society (MDS).
2. Subjects with Hoehn and Yahr scale score ≤ 4.
3. Males or females, aged between 18 and 80 years.
4. Body mass index > 18 kg/m^2 and < 35 kg/m^2.
5. Subjects should have a complaint of daytime sleepiness impacting their quality of life and/or daytime functioning (e.g. falling asleep while reading or watching TV, while eating or talking with other people).
6. Epworth Sleepiness Scale (ESS) score ≥ 14.
7. Women of childbearing potential (not surgically sterile or < 2 years postmenopausal), must use a highly effective method of contraception, and must continue for the duration of the trial (and for 2 months after participation in the trial). Highly effective methods of contraception include hormonal contraception associated with inhibition of ovulation (combined estrogen/progestogen: oral, intravaginal, transdermal; progestogen-only: oral, implanted, and injected), **in conjunction with** a barrier method (preferably male condom). Highly effective methods further include intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that the partner is the sole sexual partner of the subject and the vasectomised partner has received medical assessment of the surgical success) and sexual abstinence, i.e. when this is in line with the preferred and usual lifestyle of the subject.
8. Subjects willing and able to follow trial procedures (including to swallow IMP capsules) and to regularly attend scheduled clinic visits as specified in the protocol, and who have signed the informed consent prior to any screening procedure.

All above-mentioned inclusion criteria will be checked at VS1.

At VR the following inclusion criteria will be re-checked: 5, 6, 7, 8.

4.3. Exclusion Criteria

1. Subjects with known or with a suspected sleep apnea syndrome or who have any other cause of excessive daytime sleepiness, such as shift work sleep disorder.
2. Psychiatric and neurological disorders (other than Parkinson's disease), such as idiopathic narcolepsy, Alzheimer's disease, Huntington's Chorea, multiple sclerosis, epilepsy, psychosis, bipolar disorder, severe clinical anxiety or depression, multiple system atrophy (Shy-Drager syndrome) or other problem that in the investigator's opinion would preclude the subject's participation and completion of this trial or comprise reliable representation of subjective symptoms.
3. Cardiovascular disorders such as
   a. Uncontrolled moderate to severe hypertension
   b. ECG QTcF duration ≥ 450 ms (men) or ≥ 470 (women)
   c. ECG signs of left ventricular hypertrophy (exclusion if at least one of the three indices is abnormal):
      - Sokolow-Lyon voltage (sum of amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 ≥ 3.5 mV), or

- Cornell voltage (S wave in V3 + R wave in aVL > 2.8 mV in men or > 2.0 mV in women), or
- Modified Cornell (R wave in aVL > 1.1 mV)

d. Recent (less than three months before screening visit VS1) myocardial infarction
e. Stable or unstable angina pectoris
f. Cardiac insufficiency
g. Previous history of heart failure
h. Previous history of cardiac valvular surgery
i. Ventricular arrhythmias considered as clinically significant
j. Atrial fibrillation unless it is stable and controlled by stable doses of amiodarone, calcium channel blocker or beta-blocker
k. 2nd or 3rd grade atrioventricular block or chronic bifascicular block, unless an adequate pacemaker is present
l. Sinus node dysfunction
m. Documented Brugada syndrome

4. Subjects with current impulse control disorder.
5. Subjects showing dementia or with MoCA < 23.
6. Subjects with current suicidal risk, based on investigator's clinical judgement or with a "yes" answer to item 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at VS1, referring to the last month before screening.
7. Current or recent (within one year) history of substance abuse or dependence disorder as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-V), e. g. alcohol. Tobacco use is accepted.
8. Other active clinically significant illness, including unstable cardiovascular or malignant pathology, significant abnormality in physical examination or clinical laboratory results at VS1, which could interfere with the trial conduct or counter-indicate the trial treatments or place the subject at risk during the trial or compromise the trial participation.
9. Subjects with hepatic impairment (serum total bilirubin ≥ 2 mg/dL, except in patients diagnosed with Gilbert's syndrome, or prothrombin time [PT] ≥ 13.7 s (except in patients on therapeutic anti-coagulation), or serum albumin < 3.5 g/dL), or renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2, according to Kidney Disease Improving Global Outcomes (KDIGO, [32])).
10. Known hypersensitivity to IMP (active ingredients or excipients of modafinil or flecainide capsules).
11. Subjects currently (or within 6 weeks before VS1) under one of the following medications (isolated intake up to 1 week can be accepted):
    a. Neuroleptics, anxiolytics, anticonvulsants. Benzodiazepines and benzodiazepine-like drugs are only authorised if used regularly at stable indicated doses with an evening intake as sleep promoting agents.
    b. Flecainide or other class I antiarrhythmic drugs (see Section 14.3).
    c. Psychostimulants (except caffeine if no abuse and stable consumption) such as, but not limited to, modafinil, methylphenidate, amphetamine.
    d. Antidepressants except if maintained at stable dose for at least 6 weeks prior to VS1 and anticipated to remain stable during the trial in subjects with mild or moderate unipolar depression.
    e. Antiemetic medications (except domperidone), myo-relaxing drugs and opioids.
    f. Dopaminergic medications, unless they have been used at stable doses for at least 4 weeks before screening and it is anticipated that the doses will not be changed throughout the trial. Efficacious medication for Parkinson's disease should not be discontinued for the sole purpose of the subject's enrolment into this clinical trial but must be maintained at stable dosage levels.
    g. Centrally acting anti-obesity drugs.
    h. TNF-alpha inhibitors.
12. Pregnancy or lactation. Women of childbearing potential who intend to be pregnant during the next few months.
13. Subjects protected by the law (legal guardianship).
14. Subjects participating in any other clinical trial within 60 days prior to entry in this trial or still in the protected period imposed by a previous trial.
15. Subjects working in an occupation requiring variable shift work or routine night shifts.

16. Subjects who plan to travel involving time zone changes.

All above-mentioned exclusion criteria will be checked at VS1.
At VS2 it will be checked if laboratory results, new AEs or new concomitant medication conflict with any of the exclusion criteria.
At VR the following exclusion criteria will be re-checked: 5, 11-12, 15, 16.

4.4. Screening Failures and Withdrawals

4.4.1. Screening failures

Screening failures will be all subjects who have been enrolled in the trial (i.e. ICF signed), but discontinue the trial prior to randomisation (at visit VR) due to whatever reason (withdraw consent, do not fulfil criteria, by decision of investigator, etc.).

All subjects pre-screened, but not enrolled (i.e. no ICF signed), and all subjects enrolled (i.e. ICF signed) will be recorded in respective log forms.

4.4.2. Withdrawals

Subjects will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care, and without having to justify their reasons and decision. Additionally, the investigator may discontinue the treatment of a subject at any time if he/she considers this to be in the subject's best interest or if lack of compliance with recommendations has been noted.

The investigator will decide on trial continuation after consideration of all available clinical elements presumed to impact on the subject's safety.

Subjects may withdraw or may be withdrawn from the trial for the following reasons:

- at their own request (withdrawal of consent)
- if in the investigator's opinion, for reasons of safety or ethics, continuation in the trial would be detrimental to the subject's well-being
- major protocol deviations
- treatment incompliance
- prohibited concomitant therapy
- adverse event
- pregnancy
- if the subject answered "yes" to point 4 and/or 5 of the C-SSRS. In this case the subject must be sent for psychiatric consultation
- elevation of liver enzymes ALT or AST $\geq$ 5 times the upper limit of normal, or ALT or AST $\geq$ 3 times the upper limit of normal together with increased (total or conjugated) bilirubin $\geq$ 2 times the upper limit of normal
- ECG signs of left ventricular hypertrophy, showing abnormality of at least one of the three indices listed below, confirmed by a cardiologist:
  - Sokolow-Lyon voltage (sum of amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 $\geq$ 3.5 mV), or
  - Cornell voltage (S wave in V3 + R wave in aVL > 2.8 mV in men or > 2.0 mV in women), or
  - Modified Cornell (R wave in aVL > 1.1 mV)

In this case, the subject must be referred to a cardiologist for further examinations.

- at the specific request of the sponsor

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. The subject must be followed up to establish whether the reason was an adverse event, and, if so, this must be reported in accordance with the procedures in this protocol.

As far as possible, all examinations scheduled for visit V3B must be performed on all subjects who receive IMP but do not complete the trial according to protocol (early discontinuation visit, EDV). The investigator must make every effort to contact subjects lost to follow-up.

In addition, visit V3C must be performed within 7 ±1 days after EDV.

Efforts will be made to try maintaining all subjects in the trial until completion.

4.5. Subject Identification

A 6-digit number will be used to identify the subjects. The first 3 digits of the number will correspond to the site number. For example: Subject 101-001 will be the number given to the first subject who signed an ICF at site 101.

The reference to the full names will be made in the subject’s identification list which must be kept strictly confidential. Only site number, subject number and randomisation number (if applicable) should appear in the eCRF and questionnaires. Age will be provided in eCRF for demographics. In the eCRF the randomisation number will be associated to the subject number in order to allocate the randomised sequence of treatment period.

Subjects will wear a subject card during the trial, stating that they participate in a clinical trial and providing a contact name and telephone number of the investigator in case of need or of an emergency.

5. TREATMENTS

5.1. Investigational Medicinal Product (IMP)

5.1.1. Test drug formulations

THN102 is a combination drug constituted by modafinil 100 mg tablets over-encapsulated and flecainide capsules of 1 mg or 9 mg. Daily dosages are: Modafinil 200 mg and flecainide: 2 or 18 mg.

Drug code:	**Modafinil (Modiodal® Teva)**
Dosage form:	1 tablet of 100 mg, over-encapsulated (orange capsule)
Excipients:	Tablet: Lactose monohydrate, pregelatinised starch (maize), microcrystalline cellulose, croscarmellose sodium, Povidone K29/32, magnesium stearate. Capsule, filler: Gelatine, Swedish Orange, microcrystalline cellulose.
Vials:	Capsules will be provided into HDPE snap-cap vials containing 18 capsules each.
Storage:	15-25 °C (avoid exposure >25°C)
Route:	Oral
Dose:	2 capsules containing 100 mg each, at 8:00 h (± 1:00 h) in the morning. A 24-hour (± 1:00 h) interval between two consecutive doses is required. For subjects aged above 65 years: On the first, second and third day of each treatment period, 1 capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.

Drug code:	**Flecainide (manufactured by PCA, Central Pharmacy of the French Army)**
Dosage form:	1 or 9 mg of flecainide powder per capsule (white capsule)
Excipients:	Tablet: Microcrystalline cellulose (Avicel PH112), magnesium stearate. Capsules: Hypromellose (HPMC)
Storage:	15-25 °C
Route:	Oral
Vial:	Capsules will be provided in HDPE snap-cap vials containing 18 capsules each.
Dose:	2 capsules containing 1 or 9 mg each, in the morning at the same time as modafinil. For subjects aged above 65 years: On the first, second and third day of each treatment period, 1 capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.

5.1.2. Reference drug formulations

THN102 Placebo is a combination drug constituted by modafinil 100 mg placebo tablets over-encapsulated and by flecainide placebo capsules. Daily dosages are: Modafinil 0 mg and flecainide: 0 mg.

Drug code:	**Modafinil placebo**
Dosage form:	1 tablet of 0 mg, over-encapsulated (orange capsule)
Excipients:	Tablet: Lactose monohydrate, pregelatinised starch (maize), microcrystalline cellulose, croscarmellose sodium, Povidone K29/32, magnesium stearate. Capsule, filler: Gelatine, Swedish Orange, microcrystalline cellulose.
Vials:	Capsules will be provided into HDPE snap-cap vials containing 18 capsules each.
Storage:	15-25 °C (avoid exposure >25°C)
Route:	Oral

Dose:	2 capsules containing 0 mg each, at 8:00 h (± 1:00 h) in the morning A 24-hour (± 1:00 h) interval between two consecutive doses is required. For subjects aged above 65 years: On the first, second and third day of each treatment period, 1 capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.
Drug code:	**Flecainide placebo**
Dosage form:	0 mg of flecainide powder per capsule (white capsule)
Excipients:	Tablet: Microcrystalline cellulose (Avicel PH112), magnesium stearate. Capsules: Hypromellose (HPMC)
Storage:	15-25 °C
Route:	Oral
Vial:	Capsules will be provided in HDPE snap-cap vials containing 18 capsules each.
Dose:	2 capsules containing 0 mg each, in the morning at the same time as modafinil placebo. For subjects aged above 65 years: On the first, second and third day of each treatment period, 1 capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.

5.1.3. Timing of IMP doses and administration

IMP will be administered only to subjects included in this trial, following the procedures set out in the trial protocol.

IMP (2 capsules modafinil or placebo plus 2 capsules flecainide or placebo; 4 capsules in total) will be administered in the morning. IMP will be swallowed before meal with 150 mL tap water at 8:00 h (± 1 h).

For subjects aged above 65 years:

On the first, second and third day of each treatment period, 1 modafinil and 1 flecainide capsule will be taken. From the fourth to the last day of each treatment period, the regimen will be as described above.

The time of IMP intake will be recorded in the subject diary daily.

Dose adjustments will not be permitted.

In each treatment period, first IMP intake will take place on the day after IMP dispensation, i.e. on the day after visit VR, V1C or V2C, respectively.

In each treatment period, last IMP intake will take place on the day of visit V1B, V2B or V3B, respectively.

5.1.4. Labelling and Packaging

[redacted] (for contact details, see Section 14.1) will be in charge for over-encapsulation, labelling, preparation of treatment period kits and trial supply management in accordance with the randomisation list. 18 capsules will be packed into a vial (sufficient for 1 week, with 4 capsules as reserve). Modafinil and flecainide capsules will be packed in separate vials.

The IMP vials, boxes and kits will be labelled individually according to allocation schedule, site, subject number, trial period and content. All labels will be in the respective language of the country and will be in accordance with local regulations. (Multi-language label booklets will be used.) Label terminology may vary according to local regulations, and country-specific remarks will be added as needed. Sample labels will be filed in the TMF.

5.1.5. Drug storage and distribution

Clinical supplies will be stored at trial site for subjects recruited if a locked, dedicated cupboard with temperature control and logging is available. If not, the clinical supply should be stored at the hospital pharmacy.

For each treatment period, the box contains two vials with 18 capsules of modafinil 100 mg or its placebo and two vials of 18 capsules of flecainide of the corresponding assigned dosage or its placebo. The boxes will be kept under lock until treatment dispensation to the subject. The subjects will be provided with sufficient IMP for the next treatment period as defined by the randomisation scheme. Dispensations will be done at the end of VR, V1C and V2C.

Subjects must be instructed to return all the dispensed medication vials, boxes and packaging material at the visit scheduled at the end of each period (V1B, V2B, V3B) whatever the state (intact, empty or partially used vials). Treatment medications accountability and compliance should be done at V1B, V2B and V3B by the investigators or their designee.

5.2. Randomisation and Blinding

5.2.1. Randomisation

Subjects will be randomised to receive all three treatments, according to one of the six possible sequences (see Table 3).

The statistics department of the clinical CRO will prepare the randomisation list using SAS® in the version specified in the data management plan (DMP). Randomisation data will be kept strictly confidential, accessible only to authorised persons, until the time of unblinding. The randomisation scheme will be included in the clinical trial report for this protocol.

The procedure will be as follows:

- After a subject's preliminary eligibility is confirmed, the site will enter the subject into the eCRF system.
- The eCRF system will send a notification to the randomisation coordinator at the clinical CRO.
- The randomisation coordinator will allocate the subject to the randomisation code as follows:
    - He/she will assign each screened subject to the next available randomisation number from the randomisation list until the first screening failure of a subject with an assigned randomisation code is documented.
    - After such a screening failure has occurred, the randomisation coordinator will assign randomisation numbers to subjects by taking into account the number of subjects allocated to each sequence, to ensure the balance (manual randomisation).
    - At sites with an unused kit from a previous screening failure, any new eligible subject will be assigned the randomisation number corresponding to the unused kit (forced randomisation).
- The randomisation coordinator will enter the randomisation code into the eCRF system and request the warehouse to send the treatment kit (labelled with the randomisation code) and the emergency unblinding envelope to the respective site.
- The randomisation coordinator will document the status of all screened subjects and kits and will keep track of the balance between treatment sequences and unused kits available at the sites.
- A subject will only be considered randomised after his/her eligibility has been confirmed at VR.

5.2.2. Blinding

Modafinil 100 mg capsules and modafinil placebo capsules will be identical in size, colour and appearance. The packaging and labelling will not allow for any distinction between them.

Likewise, flecainide 1 mg capsules, flecainide 9 mg capsules and flecainide placebo capsules will be identical in size, colour and appearance. The packaging and labelling will not allow for any distinction between them.

During the trial, the subject and all personnel involved with the conduct and the interpretation of the trial, including the investigators, site personnel, and the sponsor's staff, will be blinded to the treatment assignment. The randomisation schedule will be filed securely by the clinical CRO, in a manner such that blinding is properly maintained throughout the trial. Treatment assignment will not be available until the completion of the trial and until after final data review (clinical data base lock), except in the case of emergency.
Emergency unblinding will be done via sealed emergency code envelopes. Unblinding will not to be done unless an actual emergency occurs, and knowledge of the subject's treatment assignment affects his/her medical treatment. If possible, before breaking the blind the investigator consults with the medical monitor to ascertain the necessity of breaking the code. A record will be made of the date, time and reason for breaking the blind. Subjects with SUSARs will be unblinded for regulatory reporting by the CRO pharmacovigilance representative. Other trial personnel and the investigators will receive blind information on the SUSAR until the trial has been unblinded.

The principal investigator at each trial site and the pharmacovigilance representative will be provided with individual sealed emergency envelopes containing treatment assignment to be maintained in locked area and to be opened only in case of a medical emergency. The integrity of these sealed envelopes will be checked by the CRA at the end of the trial.

The allocation schedule will be transmitted electronically to the CRO in charge of secondary packaging. A secrecy agreement will be signed by the PK analyst and no individual data will be distributed or discussed with any other party until the database has been frozen and the code has been released. The pharmacists at trial site are blinded to trial treatment.

All other groups involved in trial support will only have access to treatment assignment after delivering data planned as per protocol and after data freezing. Electronic transfer of allocation schedule to investigators, sponsor, CRO's trial manager, and to other parties will be performed after freezing of the database. All documents for blinding and for signature of secrecy agreements will be filed in the TMF. The set of envelopes from principal investigators at each trial site and from pharmacovigilance will be recovered at trial completion, inspected for integrity and destroyed by the sponsor. The integrity statements will be stored in the TMF.

5.3. Clinical Supplies Accountability

The investigator or pharmacist will document IMP dispense and return on a drug accountability form. This will be verified by the CRA and documented on the same form. In addition, the investigator or pharmacist will maintain a site inventory.

Drug dispensation logs will be maintained throughout the trial at each visit and for each subject by site staff. Comparison between capsules count and eCRF as well as comparison between capsules count and subject diaries will be performed to obtain information on compliance. The originals of these log forms, along with the filled drug accountability form will be filed in the ISF and copies will be collected for the TMF.

After reconciliation at the end of the trial, all unused IMP will be returned to the warehouse.

5.4. Treatment Compliance

The trial medication will be administered at home by the subject and to ensure adequate drug compliance is consequently a key issue. Instructions will be provided to the subject on respecting time schedule trying to maintain same time schedule throughout the trial and a 24-hour interval (± 1 hour) between daily doses.

5.5. Prior and Concomitant medication

Efficacious medication for Parkinson's disease should not be discontinued for the sole purpose of the subject's enrolment into this clinical trial but must be maintained at stable dosage levels (exclusion criterion no. 11f).

The following concomitant medication is prohibited during the trial and within 6 weeks before VS1:

1. Neuroleptics, anxiolytics, anticonvulsants. Benzodiazepines and benzodiazepine-like drugs are only authorised if used regularly at stable indicated doses with an evening intake as sleep promoting agents.
2. Psychostimulants (except caffeine if no abuse and stable consumption) such as, but not limited to, modafinil, methylphenidate, amphetamine.
3. Antidepressants except if maintained at stable dose for at least 6 weeks prior to VS1 and anticipated to remain stable during the trial in subjects with mild or moderate unipolar depression, providing the treatment is well tolerated and devoid of orthostatic hypotension and QT prolongation as documented at screening.
4. Antiemetic medications (except domperidone), myo-relaxing drugs and opioids.
5. Antiarrhythmic drugs class I (see Section 14.3).
6. Dopaminergic medications, unless they have been used at stable doses for at least 4 weeks before screening and it is anticipated that the doses will not be changed throughout the trial.
7. Centrally acting anti-obesity drugs.
8. TNF-alpha inhibitors.

Co-prescription of CYP2D6 inhibitors, CYP3A4,5 or CYP2C19 substrates has to be closely monitored. The doses of such co-prescribed drugs have to be decreased as appropriate. The decision will be made by the investigator after consulting with the medical monitor, if necessary. A list of the most important CYP2D6 inhibitors and of CYP3A4,5 and CYP2C19 substrates is provided in Section 14.4.

Sexually active women of child-bearing potential must be established on a contraceptive programme (see inclusion criterion no. 7). Since the effectiveness of steroidal contraceptives may be reduced when used with IMP, alternative or concomitant methods of contraception are recommended during the trial, and for two months after discontinuation of IMP.

For more information, please refer to the Investigator's Brochure (Section 5.3, Drug-drug interactions; Sections 7 and 12.3 of Modafinil SmPC, and Section 8.1 of Flecainide SmPC).

5.6. Lifestyle and Diet

Subjects should be advised that driving ability, operation of machinery and work without a secure fit may be affected by adverse reactions such as dizziness and visual disturbances.

There are no trial restrictions with respect to smoking. Moderate consumption of caffeine (tea, coffee, cola, energy drinks etc.) and alcoholic beverages (such as 200 mL of beer or 100 mL wine per day) will be permitted. Grapefruit consumption and quinine-containing drinks should be avoided.

Additional information regarding contraindications, precautions and warnings concerning IMP are provided in the current version of the IB. [31]

5.7. Further Treatment after the End of the Trial

After the end of the trial, the subjects will be treated according to local standard practice.

6. ASSESSMENTS

The schedule of tests performed is described in the trial flow chart (Page 12).

All measurements performed in this trial are recognised standard methods. Therefore, no further details concerning reliability or relevance will be discussed here.

6.1. Description of Trial Visits

Seven on-site visits and five phone call visits are planned.

Due to the PVT and MoCA assessments on-site visits should always start in the morning.

Unscheduled (on-site or phone) visits at additional time points may be performed, if required. An administrative/logistic phone contact or on-site presence will not be documented as unscheduled visit in the eCRF.

6.1.1. Visit VS1

This screening visit 1 is an on-site visit and will take place between Day -15 and Day -7.

The following procedures will be performed:

- Informed consent
- Hand out subject card
- Demography (incl. height measurement)
- Medical history, prior medication
- Concomitant medication
- Hoehn & Yahr staging
- Check for eligibility
- Adverse event collection
- Safety laboratory (blood [including serology and blood coagulation], urine)
- Pregnancy test (urine), for women of childbearing potential only
- Vital signs (after 5 minutes of supine rest and after 2 minutes in standing position, i.e. 1 set)
- Weight
- 12-lead ECG (10 min supine)
- C-SSRS Screening version
- Physical examination
- ESS
- MoCA
- Issue actigraphy device (fully charged)
- Issue subject diary (screening phase diary)

6.1.2. Visit VS2

This screening visit 2 is a phone call visit and will take place on Day -5 ±1.

The following procedures will be performed:

- Concomitant medication
- Check for eligibility
- Adverse event collection
- Remind subject to wear actigraphy device

6.1.3. Visit VR

This randomisation/baseline visit is an on-site visit and will per definition take place on Day -1.
(Please note that there is no Day 0. The day after Day -1 is Day 1. Day 1 is the day of first IMP intake.)
The following procedures will be performed:

- Concomitant medication
- Check for eligibility
- Randomisation
- IMP dispensation
- Adverse event collection
- Safety laboratory (blood, urine)
- Pregnancy test (urine), for women of childbearing potential only
- Vital signs (3 sets of orthostatic vital signs 15-20 min apart)
- Weight
- 12-lead ECG (10 min supine)
- C-SSRS Since Last Visit version
- MDS-UPDRS
- QUIP-RS
- Physical examination
- ESS
- PVT at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each). If this PVT assessment schedule is too burdensome for the subject, it may be individually adapted to at least 3 assessments, with a time window of not less than 1 h between two PVT assessments. Once chosen, the timeframe should remain constant during the trial for each subject. Upload data
- MoCA
- Collect and charge actigraphy device
- Read out actigraphy device, upload data
- Issue actigraphy device (fully charged)
- Issue subject diary (treatment phase diary)
- Check subject diary (screening phase diary)
- Collect subject diary (screening phase diary)
- PK blood sample

6.1.4. Visits V1A, V2A and V3A

These actigraphy sensor visits are phone call visits and will take place

- on Day 10 ±1 (V1A)
- on Day 31 ±1 (V2A)
- on Day 52 ±1 (V3A)

The following procedures will be performed:

- Concomitant medication
- Adverse event collection
- Remind subject to wear actigraphy device

6.1.5. Visits V1B, V2B and V3B

These end-of-treatment period visits are on-site visits and will take place

- on Day 14 ±2 (V1B)
- on Day 35 ±2 (V2B)
- on Day 56 ±2 (V3B)

The following procedures will be performed:

- Concomitant medication
- IMP accountability, compliance check, collect IMP
- Adverse event collection
- Safety laboratory (blood, urine)
- Pregnancy test (urine), for women of childbearing potential only
- Vital signs (after 5 minutes of supine rest and after 2 minutes in standing position, i.e. 1 set)
- Weight
- 12-lead ECG (10 min supine)
- C-SSRS Since Last Visit version
- MDS-UPDRS
- QUIP-RS
- Physical examination
- ESS
- PVT at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each) or individually adapted PVT schedule with the same timeframe as at VR. Upload data
- MoCA
- Collect and charge actigraphy device
- Read out actigraphy device, upload data
- Check subject diary (treatment diary)
- Collect subject diary (treatment phase diary, V3B only)
- PK blood sample

In case of early discontinuation, the same procedures as required for V3B will be performed.

6.1.6. Visits V1C and V2C

These end-of-washout visits are on-site visits and will take place

- on Day 21-1/+7 (V1C)
- on Day 42-1/+7 (V2C)

The washout periods can be extended from 1 week to 2 weeks, if this is more convenient for the subject.

The following procedures will be performed:

- Concomitant medication
- IMP dispensation
- Adverse event collection
- Vital signs (3 sets of orthostatic vital signs 15-20 min apart)
- 12-lead ECG (10 min supine)
- C-SSRS Since Last Visit version
- ESS
- PVT at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each) or individually adapted PVT schedule with the same timeframe as at VR. Upload data
- MoCA
- Issue actigraphy device (fully charged)
- Issue subject diary (treatment phase diary)
- Check subject diary (treatment phase diary)
- Collect subject diary (treatment phase diary)

- PK blood sample

6.1.7. Visit V3C

This follow-up visit is a phone call visit and will take place between Day 63 ±1 or 7 ±1 days after EDV (whatever comes first). This visit is also mandatory for subjects who discontinue early.

The following procedures will be performed:
- Concomitant medication
- Adverse event collection

6.2. Baseline Assessments

6.2.1. Demography

The investigator will record demographic data, including (but not limited to) age, gender, race, and will measure height (also used for BMI calculation).

6.2.2. Medical history, concomitant diseases

In an interview, medical history will be evaluated by the investigator in order to determine whether the subject fulfils the inclusion criteria and meets none of the exclusion criteria. Concomitant diseases that might be present at VS1 must be recorded in the eCRF.

Medical conditions that are diagnosed at VS1 will only be documented as adverse events, if they are known to have started or are suspected to have started after the ICF has been signed. All other medical findings at the medical examination at VS1 will be documented as medical history.

6.2.3. Prior and concomitant treatments and lifestyle

Any treatment that was given in addition to IMP during the trial is regarded as a concomitant treatment and must be documented on the appropriate pages of the eCRF, specifying drug taken, dose, route, start/stop date and reason for use.

Therapies administered within 3 months before VS1 will also be documented in the eCRF.

All concomitant drugs must be known to and approved by the investigator and should be maintained stable during the trial unless mandatory to increase or decrease the dose to ensure a better efficacy or a better safety for the subjects. All changes in therapy or in doses must be documented in the eCRF. The subject should mention all other drugs, including over the counter medication such as acetylsalicylic acid.

Consumption of alcohol will be recorded in the eCRF at VS1, consumption of grapefruit products and quinine-containing drinks not.

6.2.4. Modified Hoehn & Yahr stage

The investigator will assess the subject's Hoehn & Yahr stage as follows:

0 No signs of disease.

1 Unilateral disease.

1.5 Unilateral plus axial involvement.

2 Bilateral disease, without impairment of balance.

2.5 Mild bilateral disease, with recovery on pull test.

3 Mild to moderate bilateral disease; some postural instability; physically independent.

4 Severe disability; still able to walk or stand unassisted.

5 Wheelchair bound or bedridden unless aided.

6.2.5. Calculation of glomerular filtration rate

For the verification of exclusion criterion no. 9, the glomerular filtration rate will be calculated based on 2009 CKD-EPI creatinine equation [32] as follows:

GFR [mL/min/1.73 m^2] =
141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x $\max(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black]

S_{Cr} = standardised serum creatinine [mg/dL]

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

$\min(S_{Cr}/\kappa, 1)$ = indicates the minimum of S_{Cr}/κ or 1

$\max(S_{Cr}/\kappa, 1)$ = indicates the maximum of S_{Cr}/κ or 1

age [years]

6.3. Safety Assessments

6.3.1. Adverse events

For adverse events see Section 7.

6.3.2. Safety laboratory and pregnancy tests

Serology, haematology, blood coagulation and biochemistry analyses will be performed by a central laboratory. Urinalysis (dipstick) and urine pregnancy test (women of childbearing potential only) will be performed by trial site staff on-site. For the list of parameters, see Section 14.2.

For safety laboratory tests, approximately 10 mL of blood will be collected at each blood withdrawal.

Laboratory values outside the normal ranges have to be assessed by the investigators if clinically significant abnormal or not clinically significant abnormal.

Each change to clinically significant abnormal laboratory value during the trial has to be documented as an AE in the eCRF unless the measurement is identified to be caused by a laboratory error and unless the underlying disease causing the change to laboratory abnormality is already documented. Clinically significant abnormal laboratory values at VS1 not related to any already documented underlying disease have to be documented as medical history.

6.3.3. Vital signs and weight

Vital signs (systolic and diastolic blood pressure as well as heart rate) will be measured twice: after 5 minutes supine rest and after 2 minutes in standing position (one set of supine and standing vital signs).

At VR, V1C and V2C three sets of supine and standing vital signs will be measured with 15-20 min intervals between the sets.

Weight will be measured in street clothes without shoes.

6.3.4. Electrocardiogram (ECG)

The sponsor will provide the investigator with the ECG device that shall be used in this trial. Twelve-lead ECG will be recorded after 10 minutes in supine position. ECG reading will be performed centrally by the provider specified in Section 14.1 and will include

- ECG measured parameters as intervals (PR, QRS, QT)
- Pattern of change for PR, QRS and QT versus ECG from baseline
- Derived ECG parameters (QTcF, heart rate)

ECG will be recorded at VS1, VR, V1B, V1C, V2B, V2C and V3B.

6.3.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a tool that was developed to facilitate a prospective, systematic monitoring for the emergence of suicidal tendencies in clinical studies. It is used to compare the occurrence, severity, and frequency of suicide-related thoughts and behaviours during treatment in a clinical trial.

The C-SSRS Screening version will be used at VS1 to obtain baseline data. The recall period will be set to 12 months / 1 year. Exclusion criterion no.6 will be met if the subject answers “yes” to items 4 and/or 5 of the C-SSRS only referring to the last month before VS1.

The C-SSRS Since Last Visit version will be used to capture changes in the subject’s status at VR, V1B, V1C, V2B, V2C and V3B.

Subjects who answer “yes” to point 4 and/or 5 of the C-SSRS will be withdrawn from the trial and will be sent for psychiatric consultation.

6.3.6. Movement Disorder Society-Sponsored Version of Unified Parkinson's Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a comprehensive assessment of both motor and non-motor symptoms associated with Parkinson's disease. [33] It has four parts:

- Part I (non-motor experiences of daily living, 13 items), further divided into:
  - Part IA focuses on complex behaviors and is completed by the investigator, based on interview with the subject
  - Part IB focuses on non-motor experiences of daily living and is completed by the subject
- Part II (motor experiences of daily living, 13 items), completed by the subject
- Part III (motor examination, 33 items), completed by the investigator
- Part IV (motor complications, 6 items) completed by the investigator, based on interview with the subject.

The MDS-UPDRS rates 65 items on a 5-point scale: normal (0), slight (1), mild (2), moderate (3) and severe (4).

The MDS-UPDRS will be completed at baseline and at the end of each treatment period, i.e. at visits: VR, V1B, V2B and V3B.

6.3.7. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS)

The QUIP-RS is a validated tool designed to measure the severity of symptoms of impulse control disorders (ICDs) and related disorders. [34] The QUIP-RS consists of four primary questions, each applied to four ICDs (compulsive gambling, buying, eating and sexual behaviour) and three related disorders (medication use, punding and hobbyism). The QUIP-RS uses a 5-point Likert scale (score 0-4 for each question) to rate the severity of each symptom based on its weekly frequency. To be applicable in this trial, the standard 4-week recall period will be reduced to one week.

The total ICD score ranges from 0 to 64, and the total QUIP-RS score for all ICDs and related disorders ranges from 0 to 112.

The QUIP-RS will be provided in a local language. The investigator will complete the scales based on interview with the subject.

The QUIP-RS will be completed at baseline and at the end of each treatment period (visits: VR, V1B, V2B and V3B).

6.3.8. Physical examination

Physical examination includes an examination of the organ systems head, neck, eyes, ear-nose-throat, heart, respiratory, gastrointestinal, hepatic, urogenital, musculoskeletal, vascular, lymphatic, dermatologic, central-nervous system (CNS) and psychiatric.

6.4. Efficacy Assessments

6.4.1. Epworth Sleepiness Scale (ESS)

The subject will complete the Epworth Sleepiness Scale (ESS, 1-week recall period). The questionnaire will be provided in local language. Site staff will enter ESS data into the eCRF.

6.4.2. Psychomotor Vigilance Test (PVT)

The psychomotor vigilance test is an objective tool used to measure the subject's behavioural alertness. [35] It is a visual test which involves measuring

- Mean response time (ms)
- Number of lapses
- Number of total errors

The PVT requires no training, only a brief explanation of the procedure to the subject prior to the start of the test. It will be performed in the 'on' state.

PVT will be performed at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each). If this PVT assessment schedule is too burdensome for the subject, it may be individually adapted to at least 3 assessments, with a time window of not less than 1 h between two PVT assessments. Once chosen, the timeframe of PVT assessments should remain constant during the trial for each subject.

The sponsor will provide the investigator with a PVT-192 device to perform a 3-minutes PVT and a notebook computer to read out data.

6.4.3. Montreal Cognitive Assessment (MoCA)

The MoCA is a brief screening instrument to detect mild cognitive impairment. It is a paper-and-pencil tool that requires approximately 10 minutes and will be administered by the investigator. It will be

performed in the 'on' state. The MoCA assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation. One part of the paper questionnaire will be completed by the subject, another part will be completed by the investigator. Site staff will enter MoCA data into the eCRF.

The MoCA questionnaire will be provided in local language. To decrease possible learning effects, the three (equivalent) versions 7.1, 7.2 and 7.3 will be used in alternation.

MoCA should be performed in the morning.

MoCA scores range between 0 and 30. A score of 26 or over is considered to be normal.

6.4.4. Actigraphy assessment

Actigraphy is a non-invasive method of monitoring a person's rest and activity cycles. The movements the actigraphy sensor undergoes are continually recorded.

The sponsor will provide the investigator with actigraphy sensors for the trial subjects and a notebook computer to read out data. The actigraphy data will be transferred to [redacted]), where they will be further processed and stored.

Actigraphy assessments will be performed for 3 days prior to baseline and for 3 days at the end of each treatment period. At phone call visits VS2, V1A, V2A and V3A, trial staff will call the subjects and remind them to put on their actigraphy sensor bracelet and wear it until the next on-site visit.

6.4.5. Subject diaries

The paper-based subject diaries are intended for the daily documentation of

- Get-up time
- Total time (hours) slept last night
- Wake-up periods during night sleep
- Time of drug intake (except screening phase diary)
- Number of capsules taken (except screening phase diary)
- Somnolence episodes
- Diurnal involuntary sleep attacks
- Voluntary naps
- Number of caffeinated drinks
- Going-to-bed time

The diaries will be translated in the local languages of the countries involved. Only the subject is allowed to make any entry in the diaries. In case of difficulties with writing, however, a caregiver may help.

The subject will complete four paper diaries: One screening phase diary (started at VS1, without time of IMP intake and number of capsules taken) and treatment phase diaries (started at VR, V1C and V2C) for each treatment period. The subject has to bring the diaries for inspection by the investigator at all visits. The screening phase diary will be collected at VR, the treatment phase diaries will be collected at V1C, V2C and V3B.

Thus, the diaries will be completed continuously from VS1 to V3B, i.e. also during the washout periods after treatment periods I and II.

6.5. Pharmacokinetics (PK)

For PK laboratory tests, approximately 4.5 mL of blood will be collected at each blood withdrawal. The sample will be taken when the subject arrives on the site. The times of blood withdrawal must be recorded.

Modafinil and flecainide concentrations in plasma will be measured by a central laboratory (for contact details, see Section 14.1) using a validated LC-MS/MS method.

7. ADVERSE EVENT, PREGNANCY AND EMERGENCY

7.1. Adverse Event (AE)

7.1.1. Definition of an adverse event

An adverse event is any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

AEs can be symptoms, signs, or clinically relevant laboratory abnormalities occurring during the course of the trial.

All other medical conditions, which are present at VS1, should not be considered as AEs unless a worsening in severity or frequency has occurred during the trial. These medical conditions should be adequately documented on the appropriate page of the eCRF.

When reporting abnormal laboratory results on the AE pages of the eCRF, a clinical diagnosis should be recorded rather than the abnormal value itself if this is available (e.g. “anaemia” rather than “decreased red blood cell count” or “haemoglobin = 10.5 g/dL”).

In case of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

7.1.2. Severity assessment

The investigator must systematically assess the severity of adverse events according to the following definitions:

- **Mild:** a type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate:** a type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- **Severe:** a type of adverse event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalisation may be required.

Changes in the severity of an AE should be documented as a new AE. Adverse events characterised as intermittent requires documentation of the onset and duration of each episode.

7.1.3. Relationship assessment

The investigator must systematically assess the relationship of adverse events to the IMP using the following definitions:

- **Unrelated:** A clinical event with no evidence of any causal relationship.
- **Unlikely:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Probable:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

- **Definite:** A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

The relationship to IMP can be modified during the trial or AE assessment. For example, although an AE may rate only as "possibly" related to IMP soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably". Changes in the assessment of relationship to IMP should be clearly documented.

Mapping to the two categories "related" and "unrelated": The categories "unrelated" and "unlikely" will be mapped to "unrelated", the categories "possible", "probable" and "definite" will be mapped to "related".

7.1.4. Procedures for reporting of adverse events

Assessing of adverse events

Data on AEs will be obtained at scheduled or unscheduled trial visits, based on information spontaneously provided by the subject and/or through questioning of the subject. AE data may also be obtained from subject's diary cards, but information thus collected must be reviewed and assessed medically before it is transcribed to the eCRF.

If a subject is seen by a physician not involved in the trial because of an adverse event, the investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to appropriate reporting of the event.

Recording of adverse events

Complete description of all adverse events must be available in the source documents.

All AEs including local and systemic reactions should be captured on the appropriate pages of the eCRF.

Information to be recorded, based on above assessment criteria, includes event description, its duration (time of onset and time of resolution), its severity, whether it is considered serious (and if so the criterion satisfied), its relationship to IMP, any action taken (concerning the IMP or other) and its outcome.

Any AE that is still ongoing after final visit will be left as ongoing in the eCRF. However, the investigator will continue to follow up ongoing SAEs and record information in the source documents and on the Follow-Up SAE Form, until resolution or no further improvement can be expected.

AEs must be recorded on the eCRF according to the following guidelines:

- Whenever possible, recognised medical terms should be used to describe an AE rather than colloquialism (e.g. "influenza" rather than "flu") and abbreviations should be avoided.
- The description of an AE should use a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (e.g. "congestive heart failure" rather than "dyspnea, rales and cyanosis").
- Signs and symptoms that are not linked to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported separately, as individual AEs.
- Provisional diagnosis (e.g. "suspected myocardial infarction") is acceptable but should be followed up to a definite diagnosis if finally available.

Reporting of adverse events

Complete and accurate data on all AEs experienced, for the duration of the reporting period, will be reported on an ongoing basis in the AE pages of the eCRF.

The period of observation for the collection of AEs extends from the time when the subject gives informed consent until the date of final visit.

Serious adverse events occurring after a subject has taken the last dose of IMP will be collected until the date of final visit, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either IMP administration or to a protocol procedure.

All AEs with onset or worsening after first intake of IMP until 7 days after last intake of IMP are defined as treatment emergent.

If a subject is documented as lost-to follow-up, ongoing/unknown outcome AEs will not be followed up.

For screening failure subjects, new AEs and updates must be recorded in the source and trial documents until the date the subject is determined to be a screening failure. Beyond this date, only SAEs will be followed up by CRO's pharmacovigilance representative.

7.2. Serious Adverse Event (SAE)

7.2.1. Definition of a serious adverse event

A serious adverse event (SAE) is defined as an AE which at any dose meets one of the following conditions:

- Death during the period of protocol defined surveillance, i.e. the AE causes or contributes to the death. In case of fatality, the cause of death is considered as the AE, and the death is its outcome.
- Life threatening event (defined as a subject at immediate risk of death at the time of the event), i.e. the AE places the subject at immediate risk of death (the definition does not apply to an AE that hypothetically might cause death if it was more severe).
- An event requiring inpatient hospitalisation or prolongation of existing hospitalisation during the period of protocol defined surveillance, i.e. the AE requires at inpatient hospitalisation or prolongs a hospitalisation beyond the expected length of stay.
- Hospital admissions are not to be considered as SAE according to this criterion in the following purposes: surgery planned before trial entry, social reasons, normal disease management (including treatment adjustment), if the protocol procedures or the standard management of the disease under study requires planned hospitalisations.
- Results in a persistent or significant disability/incapacity, i.e. the AE resulted in a substantial disruption of the subject's ability to conduct normal activities.
- Any other important medical condition, i.e. AE that may not immediately result in death, be life threatening, or require hospitalisation, but is clearly of major clinical significance. Based upon appropriate medical judgment, the event may jeopardise the subject or may require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Any serious adverse event requires an expedited reporting to the pharmacovigilance delegate regardless of its relationship to the IMP.

7.2.2. Definitions of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected unexpected serious adverse reaction (SUSAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product).

7.2.3. Procedures for reporting of SAEs and SUSARs

All serious adverse events must be recorded on the SAE report form, followed through resolution by the investigator.

The investigator must complete the SAE report form and notify the CRO's pharmacovigilance delegate, be it a new SAE or new information on a previously reported SAE (i.e. so-called SAE follow-up), within the following timelines:

- The investigator must report all SAEs to the CRO's pharmacovigilance delegate within 24 hours of identifying the SAE.
- Other supporting documentation of the event may be requested by CRO's pharmacovigilance delegate and should be provided as soon as possible.
- All reportable SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable.

The SAE report form must be sent directly to the CRO's pharmacovigilance delegate by electronic mail or facsimile as specified below:

[redacted]

For any new SAE, the following minimum information is required as initial notification:

- Identification of the investigator,
- Subject identification details (subject number)
- IMP details (name, dose(s), route and date(s) of administration, indication)
- Diagnosis of the event (or an outcome) with the description (or a brief description of signs/ symptoms/clinical course if the diagnosis is not available) and the date of onset
- Reason(s) for considering the event as serious
- Relationship of the event with the IMP or with the trial procedure (i.e. the causality according to the investigator).

Information about SAEs and important medical conditions with any relevant ongoing/unknown outcomes will be followed-up until resolution, even if eCRFs and database will no longer be updated. SAEs occurring after a subject has taken the last dose of trial drug will be collected until final study visit, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either IMP administration or a protocol procedure.

7.2.4. Procedures for regulatory reporting of serious adverse events

Following notification by the investigator, sponsor or designee will report events that are both serious and unexpected (i.e. using the current version of the THN102 IB at the time of SAE reporting as reference) and that are associated with IMP to the competent authorities (CAs) in expedited reporting. Unblinding will be performed as described in Section 5.2.2 by opening the individual sealed envelope for the involved subject.

Moreover, any other new information that might influence the benefit-risk assessment of the IMP or that would be sufficient to consider changes in IMP administration or in the overall conduct of the clinical trial necessitate an expedited reporting to the CAs as well.

CAs should be notified of any expedited reporting within the required timelines as specified in ICH-E2A: fatal and life-threatening events within 7 calendar days (by phone/fax/writing/electronic communication) after first knowledge by CRO's pharmacovigilance delegate who will issue a complete report within 8 additional calendar days, with copy to investigator, CRA, CRO's trial manager, and sponsor. All other serious adverse events and SUSARs must be filed in writing within 15 calendar days after first knowledge by CRO's pharmacovigilance delegate.

All serious adverse events will be reported to the CAs in the development safety update report (DSUR) annually, if appropriate.

In accordance with the ICH GCP guidelines, the responsible person for pharmacovigilance on behalf of the sponsor Theranexus will inform the investigators of findings that could affect adversely the safety of the subjects, impact the conduct of the trial, or alter the IEC/IRB's approval/favourable opinion to continue the trial.

In particular, sponsor or designee will inform the investigators of SUSARs and serious adverse events that are considered to be related to the administered IMP. The investigators will keep copies of these safety reports in the investigator site file (ISF). National regulations with regards to safety reports notifications to investigators will be taken into account.

Unless clearly defined otherwise by national or site-specific regulations and duly documented, the clinical CRO will promptly notify the concerned IEC/IRB of any safety reports provided by the pharmacovigilance delegate and provide copies of all related correspondence to the CRA and the CRO's trial manager.

7.3. Pregnancy

Women of childbearing potential (defined as not surgically sterile or less than 2 years postmenopausal), must use a highly effective method of contraception, and must continue for the duration of the trial (and for 2 months after participation in the trial). Highly effective methods of contraception include: hormonal contraception associated with inhibition of ovulation (combined estrogen/progestogen: oral, intravaginal, transdermal; progestogen-only: oral, implanted, and injected) **in conjunction with** a barrier method (preferably male condom). Highly effective methods further include intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that the partner is the sole sexual partner of the subject and the vasectomised partner has received medical assessment of the surgical success) and sexual abstinence, i.e. when this is in line with the preferred and usual lifestyle of the subject.

Women of child-bearing potential will undergo sensitive urinary pregnancy tests (hCG, human chorionic gonadotropin).

Pregnancy discovered during the clinical trial must lead immediately to exclusion (if at screening) or withdrawal of the subject.

If the subject has already received IMP, the pregnancy will be documented on a pregnancy report form. The case must be reported within 24 hours of knowledge to the CRO's pharmacovigilance delegate or the CRA. The subjects will be asked to report also pregnancies within 3 months after (regular or premature) termination of the trial to the investigator.

The investigator must follow up on pregnancies discovered after IMP administration until the end of pregnancy to document the outcome on the pregnancy outcome report form.

7.4. Emergency

In case of emergency situations, the investigator should contact first his/her assigned CRA, and in case of no answer the CRO's trial manager and/or the sponsor's trial manager.

Emergency identification of IMP:

Since this trial is blinded for treatment periods I, II, and III, two sets of individual sealed randomisation envelopes with treatment code (individual sealed envelopes with scratch labels for disclosure of treatment) will be prepared. One set will be delivered to the principal investigator at each site and one full set to the CRO's medical monitor prior to trial start.

In case of urgent need during the trial, the envelope pertaining to the involved subject may be opened by the investigator in case of an SAE for which knowledge of exact treatment may be useful for medical decision or for treatment. Such an event must be documented by the investigator by signing and dating the envelope (including precise time) and indicating the reason for breaking the code on the appropriate form. Efforts must be made to reach the medical monitor before undertaking this step. All envelopes must be retrieved at trial completion from trial site by the CRA and inspected for integrity. All envelopes from investigator, intact or opened, will be filed in the TMF.

8. STATISTICAL PROCEDURES

Prior to freezing the database, an overall Statistical Analysis Plan (SAP) will be prepared by the statistician. The SAP will be signed by the involved statistician and the sponsor prior to unblinding.

8.1. Analysis Variables

8.1.1. Safety variables

1. Adverse events
2. Safety laboratory
3. Vital signs change
4. Electrocardiogram assessments
5. Columbia-Suicide Severity Rating Scale (C-SSRS)
6. MDS-UPDRS
7. QUIP-RS

8.1.2. Efficacy variables

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 patients 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

8.1.3. Pharmacokinetic variables

See Section 8.3.3.

8.2. Trial Populations

- The Safety Set (SS) includes all subjects who have received IMP at least once.
- The Full Analysis Set (FAS) includes all randomised subjects with an evaluable ESS score at the end of at least one treatment period. The efficacy analyses will be conducted on the FAS.
- The Per Protocol (PP) set includes all subjects who have completed the trial without major protocol deviation. Major and minor violations will be defined in the SAP. The main secondary endpoints (ESS, PVT and cognition) will be analysed with the PP set to demonstrate robustness of the primary analysis.

- The PK analysis set will include all subjects who have received treatment as per protocol (even if the trial was not completed) and who present no major protocol deviations with an impact on PK.

8.3. Statistical Methods

Details of the planned analyses will be described in the SAP. Some important features are listed below:

- For all analyses, the results will be pooled and presented by treatment and over time. Graphical representations will be done for individual subject data and for treatment means ± SD over time.
- Efficacy data will be analysed according to the treatment as randomised. Safety and pharmacokinetic data will be summarised according to the actual treatment received.
- Continuous (quantitative) variables will be tabulated using standard descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum values, for efficacy and some safety parameters, with geometric mean and geometric CV) if appropriate. Continuous variables may be categorised into grouped intervals for analysis; in which case frequencies and percentages will also be presented.
- Categorical (qualitative) variables will be tabulated using frequencies and percentages.

8.3.1. Efficacy

Continuous efficacy endpoints – the change from baseline at each key visit (end of treatment period I, II, and III) in ESS, PVT and MoCA - will be analysed using a mixed linear regression model. The model will include 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 – will be analysed using a mixed effects logistic regression model, 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 will be reported with their standard errors and 95% confidence intervals. The significance of the differences between Treatment A (THN102 Placebo), Treatment B (THN102 200/2) and Treatment C (THN102 200/18) will be assessed with a contrast t-test at the two-sided 5% level.

Handling of missing values/censoring/discontinuations: Subjects who misused their planned treatments or doses or have missing outcome measurements will not be excluded from the primary analysis in the FAS. Under the assumption that outcomes are missing at random, the mixed-model can propagate uncertainty due to missing data into estimates of treatment efficacy and other quantities of interest. Hence, missing data will not be imputed or replaced prior to the analysis.

Supportive analysis: The same analysis will be repeated on the PP set, to assess robustness of the analysis of the variables from ESS and PVT and possibly on other efficacy results. Subgroup analyses may be performed to investigate the effect of the main demographics (age, gender) and disease characteristics (in term of daily sleepiness extent, and cognitive impairment) on the efficacy outcomes.

The presence of a significant treatment by period interaction term in the main model may indicate a residual treatment (carryover) effect. In case of a significant treatment by period interaction, period I results will be analysed separately, and further analyses will be performed to explore the carry-over effects. The methods for evaluation of carryover effects will be defined in the SAP.

8.3.2. Safety

Safety parameters will be analysed as follows:

Vital signs: All vital signs data will be listed by treatment, subject, and visit/time and will be flagged vs. predefined clinical normal range. The mean value of vital sign parameter assessments during a visit will be summarized. Summary statistics will be provided by treatment and visit/time. Shift tables will be provided for vital sign abnormality change from baseline to endpoint within each treatment period.

ECG parameters: All ECG parameters data will be listed by treatment, subject, and visit/time and abnormalities will be flagged vs. predefined clinical normal range. Summary statistics will be provided by treatment and visit/time.
A shift table will be prepared to document QT change and distribution vs. baseline.

C-SSRS: C-SSRS score data will be listed by treatment, subject, and visit/time. Summary statistics will be provided by treatment and visit/time.

QUIP-RS: QUIP-RS score data will be listed by treatment, subject and visit/time. Summary statistics will be provided by treatment and visit/time.

MDS-UPDRS: MDS-UPDRS score data will be listed by treatment, subject and visit/time. Summary statistics for each part of the MDS-UPDRS as well as the total score will be provided by treatment and visit/time.

Clinical laboratory evaluations: All laboratory data will be listed by treatment, subject, and visit/time and abnormalities will be flagged vs. common normal range if considered by investigator as clinically relevant. Summary statistics will be provided by treatment and visit/time. Shift tables will be provided for clinical laboratory variables' change from baseline to endpoint.

Adverse events: All information obtained on adverse events will be displayed by treatment and subject after coding with pertinent MedDRA version. All adverse events and related adverse events will be presented. The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

Concomitant medications / Significant non-drug therapies: All concomitant therapies will be coded by WHO version and listed by treatment group and subject.

8.3.3. Pharmacokinetics

As soon as they are available but only after database has been frozen, analytical determinations will be sent by e-mail (Microsoft Excel® file) by the bioanalytical center of [redacted] to the sponsor's PK expert (with copy to Theranexus, CRO's trial manager). All the transmission of data must be done in blinded condition up to the reception of the certificate of database lock by CRO.

Subsequently, plasma concentrations will be processed for PK data generation.

For the calculation of the PK parameters and characteristics the following rules are usually applied:

- All the plasma concentrations validated by the bioanalytical laboratory and provided to the pharmacokineticist will be used for the PK analysis.
- The actual blood sampling time points related to the preceding administration will be used.
- At time points in the lag-time between time zero and the first concentration equal or above LLOQ (lower limit of quantification), concentrations below LLOQ will be set to zero. Concentrations below LLOQ between two concentrations equal or above LLOQ will be set to half the LLOQ. Trailing concentrations below LLOQ will not be used in calculations.

- For plasma concentration above the upper limit of quantification and reported as ALQ (above limit of quantification) in the final plasma concentration tables, ALQ will be replaced by the first measurement for the PK analysis.
- Not reported concentration will be excluded from the PK analysis.

Plasma concentrations reached at steady state will be presented for modafinil and for flecainide for each visit, considering time after last IMP intake.

Concentration-time data will be listed per treatment and subject for modafinil and for flecainide. Plasma concentrations and time post IMP intake will also be plotted to assess range of exposure at steady state for each treatment and to assess reliability of prediction made by extrapolation from phase I studies for flecainide.

Further details of the pharmacokinetic analyses will be defined in the SAP.

8.4. Interim Analysis

No formal interim analysis is planned.

8.5. Sample Size Justification

For the purpose of sample size planning ESS is considered to be the key efficacy endpoint. Solid information on the expected difference between placebo and THN102 dose and the associated intrasubject variance are not available. Using results reported in Adler et al. [5] 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 will 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 will be randomised.

9. ETHICAL AND LEGAL ASPECTS

9.1. Good Clinical Practice

This trial will be conducted in compliance with the protocol, good clinical practice (GCP) and the applicable regulatory requirements.

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that investigators, sponsor, CRO's pharmacovigilance delegate, CRAs and CRO's trial manager all abide by the principles of GCP, ICH guidelines and all applicable international and local regulations as well as the ethical principles laid down in the current revision of the Declaration of Helsinki.

9.2. Delegation of Investigator Responsibilities

The investigator should ensure that all persons assisting with the trial are adequately informed about all relevant trial procedures and well-trained on the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions.

Each investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he/she has delegated significant trial-related duties.

9.3. Subject Information and Informed Consent

Before being admitted to the clinical trial, the subject must consent to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him/her. An informed consent document that includes both information about the trial and the consent form will be prepared and given to the subject. This document will contain all elements required by law and sponsor's requirements. The document must be in a language understandable to the subject and must specify who informed the subject.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed at the time of consent by the personally dated signature of the subject. It is not considered appropriate to allow a subject who is legally incompetent to enter this trial under the coverage of the subject's legally authorised representative.

A copy of the signed informed consent document must be given to the subject.

The investigator will not undertake any measures specifically required for the clinical trial purposes until valid consent has been obtained.

9.4. Confidentiality

Only the subject number will be recorded in the eCRF and transfer documents (no initials), and if the subject name appears on any other document (e.g. ECG, laboratory report, pathologist report), it must be obliterated before a copy of the document is supplied to other parties. The subjects will be told that principal investigator and his/her staff, CRO's staff, IEC/IRB, regulatory authorities, and representatives of the sponsor may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with all applicable data protection laws.

Biological samples collected during the trial will be used for assays specifically described in the protocol. The samples will be destroyed after approval of the clinical trial report (CTR) upon written request.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

9.5. Protocol Amendments

No signee of this protocol (coordinating investigator, principal investigator, sponsor), nor the CRO's trial manager will alter this trial protocol without obtaining the written agreement of the other parties. Once the trial has started, amendments should be made only in exceptional cases. The changes then become part of the trial protocol and request a protocol amendment.

9.6. Approval of the Trial Protocol and Amendments

Before the start of the trial, the clinical CRO will submit to the IEC/IRBs and the competent authorities (CAs) all relevant trial documents. The trial will not start until authorisation by CAs and by IEC/IRBs have been received in writing and until the administrative requirements and workload (grid costs) have been discussed with the hospital administration and the agreements have been signed.

Trial medication can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the trial has been received by the trial CRA. This documentation must also include a list of the members of the IEC/IRB and their occupation and qualifications. The opinion given by the IEC/IRB should specify the trial title, trial code, trial site, amendment number if appropriate and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met.

The IEC/IRB and, if applicable, the authorities must be informed of all subsequent protocol amendments, in accordance with legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IEC/IRB. This also applies to any communication between the investigator and the authorities.

9.7. Ongoing Information for the Independent Ethics Committee / Institutional Review Board

The responsible IEC/IRB will be informed by the clinical CRO of all subsequent protocol amendments and of SUSARs occurring during the trial that are likely to affect the safety of the subjects or the conduct of the trial.

Protocol amendments referring to logistical or administrative changes (non substantial) may be implemented with notification of the IEC/IRB and competent authority only.

9.8. Premature Closure of the Trial

The sponsor (Theranexus) has the right to close this trial under special considerations or events involving safety considerations or issues with recruitment. As far as possible, this should occur after mutual consultation and attempt of remedy with all trial sites. The IEC/IRB and the CA must be promptly informed.

Should the trial be closed prematurely, all IMP must be returned to the warehouse, as if the trial had been completed. All other trial material (actigraphy sensors, PVT device, notebook, ECG device etc.) must also be returned.

The sponsor reserves the right to close the trial at a site for one of the following (or other) reasons:

- Non-compliance with GCP and/or regulatory requirements
- Centre cannot recruit an adequate number of subjects
- False documentation in the eCRF due to carelessness or deliberation

- Inadequate co-operation with the sponsor or its representatives

If the trial is prematurely terminated at a trial site, all investigators at this trial site have to inform their subjects and take care of appropriate follow-up and further treatment of the subjects. IEC/IRBs and the CA will be informed according to the applicable laws and regulations.

9.9. Regular Termination of the Trial

The end of this trial is defined as the date of the last visit of the last subject undergoing this trial.

Within 90 days of the end of the clinical trial, the clinical CRO will notify IECs/IRBs and regulatory authorities about the regular termination of the trial as required according to national laws and regulations.

If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

9.10. Archiving and Record Retention

The following records must be retained by the principal investigator in the investigator site file (ISF) for a **minimum of 15 years** after the completion or termination of the trial:

- Signed informed consent documents for all subjects
- Subject identification list, subject non-eligibility log and subject enrolment log
- Record of all communications between the investigator and the IEC/IRB
- Composition of the IEC/IRB
- Record of all relevant communications between the investigator and sponsor's representatives
- List of sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant trial-related duties, together with their roles and their signatures
- Copies of case report forms and of documentation of corrections for all subjects
- Drug accountability records
- Record of any body fluids or tissue samples retained
- All other source documents (patient records, hospital records, laboratory records, worksheets etc.)
- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial)

However, because of international regulatory requirements, Theranexus may request retention for a longer period of time. The investigator must therefore obtain approval in writing from Theranexus or from the CRO's trial manager prior to destruction of any records.

Normally, these records will be held in the investigator's archives. If the investigator is unable to meet this obligation, he must ask Theranexus for permission to make alternative arrangements. Details of these arrangements should be documented.

9.11. Liability and Insurance

In accordance with GCP and ICH guidelines, the clinical CRO (authorised by the sponsor) has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

The insurance certificate will be submitted with the documents to the IEC/IRB.

10. TRIAL MONITORING AND AUDITING

10.1. Trial Monitoring

The CRO's CRAs will review the eCRFs and source documents, supported on occasions by the CRO's trial manager or the sponsor. By frequent communications (letter, e-mail, telephone and fax), the CRO's trial manager and the CRAs will ensure:

- that the investigation is conducted according to protocol design and requirements,
- that potential deviations are discussed and queries solved, always working according to regulatory guidelines.

The sponsor, the CRO's trial manager and the CRAs may at any time demand information on the progress of the trial by phone or in writing, or may visit the trial centre in order to monitor trial procedures and to review the original trial documents and subject's data.

After trial completion, used and unused IMP will be verified, reconciled with eCRF, diaries and log forms. Intact and used clinical supplies will be returned to the CRO involved with clinical packaging after reconciliation of clinical supplies by CRA and after written instruction.

CRO’s standard operating procedures (SOPs) are available for all activities relevant to trial monitoring and to process at trial sites.

10.2. Source Data Verification and On-Site Audits

The local IEC/IRB, and/or a clinical quality assurance group delegated by the sponsor (Theranexus), or the CA acting on its own or at specific request of EMA or FDA may request access to all source documents, eCRF, and other trial documentation for on-site audit or inspection as may be indicated. Direct access to these documents must be guaranteed by the investigators, who must provide support at all times for these activities.

11. DATA HANDLING AND RECORD KEEPING

11.1. Electronic CRF and Database

An electronic case report form (eCRF) will be used. The clinical CRO will provide the system. Questionnaires filled by subject will be provided on paper. Trial staff will transfer the results into the eCRF.

Electronic device for PVT tests and actigraphy will be provided by the CRO to each site. The questionnaires will be considered as source documents and filed in the ISF.

The investigator or delegate must maintain adequate and precise source documents (safety laboratory test results, ECG, physical examination etc.), also including the diaries and the questionnaires filled by the subject. The trial data will be entered into the eCRF by dedicated site personnel.

Medical history and AE data will be coded by system organ class and Lowest Level Term, using the current version of the MedDRA dictionary. Concomitant medication data will be coded by Drug Name, taking Preferred Name and ATC into account, using the World Health Organization Drug Dictionary Enhanced (WHO DDE), current version.

Further details will be provided in the DMP and in the pertinent SAP.

11.2. Documentation of Trial Findings

Details on monitoring process by the CRA will be included in the monitoring plan.

The plasma concentrations data will be transmitted by [redacted] to data management for inclusion into the trial database. The format and the details however will be provided in the analytical protocol to be prepared by [redacted] and in the SAP.

The investigator, or designated representative, should complete the source documents (including worksheet pages, if applicable) immediately after information is collected, when a trial subject is seen for an examination, treatment, or any other trial procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be provided for all missing data.

A source data location list will be prepared and updated as required.

The completed eCRF must be reviewed and signed by the principal investigator named in the trial protocol prior to transmission to the sponsor.

11.3. Use of Trial Findings

All information concerning the drug product, such as clinical indications for the drug, its formula, methods of manufacture and formulations and other scientific data relating to it, that have been provided to investigators and are unpublished, will be considered as confidential and must remain the sole property of Theranexus. The investigator agrees to use the information only for the purposes of carrying out this trial and for no other purpose unless prior written permission from Theranexus is obtained.

By signing the trial protocol, the principal investigator agrees that the results of the trial may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The principal investigator also agrees that one or more designated staff members will be responsible for maintaining the investigator site file (ISF). The trial master file (TMF) will be maintained by the clinical CRO and transferred to sponsor after trial completion.

The sponsor or designee will be responsible for preparing the CTR. The coordinating investigator will be required to sign a statement that he has read the CTR and that he confirms that, to the best of his knowledge, it accurately describes the conduct and results of the trial.

Theranexus shall have the right to present and to publish the scientific findings from this phase II trial within reasonable time after termination of the trial and availability of the CTR, providing appropriate circulation of the manuscript among involved partners at least 60 days in advance. Co-authorship will reflect scientific involvement in trial design, trial performance, and/or analysis.

Suggestions made by Theranexus shall be implemented as appropriate to ensure strict protection of its commercial knowhow, to enable a timely patent submission prior to disclosure, to protect its commercial and proprietary interests and/or to support its strategy, unless competing with scientific accuracy and objectivity.

12. DECLARATIONS OF SPONSOR AND INVESTIGATOR

12.1. Declaration of Sponsor

This trial protocol was subject to critical review and has been approved by the sponsor and its representatives. The information it contains is consistent with:

- The current risk-benefit evaluation of the investigational product
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP as described in the GCP and ICH guidelines.

The investigator will be supplied with details of any significance or new findings, including adverse events, relating to treatment with the investigational product.

Date:_____ _____

[redacted]
Chief Medical Officer's signature
Theranexus S. A.

12.2. Declaration of Coordinating Investigator

I have received the following:

- The THN102 investigator brochure, Version 4.0, 24 January 2019.

And I confirm that:

- I have been adequately informed about the development of the investigational product to date. I will confirm the receipt of updated investigator brochures.
- I have read this trial protocol and agree that it contains all the information required to conduct the trial.
- I agree to conduct the trial as set out in this protocol and further written trial instructions (including, but not limited to, laboratory manual, CRF completion instructions, as well as instructions for PVT, AX3 and ECG assessments).
- I will not enrol the first subject in the trial until I have received approval from the appropriate IEC/IRB and until all legal requirements in my country have been fulfilled.
- The trial will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the GCP and ICH Guidelines.
- I agree to obtain, in the manner described in this trial protocol, written informed consent to participate for all subjects enrolled in this trial.
- I am aware of the requirements for the correct reporting of serious adverse events, and I undertake to document and to report such events as requested.
- I agree with the use of results of the trial for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and eCRF as specified in this protocol.
- I will provide my curriculum vitae before the trial starts, which may be submitted to regulatory authorities and will request my collaborators to forward their curriculum vitae as appropriate.

Site (name and address):

[redacted]

Date:_____ _____

Coordinating Investigator's signature

12.3. Declaration of Principal Investigator

I have received the following:

- The THN102 investigator brochure, Version 4.0, 24 January 2019.

And I confirm that:

- I have been adequately informed about the development of the investigational product to date. I will confirm the receipt of updated investigator brochures.
- I have read this trial protocol and agree that it contains all the information required to conduct the trial.
- I agree to conduct the trial as set out in this protocol and further written trial instructions (including, but not limited to, laboratory manual, CRF completion instructions, as well as instructions for PVT, AX3 and ECG assessments).
- I will not enrol the first subject in the trial until I have received approval from the appropriate IEC/IRB and until all legal requirements in my country have been fulfilled.
- The trial will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the GCP and ICH Guidelines.
- I agree to obtain, in the manner described in this trial protocol, written informed consent to participate for all subjects enrolled in this trial.
- I am aware of the requirements for the correct reporting of serious adverse events, and I undertake to document and to report such events as requested.
- I agree with the use of results of the trial for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and eCRF as specified in this protocol.
- I will provide my curriculum vitae before the trial starts, which may be submitted to regulatory authorities and will request my collaborators to forward their curriculum vitae as appropriate.

Site (name and address):

Date:_____ _____

Principal Investigator's signature

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14. APPENDICES

14.1. Appendix A – Trial Administrative Structure

This trial will be conducted in an estimated 28 centres located in Europe and the USA. A list of principal investigators and their affiliations will be kept in the trial master file (TMF).

Sponsor
Theranexus S. A.
86, rue de Paris
F-91400 Orsay
France
Tel. +33 6 80 02 67 79
www.theranexus.com

Trial manager: [redacted]
Medical expert: [redacted]

The sponsor will contract planning, conduct, data management, statistical analysis, safety management, medical writing and medical monitoring in Europe to the contract research organisation (CRO) given below.

Contract research organisation
[redacted]

Coordinating investigator
[redacted]

Electronic data capture (EDC) system provider (electronic case report form)
[redacted]

Laboratories

Safety laboratory assessments (haematology, biochemistry, blood coagulation and serology) will be performed by

Central laboratory

[redacted]

Urinalyses and pregnancy tests will be performed on-site.

Pharmacokinetic analyses will be performed by

[redacted]

Processing of actigraphy data

[redacted]

Contract research organisation for clinical trial supply management / warehouse

[redacted]

For sites in the USA this will be done by a local warehouse.

Central ECG reading

[redacted]

Medical monitoring in the USA:

[redacted]

All other trial personnel not included in this section is identified in a separate personnel list as appropriate. This list will be regularly updated as needed. Its most current version will be available in each centre's investigator site file (ISF) and/or in the TMF.

14.2. Appendix B – Safety Laboratory Parameters

Serology (at VS1 only)

Hepatitis A antibody IgM
Hepatitis B surface antigen
Hepatitis C virus antibody
HIV antibodies (dual screen, HIV1, HIV2)

Blood coagulation (at VS1 only)

Prothrombin time

Haematology

Haemoglobin total
Haematocrit
Red blood cells (RBC)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
White blood cells (WBC) differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Platelet count

Biochemistry

Fasting glucose (may not be fasting)
Total protein
Albumin
Creatinine
GFR (at VS1 only)
Urea
Uric acid
Sodium, potassium
Cholesterol, triglycerides
AST, ALT
Alkaline phosphatase
Total bilirubin, conjugated bilirubin

Urinalysis (performed at trial site on fresh urine)

- Dipstick for pH, protein, glucose, blood, ketones, leukocytes, urobilinogen, bilirubin
- Pregnancy test (hCG) for women of child-bearing potential

14.3. Appendix C – Most Common Antiarrhythmic Drugs Class I

Ajmaline
Disopyramide
Flecainide
Hydroquinidine (dihydroquinidine)
Lidocaine
Mexiletine
Prajmaline (prajmalium)
Procainamide
Propafenone
Quinidine
Tocainide

This list is not complete. In case of doubt, please contact the medical monitor.

14.4. Appendix D – CYP2D6 Inhibitors and CYP3A4,5 and CYP2C19 Substrates

CYP2D6 inhibitors [36]

Strong:
- Bupropion
- Cinacalcet
- Fluoxetine
- Paroxetine
- Quinidine

Moderate:
- Duloxetine
- Sertraline
- Terbinafine

Weak:
- Amiodarone
- Cimetidine

CYP3A4,5 substrates [36]

Macrolide antibiotics:
- Clarithromycin
- Erythromycin
- NOT: Azithromycin
- Telithromycin

Anti-arrhythmics:
- Quinidine

Benzodiazepines:
- Alprazolam
- Diazepam
- Midazolam
- Triazolam

Immune modulators:
- Cyclosporine
- Tacrolimus (FK506)

HIV antivirals:
- Indinavir
- Nelfinavir
- Ritonavir
- Saquinavir

Prokinetics:
- Cisapride

Antihistamines:
- Astemizole
- Chlorpheniramine

Terfenadine

Calcium channel blockers:

Amlodipine
Ditiazem
Felodipine
Lercanidipine
Nifedipine
Nisoldipine
Nitrendipine
Verapamil

HMG COA reductase inhibitors:

Atorvastatin
Cerivastatin
Lovastatin
NOT: Pravastatin
NOT: Rosuvastatin
Simvastatin

Steroid 6β-OH:

Estradiol
Hydrocortisone
Progesterone
Testosterone

Miscellaneous:

Alfentanil
Aprepitant
Aripiprazole
Boceprevir
Buspirone
Carbamazepine
Cafergot
Caffeine
Cilostazol
Cocaine
Codeine-n-demethylation
Dapsone
Dexamethasone
Dextromethorphan
Docetaxel
Domperidone
Eplerenone
Fentanyl
Finasteride
Gleevec
Haloperidol
Irinotecan
Levo-alpha-acetylmethadol

Lidocaine
Methadone
Nateglinide
Nevirapine
Ondansetron
Pimozide
Propranolol
Quetiapine
Quinine
Risperidone
Romidepsin
Salmeterol
Sildenafil
Sirolimus
Sorafenib
Sunitinib
Tamoxifen
Taxol
Telaprevir
Terfenadine
Torisel
Trazodone
Vemurafenib
Vincristine
Zaleplon
Ziprasidone
Zolpidem

CYP2C19 Substrates [36]

Proton pump inhibitors:

Esomeprazole
Lansoprazole
Omeprazole
Pantoprazole

Anti-epileptics:

Diazepam
Phenytoin
S-mephenytoin
Phenobarbitone
Amitriptyline
Carisoprodol
Citalopram
Chloramphenicol
Clomipramide
Clopidogrel
Cyclophosphamide
Hexobarbital

Imipramine N-DeMe
Indomethacin
Labetalol
R-Mephobarbital
Moclobemide
Nelfinavir
Nilutamide
Primidone
Progesterone
Proguanil
Propanolol
Teniposide
R-Warfarin
Voriconazole

The lists are not complete. In case of doubt, please contact the medical monitor.