Theranexus

CLINICAL STUDY PROTOCOL

SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS

Study code: THN102-201
EudraCT: 2015-005035-41
Phase: IIa (Proof-of-Concept)

Study Protocol version 6.0 - dated on 11 May 2018

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STUDY SYNOPSIS

STUDY TITLE	Safety and efficacy of THN102 on sleepiness in narcoleptic patients
SHORT TITLE	Safety and efficacy of THN102 on sleepiness in narcoleptic patients
Protocol Number **EudraCT**	**THN102-201** **2015-005035-41**
Clinical Study Phase	**IIa** **Proof-of-Concept**
Number of planned centres	Approximately 8 centres in Europe
Study Population	48 patients with narcolepsy (with or without cataplexy) and exhibiting residual excessive daytime sleepiness despite modafinil treatment. The goal is to complete 42 patients. In case of high dropout rate, up to 54 patients might be recruited.
Study Drugs	THN102: Modafinil 100 mg tablets (TEVA) AND Flecainide Acetate capsules (PCA) 0, 1, 9 mg Reference drug: Modafinil 100 mg tablets (TEVA) Placebo: Flecainide Acetate placebo capsules (PCA)
Study Treatments	**Oral daily treatments given during double-blind Period I, II, and III (split as 2/3 dose at 7:00 and 1/3 dose at 13:00) with:** • 3 tablets modafinil 100 mg + 3 capsules placebo (THN102 as 300 + 0 mg, comparator as Modafinil) • 3 tablets modafinil 100 mg + 3 capsules flecainide 1 mg (THN102 as 300 + 3 mg) • 3 tablets modafinil 100 mg + 3 capsules flecainide 9 mg (THN102 as 300 + 27 mg) **Allocation ratio: 1:1:1**
Primary Objective	• To determine the superiority of THN102 (combination modafinil and flecainide acetate) vs modafinil for improving the excessive daytime sleepiness (EDS) assessed by Epworth Sleepiness Scale (ESS) in patients with narcolepsy treated by modafinil
Secondary Objectives	• To quantify the efficacy of THN102 (modafinil/flecainide acetate combination) for two daily doses (300/27 mg and 300/3 mg) vs modafinil (300/0 mg) for improving cataplexy (in type 1), sleep paralysis, fatigue, hallucinations, and quality of life • To determine the dose response profile of THN102 vs. modafinil on efficacy parameters • To assess the safety profile of THN102 doses vs. modafinil • To determine the plasma levels of modafinil and flecainide at steady state

<table>
<tr><td>Endpoints
Primary Efficacy</td><td>• Mean Epworth Sleepiness Scale (ESS) total score at the end of each treatment period</td></tr>
<tr><td>Secondary Efficacy</td><td>• Good response on ESS scale: decrease from baseline ΔESS ≥3
• Absence of residual somnolence: ESS<11
• Daily sleepiness assessment (modified ESS for EDS daily pattern)
• 14-item fatigue scale
• European Scale of Quality of Life (EQ-5D)
• PGI-S (Patient Global Impression for Severity)
• PGI-C (Patient Global Impression for Change vs. baseline)
• CGI-S (Clinical Global Impression for Severity)
• CGI-C for change vs. baseline for sleepiness and cataplexy
• Information reported on patient diary – completed at home daily:
o Number of diurnal involuntary episodes of sleepiness
o Number of diurnal involuntary sleep attacks
o Number and total duration of voluntary naps during day time
o Number of cataplexy episodes: partial vs generalised
o Occurrence of hypnagogic hallucinations and sleep paralysis
o Nocturnal awakening
o Total duration of nocturnal sleep time</td></tr>
<tr><td>Endpoints safety</td><td>• Adverse events
• Vital signs (10 min sitting)
• Electrocardiogram (ECG), physical examination
• Beck Depression Inventory (BDI) evaluation for depressive symptoms (including suicidal thoughts)
• Haematology, biochemistry, urinalysis
• Pregnancy tests</td></tr>
<tr><td>Endpoints PK</td><td>• Plasma levels of modafinil and flecainide at steady state</td></tr>
<tr><td>Study Design</td><td>This is a prospective, 3-sites, double-blind, randomised placebo-controlled study using a complete 3-way cross-over design in narcoleptic patients with or without cataplexy (type 1 and type 2) with excessive day sleepiness:
<table>
<tr><th>Period</th><th>Design</th><th>Week</th><th>Modafinil
2 + 1 tablet</th><th>Flecainide
2 + 1 capsule</th></tr>
<tr><td>Stabilisation</td><td>Open</td><td>1 + 2</td><td>200 + 100mg</td><td></td></tr>
<tr><td>Period I</td><td>Double-blind</td><td>3 + 4</td><td>200 + 100mg</td><td>0, 1 or 9 mg</td></tr>
<tr><td>Period II</td><td>Double-blind</td><td>5 + 6</td><td>200 + 100mg</td><td>0, 1 or 9 mg</td></tr>
<tr><td>Period III</td><td>Double-blind</td><td>7 + 8</td><td>200 + 100mg</td><td>0, 1 or 9 mg</td></tr>
<tr><td>Washout</td><td>Open</td><td>9</td><td>200 + 100mg</td><td></td></tr>
</table>
*: Treatment taken at 7:00 to 8:00 in the morning and at 13:00 to 14:00 early afternoon
Type 1 patients should represent >70% of overall population.</td></tr>
</table>

Study duration	Involvement of a given patient in the study will be 9 weeks and the study will last approximately 12 to 15 months.
Data analysis and statistics	The primary efficacy parameter being the ESS total score at each key visit (end Period I, end Period II, end Period III) will be analysed in the intent-to-treat (ITT) set with a mixed-effect analysis of variance model suited to the cross-over design. The model will include the treatment, period and sequence 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 the THN102 high dose (modafinil 300mg/27mg) and modafinil alone will be assessed with a contrast t-test at the two-sided 5% level. The THN102 low-dose treatment (modafinil 300mg/3mg) will be analysed in a similar fashion. The ESS total score will also be analysed in the as per Protocol Population (PP) as a supportive analysis. The continuous secondary efficacy parameters will be analysed in the ITT set using the same method as for the primary endpoint. Key secondary efficacy endpoints may also be analysed on PP population. Subgroup analyses may be performed to investigate the effect of the main demographics (age, gender, ...) and disease (narcolepsy type) characteristics on the efficacy outcome. Categorical data will be compared in the ITT set between the each THN102 dose group and modafinil alone using a Mc-Nemar test at the 2-sided 5% level or a Wilcoxon signed-rank test for paired ordinal data. For cataplexy parameters only Type 1 patients will be included. Mainly descriptive statistics will be applied for safety parameters. Plasma concentrations at steady state will be measured, tabulated and presented as graphs.

STUDY FLOW CHART

	Pre-study V0	V1	V2 = Baseline	V3*	V4*	V5*	V6
Visit day*	**D-30 to D1**	**D1**	**D15**	**D29***	**D43***	**D57***	**D64**
Periods (2 weeks except for Washout)		**Start Stabilisation**	**End Stabilisation**	**End Period I**	**End Period II**	**End Period III**	**Washout to end-of-study**
Information to patient / History / Incl. & Excl. Doppler echocardiography (within 3 months)§	X X						
Sign informed consent	X						
Treatment 7:00 and 13:00**							
Stable dose modafinil 300 mg/day (D2-D64), as 200 mg + 100 mg	Modafinil	X	Day 2-15 2 + 1 tabl.	Day 16-29 2 + 1 tabl.	Day 30-43 2 + 1 tabl.	Day 44-57 2 + 1 tabl.	Day 58-64 2 + 1 tabl.
Flecainide or placebo as 3 capsules /day (0 + 0 mg, 2 + 1 mg, 18 + 9 mg)				Day 16-29 2 + 1 caps.	Day 30-43 2 + 1 caps.	Day 44-57 2 + 1 caps.	
Deliver instructions **Deliver & check patient diary** **Deliver & check clinical supplies**		X X X	**X** **XX** **XX**	X XX XX	X XX XX	X XX XX	 X X
Safety							
Laboratory safety (App. L, blood, urine)	(X)	X	**X**	X°	X°	X°	X
Pregnancy (urine, hCG)		X	**X**	X	X	X	X
Vital signs (10 min sitting)		X	**X**	X	X	X	X
ECG (12 lead, 10 min supine)§§	(X)	X	**X**	X	X	X	X
Patient safety scale: BDI (App. F)		X	**X**	X	X	X	X
PK (one sample/visit, 5 in total)***		X	**X**	X	X	X	
Physical examination: Complete or Abbr.°		X	X°	X°	X°	X°	X
Efficacy (6 questionnaires by patient)							
1. ESS (primary endpoint) (App. B)	X	X	**X**	X	X	X	X
2. Extended ESS for daily pattern (App. C)		X	**X**	X	X	X	X
3. Fatigue scale (14-point) (App. D)		X	**X**	X	X	X	X
4. EQ-5D (App. E)		X	**X**	X	X	X	X
Patient diary at home (App. G)		S	**X**	X	X	X	X
5+6. Patient: PGI-S and PGI-C (App. H)		S	**S**	S&C	S&C	S&C	S&C
CGI –S and CGI-C Change (App. I)		S	**S**	S&C	S&C	S&C	S&C
Adverse events							

Notes to Study Flow Chart:
Visit V0 (pre-study) and Visit V1 may be combined if patient history confirms laboratory safety is acceptable. If unclear, a laboratory safety profile at Visit 0 may be planned. In that case no laboratory profile needs to be performed on Visit 1.

§: To perform a transthoracic Doppler echocardiography is an inclusion criterion and may be performed at screening (Visit 0 or Visit 1). It does not need to be repeated if recorded recently (<3 months prior to Visit 1).

§§: Safety ECG must be inspected carefully at each visit to assess impact on conduction (QTc, PR and QRS)

*: Visit day for Visit V2 (baseline), V3, V4, and V5 should be on target if possible (D29, D43, D57) with flexibility ±1day if necessary (or exceptionally 2 days), aiming at keeping 14 days between periods as much as possible. Other visits may have a ±2-day flexibility.

: Morning treatment can be taken between 07:00 and 08:00 and early afternoon treatment between 13:00 and 14:00, but keeping the pattern stable over the 8 week study (stabilisation, Period I, Period II, Period III) for a given patient and a 5 to 6h interval between morning and early afternoon doses. It is speculated that majority of patients will take drug around 7:00 before breakfast and around 13:00 before lunch. **Treatment of a given period starts the day following the visit.

***: In the event of a prolonged visit or of an additional visit at study site or at hospital is scheduled between Day 29 and Day 60 (Period I to approximately 80 hours after end of Period III) for whatever reason, an additional plasma sample will be collected and precise time of last drug intake will be recorded.

°: Abbreviated biochemistry for V3, 4, and 5: SGP, SPT, AP, creatinine, urea, bilirubin) and for physical examination.

Filled by patient

- **At home: patient diary for drug intake daily and for key events**
- **Five (5) or six (6) efficacy questionnaires during site visit:**
  1. ESS
  2. Extended ESS for daily EDS pattern
  3. 14-item Fatigue Scale
  4. EQ-5D: European Quality of Life (EQ-5D) with VAS (visual analogue scale)
  5. PGI-S (all visits) and PGI-C (vs. baseline on V3, V4, V5 and V6)
- **One (1) safety questionnaire,** BDI: Beck Depression Inventory

Filled by investigator

- **CGI-S** (Clinical Global CGI for Severity at each visit)
- **CGI-C** (Change vs. Baseline) on V3, V4, V5 and V6 for global, sleepiness and cataplexy (by patient type)

RATIONALE FOR PROTOCOL 5

The protocol has been amended to remove site and investigator names, specific wording for France and to update Project Management Responsibilities.
In addition, minor editing issue were resolved.
All modifications are presented in the Appendix M.

PROTOCOL HISTORY

V1.0	NA, initial Version
V2.0	Echocardiography added as inclusion criteria
V3.0	Updated following French Agency comments received on 25JAN16
V4.0	Updated following French Agency comments received on 03FEB2016
V4.1	Added Sites 4 and 5
V5.0	Removal of Investigator's sites details, modification of responsibilities and correction of typo
V6.0	Updated following Belgium Agency comments received on 07MAY18

LIST OF ABBREVIATIONS

AE	Adverse event
ALQ	Above Limit of Quantification (assay)
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of variance
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé (French Health Agency)
AST	Aspartate aminotransferase (SGOT)
AUC	Area Under the Curve ie. Area Under the plasma concentration versus time Curve over time periods (AUC_{0-t}, $AUC_{0-\infty}$)
AUEC	Area Under a selected Pharmacodynamic Efficacy parameter versus time Curve
AV	Atrioventricular
BDI	Beck Depression Inventory
bpm	Beats per minute
BMI	Body Mass Index = Body weight (kg) / Height (m^2)
BW	Body Weight (kg)
BP	Blood pressure
CGI	Clinical Global Impression for global, for sleepiness and for cataplexy
CGI-C	Clinical Global Impression for Change vs. Baseline on Visit 2
CGI-S	Clinical Global Impression for Severity at each visit
CI	Confidence Interval
CNS	Central Nervous System
C_{max}	Maximal plasma concentration after oral treatment
C_{min}	Minimal or trough plasma concentration (before dose 2 and dose 3)
C_{ss}	Plasma concentration at steady state
CPP	Comité de Protection des Personnes (also called ERC)
CRF	Case Report Form
CRO	Clinical Contract Organization
CSF:	Cerebrospinal Fluid
CYP450	Cytochrome P450
CV	Coefficient of Variation
DO	Dropout
DMP	Data Management Plan
DSUR	Development Safety Update Report
ECG	Electrocardiogram, electrocardiography
EDS	Excessive Daytime Sleepiness
EMA	European Medicines Agency
ENT	Ear Nose Throat
EQ-5D	European Quality of Life (at 3 levels)
ESS	Epworth Sleepiness Scale
ERC	Ethical Review Committee
ESS	Epworth Sleepiness Scale
FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacture Practice
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Heart Rate

hCG	Human Chorionic Gonadotrophin (urine)
IB	Investigator Brochure
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Study File
i.v.	Intravenous
ICH	International Committee for Harmonization
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
MSLT:	Multiple Sleep Latency Test
N	Number of observations, subjects, or samples
OTC	Over the counter
PCA	Pharmacie Centrale des Armées (production clinical units)
PD	Pharmacodynamics
PGI-S	Patient Global Impression for Severity
PGI-C	Patient Global Impression for Change (vs. Baseline on Visit 2)
PK	Pharmacokinetics
PSG:	PolySomnoGraphy
PUI	Pharmacie pour Usage Intérieur
QT	Duration between Q wave and T wave on the ECG (expressed in ms)
QTcb	Corrected QT-interval (Bazett's formula) in ECG (expressed in ms)
QTcf	Corrected QT-interval (Fridericia's formula) in ECG (expressed in ms)
RA/HA	Regulatory Agency / Health Authorities
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SEM	Standard error of the mean
SOP	Standard Operation Procedures
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
SD	Standard deviation
SEM	Standard error of the mean
SOREMPs:	Sleep-Onset Rapid Eye Movement Periods
THN02	Theranexus internal code for flecainide acetate
THN102	Theranexus internal code for the combination modafinil and flecainide
TMF	Trial Master File
TRAE	Treatment Related Adverse Events
$t_{1/2}$	Terminal elimination half-life
t_{max}	Time to reach maximal drug concentration in biological matrix (plasma)
VAS	Visual Analogue Scale
WBC	White blood cells
WHO	World Health Organisation

1. INTRODUCTION

1.1. Background

Narcolepsy is a clinical syndrome characterised by excessive daytime sleepiness and accompanied in large majority of patients by cataplexy, a transient and abrupt loss of muscle tone triggered by strong emotions (type 1). A disturbed pattern of REM (Rapid Eye Movement) sleep control seems to be involved in cataplexy and in other symptoms such as hallucinations (when awaking or falling asleep), and sleep paralysis lasting one to two minutes after awakening [Ballon 2006; Kumar 2008].

The daytime sleepiness may be severe with patients dozing off with little warning into episodes referred to as "sleep attacks" and cataplexy can be very disabling. Narcolepsy type 1 (narcolepsy with cataplexy) is estimated to have a prevalence of 0.5 to 1 patient for 2'000 [Longstreth 2007]. It frequently starts in adolescence or early teens with similar prevalence in women and men. It represents a high burden for these patients from a medical, professional and social point of view [Dauvilliers 2007]. The prevalence of narcolepsy type 2 (narcolepsy without cataplexy) is less well documented but it is estimated to reach 0.4 to 0.7 patient for 2'000 [Silber 2002; Shin 2008].

Modafinil, a wake promoting agent with a unique profile different from amphetamine, produces enhanced vigilance and arousal, is generally well tolerated and it has demonstrated efficacy in the treatment of daytime sleepiness in narcolepsy [Ballon 2006; Kumar 2008], as in other conditions (obstructive sleep apneas, fatigue in cancer, in neurodegenerative disorders, etc). Besides, many common situations involve short or long sleep deprivation periods or wake-sleep rhythms modifications. Sleep loss alters attention and vigilance, and reduces operational performances. Modafinil works well in sleep-deprived subjects to support vigilance, cognitive performance, coping skills, and recovery sleep [Lagarde 1997; Wesensten 2002; Killgore 2009]. Positive impact on cognition, performance, and mood was seen in healthy subjects [Turner 2003; Müller 2013].

Modafinil has been the first line treatment in narcolepsy for the past 20 years due to its efficacy, good tolerance, and unique profile. Specialised clinicians stress however the shortcomings and deficiencies in modafinil efficacy profile; a residual sleepiness persists in a large majority of patients and it lacks any impact on cataplexy [Schwartz 2005; Lavault 2011]. The medical need is consequently high. Modafinil mode of action is partly understood and seems to involve modulation of several neurotransmitters in the brain (catecholamines, serotonin, glutamate, BABA, orexin, and histamine systems [review by Minzenberg and Carter 2008].

Theranexus, a biotechnology company registered in Orsay (France), has recently demonstrated that Flecainide Acetate – a class Ic antiarrhythmic compound - can significantly modify at very low dose the basic modafinil pharmacological profile. More precisely, flecainide enhances activity of modafinil on wakefulness and cognition and can even decrease the occurrence of cataplexic-like attacks in pertinent mice models, while modafinil or flecainide administered alone has no impact on this symptom.

Theranexus is consequently developing a clinical program with a combination of modafinil and flecainide acetate (THN102). This combination could be more effective than modafinil alone for treating narcolepsy and for improving other frequent symptoms such as residual sleepiness and cataplexy.

A scientific advice from the ANSM was requested by Theranexus in July 2013. It was agreed to perform a safety pharmacology study in vigile dogs monitored by telemetry over 24 hours prior to initiation of Phase I and Phase II. Vital signs, body temperature, 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 QTc (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.

In the literature the terminal plasma half-life (t1/2) reported in man is 15h for modafinil and 13h for flecainide acetate. The most appropriate ratio modafinil to flecainide acetate in THN102 remains to be selected in patients with narcolepsy on the basis of a Phase IIa study assessing outcome for efficacy on daytime sleepiness and other narcolepsy symptoms, for pharmacodynamic profile, for safety including cardiac electrophysiology, vital signs, and adverse events, and finally for drug exposure at steady state. These are the objectives of the present study THN102-201.

The mode of action of this combination, THN102, is still under investigation, and non-clinical results are presented in the THN102 Investigator Brochure, Version 2 (May 2015).

The safety and tolerance of THN102 was recently investigated in a 3-way cross-over study, randomised, double-blind study 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 (study THN102-101). The 50 mg dose selected for flecainide acetate in Phase I is approximately twice the maximum dose planned (27 mg) for treating narcoleptic patients in this Phase IIa study, THN102-201. In Phase I study (THN102-101) body temperature as well as supine blood pressure and heart rate were increased over time for both THN102 and modafinil treatment vs. 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 vs. placebo. A marginal PR shortening for both active treatments was seen in line with the clear positive chronotropic effect. Addition of flecainide acetate had no impact on modafinil kinetic profile and parameters measured were similar (including C_{max}, T_{max}, $t_{1/2}$, AUC, clearance, and volume of distribution) and flecainide had the anticipated mean terminal plasma $t_{1/2}$ (12.2h), median T_{max} (3h) and calculated PK parameters for clearance and volume of distribution but a lower C_{max}, possibly due to lack of dose linearity when administering a low flecainide dose.

It is anticipated that approximately 2 to 3 days may be required to achieve a new steady state for flecainide in plasma when switching treatment period and that no steady state change will occur thereafter during a given period for this planned study.

1.2 Test drugs

Extensive information on modafinil and flecainide acetate can be found in their respective SmPC (Summary of Product Characteristics) on the EMA (European Medicines Agency) site and in the literature (see Investigator Brochure, Section 7). A table summarising the key features for both compounds and covering mechanism of action, safety pharmacology, pharmacokinetic profile, metabolism, posology, registration, and most prevalent adverse events is provided on page 13 and 14. 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 claims worldwide and several millions have been treated with flecainide acetate.

A review of THN102 pharmacology profile and safety pharmacology is provided in the Investigator Brochure. A dedicated electrophysiology study was performed in vigile dogs under telemetry with THN102 and no change on QTc_F and QRS was detected up to maximum combination given (75mg/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.

Field	Modafinil	Flecainide Acetate
Claim 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 Acetate is used to prevent and treat tachyarrhythmias. • It has local anaesthetic activity and belongs to the membrane stabilizing (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 [Binnenmars 2012] • Well tolerated	• Prolongs QT interval and widens QRS complex. • Related to systemic exposure in conscious dogs and in man [Heath et al 2011] • Narrow therapeutic range
Pharmacokinetic Profile		
	• Oral bioavailability: 40-65% • Plasma concentrations linear and time-independent • Dose proportional between 200 to 600mg • Tmax: 2 to 4h (tablet) • Cmax delayed 1h by food • Cmax: 3.7 to 4.8µg/mL (200mg dose) • Terminal half-life: 15h (range 10-15h) • Impact of ethnicity and gender • Protein binding: 60% ~~[Review Robertson & Hellriegel 2006]~~	• Oral bioavailability: 95% • Plasma concentrations approximately dose dependent within therapeutic range but unclear when below • Tmax: 1.5 to 3h (tablet) • No food interaction • Cmax: 200 to 1,000ng/mL (100-300 mg) • Terminal half-life: 13h (mean across single dose studies, range wide). • Protein binding: 40% ~~[Conard 1984 ; Tchandra-Maga 1986]~~
Metabolism (human)		
	• Amide pathway (major) and oxidative pathway (minor) • Substrate: multiple CYP450 including CYP3A4/3A5 • Metabolised by liver • ≤5% intact drug excreted in urine	• Substrate: CYP2D6 (mainly) and 1A2 • Metabolised by liver • ~30% intact drug in urine

Field	Modafinil	Flecainide Acetate
	[Robertson et al. 2000]	[Tennezé 2002]
	No anticipated interaction with Flecainide metabolism (different CYP450 pathway)	No anticipated interaction with Modafinil metabolism (different CYP450 pathway)
	200 to 400 mg/day (in narcolepsy)	100 to 300 mg/day (in tachyarrhythmia)
	Registration: 1992 (France), 2003 (USA)	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... • Chest pain, asthenia • Increased liver function tests	• Depression, anxiety, insomnia • Paraesthesia, ataxia, tremor, syncope... • Palpitation • Nausea, vomiting, abdominal pain,... • Dyspnea • Asthenia, fatigue, oedema

A Summary of Product Characteristics (SmPC) of modafinil and of flecainide acetate has been attached as Annex 7 to the Investigator Brochure Version 3 issued in October 2017. An extensive list of adverse events is presented in this document, albeit in patients on chronic treatment and frequently on concomitant therapy for both compounds and at much higher dose for Flecainide. These documents will serve as a basis to differentiate Serious Adverse Events (SAE) from Severe Unexpected Serious Adverse Reactions (SUSAR) in this study (also see Section 8.2).

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 1'585 cases and also including serious cutaneous adverse events) and 0% in adults when involving 4'264 patients.

1.3 Rationale for Study Design and Dose Selection

Study design

Narcolepsy with cataplexy (Type 1) represents an orphan drug disease which is equally common in men and women and may start in adolescents and young adults but it may also occur in young children or in patients above 40 years of age [Ohayon 2002; Silber 2002]. Narcolepsy results from the massive loss of the neuropeptides called orexin-A and orexin B (also known as hypocretin-1 and hypocretin B), with a decrease of some 90% in their cerebrospinal fluid (CSF) [Mignot 2002; Kanbayashi 2002; Dauvilliers 2003]. Orexin-A and Orexin-B are produced by the lateral hypothalamus neurons and have excitatory effects when binding to ox1 and ox2 receptors on postsynaptic neurons. Orexins are released during wakefulness and increase the activity of many brain regions involved in controlling and promoting alertness, preventing inappropriate transitions into rapid eye movement (REM) or non-REM sleep, and inhibiting REM sleep [Saper 2001; España 2011]. Loss of orexins may initiate REM sleep-related symptoms such

as cataplexy, hypnagogic hallucinations and sleep paralysis and thus disturb pattern of daytime wakefulness and sleep.

The etiology of narcolepsy type 2 is unknown and CSF orexin-A levels are usually normal [Mignot 2002; Kanbayashi 2002]. When found to be low (~24% of type 2 patients), half of these patients will eventually develop cataplexy, thus evolving to type 1 over the years [Andlauer 2012]. Regular check for criteria is consequently required for ensuring that diagnosis is still adequate and evolution of disease profile is well captured.

This Proof-of-Concept, Phase IIa trial with THN102 should collect a sufficient body of information to assess efficacy and safety profile of THN102 versus modafinil alone. If we assume a difference in ESS between THN102 and modafinil between 2 to 2.5 we would need between 140 and 200 patients with a parallel design, numbers which are unrealistic for a Phase IIa trial and even more so with an orphan drug indication. The sample size required for a cross-over design is approximately one third of the size required in a parallel study. To switch to a cross-over option is thus a viable alternative design, the sample size remaining below 60 patients in this condition. In addition a direct comparison between THN102 doses can be performed in the same patient.

It should be stressed that careful consideration to sizing the present study should be applied when considering the mean difference since the magnitude of the effect seen with THN102 vs. modafinil will probably not be as large as the effect of modafinil versus placebo which reached 3 [Dauvilliers et al 2013]. We chose to decrease the mean difference between THN102 and modafinil for ESS to a target 2.4, since the effect is expected to be lower in magnitude when comparing the active treatment THN102 to modafinil.

The selected study design for this pilot Proof-of-Concept Phase IIa trial is consequently a randomised, placebo-controlled, 3-way cross-over study design comparing 2 dose levels of THN102 to modafinil after an open stabilisation period and followed by a one-week washout period under the same dose modafinil. It was perceived as essential to take advantage of the cross-over design for exploring 2 doses of THN102 and comparing their impact on ESS and other key efficacy endpoints. For such a study it is important to stabilise all patients at the same dose of modafinil before and during the 3 cross-over periods. A 2-week duration has been selected for all 4 periods (stabilisation, Period I, II, and III) despite the fact that the time for reaching a plateau effect for THN102 is not known.

In addition to the primary endpoint, ESS, numerous efficacy endpoints have been selected as questionnaires filled at each visit by the patient (extended ESS scale for daily pattern, European Quality of Life EQ-5D with VAS, 14-item fatigue scale as well as Patient Global Impression (PGI). The investigator will rate his clinical impression (CGI) for severity and for change.

Dose selection

The stable dose of modafinil selected to obtain comparable data across patients takes into consideration that the majority of narcoleptic patients receives a mean daily dose of 300 mg as 1 or 2 doses [Dauvilliers 2009]. Thus a stable 300 mg modafinil daily dose split as 200 mg morning dose and 100 mg early afternoon dose was considered reasonable and best adapted to help differentiate a mid- to late afternoon and an early evening impact on EDS which could possibly be elicited by the combination drug THN102. An extended ESS scale assessing morning, afternoon and evening profile separately should facilitate further this comparison of the THN102 combination, its dose response and respective duration of effect. The daily doses selected for

flecainide in the combination are 3 and 27 mg split as morning dose (2 mg or 18 mg) and as early afternoon dose (1 and 9 mg).

Based on this mean difference of 2.4 for ESS between one THN102 dose and modafinil (see Section 11.5 for detailed calculations) we need to recruit 42 patients completing the study as per protocol or 48 patients if assuming a 12.5% drop out (DO) rate. It will be jointly decided between investigators, study manager and sponsor whether DO should be replaced in the event DO rate is above 12.5%. No more than 54 patients however may be recruited for that study.

1.4 Risk/Benefit Ratio

Risk

It is anticipated that safety and tolerance profile for THN102 is likely to be similar to modafinil given alone in this narcoleptic population, with frequent occurrence of headache, gastric pain, palpitation, tachycardia, dizziness, insomnia, anxiety, confusion, and blurred vision (see list in table on page 16). Flecainide acetate is given at daily doses between 100 and 300 mg for treatment of tachyarrhythmia which implies that the two daily doses selected for narcolepsy in this study are approximately 90 to 300-fold lower (for 3 mg) and 10 to 30-fold lower (for 27 mg). Thus the contribution of flecainide for safety and tolerance of combination drug THN102 should be marginal at the periphery and modest in the central nervous system (CNS).

In Phase I with THN102 the adverse events profile seems to be fairly comparable for THN102 and modafinil. A small but significant increase in blood pressure and heart rate was noted with both THN102 (400/50 mg) and modafinil (400 mg/0 mg) in study THN102-101 with 24-hour Holter monitoring. No impact on cardiac conduction (QTc, QRS) and no arrhythmia were seen (for more details see Section 1.1).

The list of typical adverse events reported for modafinil and for flecainide are also listed in Section 12.10 and mentioned in the information for the patient.

Benefit

This is a Proof-of-Concept study in approximately 50 narcoleptic patients (target 42 completed patients as per protocol) treated with THN102 at 2 doses (300/27 mg, 300/3 mg) compared to modafinil (300/0 mg) under a 3-way, double-blind, cross-over study design. The exposure is thus limited (2 weeks at each dose) and treatment with modafinil is maintained stable for the patients during 9 weeks of the study. Thus the patients have the advantage of receiving active treatment, modafinil, throughout the study. 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 of flecainide. If successful (*i.e.* if significant on ESS, and with trend on some other key endpoints), a more elaborate Phase IIb-III study could be initiated in the future.

These patients have documented Excessive Diurnal Sleepiness (EDS) despite modafinil treatment and it is hoped that THN102 at one or both doses may significantly improve ESS, and possibly impact favourably ESS profile day pattern, fatigue and quality of life while decreasing episodes of sleepiness and sleep attacks and may even improve night sleep in quantity and quality. Peripheral events linked with REM control (such as hallucinations and sleep paralysis) could also be improved in some patients or in selected subgroups by treatment with THN102.

Based on preclinical model it is possible that cataplexy might be improved in type 1 patients but such symptoms are highly variable over time and patient numbers are low.

In summary the risk/benefit ratio for this Proof-of-Concept study is considered as satisfactory.

2. OBJECTIVES AND STUDY ENDPOINTS

2.1 Objectives

Primary objective:

- To determine the superiority of THN102 (combination modafinil and flecainide acetate) vs modafinil for improving the residual daytime sleepiness assessed by Epworth Sleepiness Scale (ESS) in patients with narcolepsy treated by modafinil

Secondary objectives:

- To quantify the added value of THN102 (modafinil/flecainide acetate combination) for both daily doses (300/27 mg and 300/3 mg) vs modafinil (300/0 mg) for improving cataplexy, sleep paralysis, fatigue, hallucinations, and quality of life
- To determine the dose response profile of THN102 vs. modafinil on efficacy parameters
- To assess the safety profile of THN102 doses vs. modafinil

- To determine the plasma levels of modafinil and flecainide at steady state

2.2 Study Endpoints

Primary and secondary endpoints for efficacy, endpoints for safety and PK are provided below and in the Study Flow Chart on page 9-10 and below.

Primary Endpoint for Efficacy

- The primary endpoint is the mean Epworth Sleepiness Scale (ESS) total score at the end of each treatment period

Secondary Endpoints for Efficacy

- Good response on ESS scale: decrease from baseline ΔESS ≥3
- Absence of residual somnolence: ESS <11
- Daily sleepiness assessment (modified ESS for EDS daily pattern)
- 14-item fatigue scale
- European Scale of Quality of Life (EQ-5D)
- PGI-S (Patient Global Impression for Severity)
- PGI-C (Patient Global Impression for Change vs. baseline)
- CGI-S (Clinical Global Impression for Severity) for sleepiness and cataplexy
- CGI-C for change vs. baseline for sleepiness and cataplexy
- Information reported on patient diary – completed at home daily:
  - Number of diurnal involuntary episodes of sleepiness
  - Number of diurnal involuntary sleep attacks
  - Number and duration of voluntary naps and total duration during day time
  - Number of cataplexy episodes: partial vs generalised
  - Occurrence of hypnagogic hallucinations and sleep paralysis
  - Nocturnal awakening
  - Total duration of nocturnal sleep time

Endpoints for Safety and Tolerability

- **Adverse events:** spontaneous reporting from signing informed consent to study completion
- **Vital signs** at each visit (10 min sitting, 6 times, V1 to V6)
- **ECG (**10 min supine, 6 times, V1 to V6):
    - Assess carefully impact on PR, QRS and QTc vs. baseline (Visit 2)
- **Physical examination (**2 complete at V1 and V6, 4 abbreviated at V2, V3, V4, and V5)
- **Biological safety** (see Appendix L for haematology, biochemistry and urinalysis):
    - With emphasis on renal and hepatic markers (hospital laboratory)
    - Urinalysis (dipstick, street drug performed at study site)
    - Pregnancy test in urine for women of child-bearing potential)
    - Performed 6 times (3 complete at V0 or V1, V2 and V6, 3 abbreviated for biochemistry for V3, V4, and V5)
- **Safety scales** (6 times, V1 to V6):
    - Beck Depression Inventory (BDI) evaluation for depressive symptoms

Plasma concentrations for modafinil and flecainide at steady state:

- Time points (5 plasma samples at V1 to V5)
- Additional PK sample(s) if any additional visit for any reason between Day 16 and 60
- Precise time of previous drug intake must be recorded in CRF

In case of an additional visit for whatever reason during the study or within 80 hours after V5 or of a prolonged visit at site, another PK sample will be collected to measure plasma concentration and precise date and time o'clock of last drug intake will be collected to help support dose-dependency assessment at steady state and population kinetics in clinical programme.

3. STUDY DESIGN

This Phase IIa study is a 3-site, double-blind, randomised, placebo controlled, 3-way cross-over trial, involving 3 treatments with the combination drug THN102 (Modafinil 300 mg/Placebo, Modafinil/Flecainide 300 /3 mg, Modafinil/Flecainide 300 /27 mg). The 3 double blind periods follow a stabilisation period for modafinil at 300 mg/day (open) and are followed by a one-week washout period with the same modafinil dose.

Drug intake is split as morning dose and as early afternoon dose time for drug intake with larger dose in morning (2/3) and lower dose (1/3) at midday. Drug intakes may fluctuate ± 1h (7:00 to 8:00 for morning dose and 13:00 to 14:00 for early afternoon dose) between patients, but keeping for a given patient a regular pattern and a 5 to 6 h interval between morning and afternoon dose whenever possible. The morning dose is 200 mg modafinil and 100 mg modafinil early afternoon during the whole study and administered under open conditions. During the double-blind Period I, II and III, flecainide doses of 0, 2 or 18 mg are administered with the morning dose as 2 capsules and 0, 1 or 9 mg early afternoon as 1 capsule, thus leading to a total daily flecainide dose of 0, 3 and 27 mg flecainide depending on period.

Modafinil tablets are provided as commercial blisters from TEVA (Modiodal® 100 mg tablets) and flecainide acetate capsules (THN02) are manufactured by the Pharmacie Centrale des Armées (PCA) in sealed vials (0 mg, 1 mg, 9 mg).

An overview of the 5 treatment periods (stabilisation, Period I, Period II, Period III, Washout), with detailed information on split and total doses, number of tablets and capsules and regimens is provided in following table:

Treatment Formulation	**Morning Dose 7:00 to 8:00**	**Early afternoon Dose 13:00 to 14:00**	**Total Daily Dose Units Days or Period**	**THN102 Modafinil / Flecainide mg/mg**	**Period Stabilisation: D2-D15 I: D16 - D29 II: D30 - D43 III: D44 - D57 Washout: D58 - D64**
Modafinil 100 mg TEVA, tablets Days	200 mg 2 tablets	100 mg 1 tablet	200 + 100 = 300 mg 3 tablets D2 to D64		
Modafinil 100 mg TEVA, tablets Days	200 mg 2 tablets	100 mg 1 tablet	Stabilisation: 3 tablets D2 to D15	Modafinil 300 mg	**Stabilisation** Open D2 to D15
Flecainide Acetate Capsules Period	0 mg x 2 caps.	0 mg x 1 caps.	0 mg x 3 = 0 mg 3 capsules (I, II or III)	THN 102 300 mg / 0 mg Comparator	Double blind **Period I, II, or III**
Flecainide Acetate Capsules Period	1 mg x 2 caps.	1 mg x 1 caps.	1 mg x 3 = 3 mg 3 capsules (I, II or III)	THN102 300 mg / 3 mg	Double blind **Period I, II, or III**
Flecainide Acetate Capsules Period	9 mg x 2 caps.	9 mg x 1 caps.	9 mg x 3 = 27 mg 3 capsules (I, II or III)	THN102 300 mg / 27 mg	Double blind **Period I, II, or III**
Modafinil 100 mg TEVA, tablets Days	200 mg 2 tablets	100 mg 1 tablet	Washout: 3 tablets D58 to D64	Modafinil 300 mg	**Washout** Open D58 to D64

This Phase IIa study involves a double-blind, randomised, 3-way cross-over design for Period I, II, and III, and consequently implies 6 possible sequences for the 3 treatments (A: THN102 300/0 or Modafinil/Flecainide 300/0 mg, B: THN102 300/3 or Modafinil/Flecainide 300/3 mg, C: THN102 300/27 or Modafinil/Flecainide 300/27 mg) as presented in the following table:

Sequence	Period I	Period II	Period III
1	A	B	C
2	B	C	A
3	C	A	B
4	A	C	B
5	C	B	A
6	B	A	C

A: THN102 as 300/0 B: THN102 as 300/3 C: THN102 as 300/27

Detailed information to assess patient type, to investigate efficacy and safety with various scales, questionnaires, and lists and to collect and ship plasma samples can be obtained in the following appendices:

- Appendix A Criteria for Type 1 and Type 2 narcoleptic patients
- Appendix B ESS (primary parameter of efficacy)
- Appendix C Extended ESS for capturing EDS pattern
- Appendix D 14-item Fatigue Scale
- Appendix E EQ-5D (European Quality of Life (3 levels), with VAS
- Appendix F BDI (Beck Depression Inventory) (21 items)
- Appendix G Patient Diary at home
- Appendix H PGI-S (Patient Global Impression for Severity) for all visits
  CGI-C at V3, V4, V5 and V6 (change from baseline at V2)
- Appendix I CGI-S at each visit for sleepiness and cataplexy
  CGI-C at V3, V4, V5 and V6 (change from baseline at V2)
- Appendix J Plasma collection for PK
- Appendix K Shipment of PK samples
- Appendix L Laboratory safety parameters

Scales, questionnaires and daily diary are provided in English for this protocol but will be filled in their validated local language version when appropriate, *i.e.*, when completed by patient (B, C, D, E, F, and H during site visit and patient diary G at home).

4. SELECTION OF SUBJECTS

4.1 Number of Subjects

A total of 48 male and female patients with narcolepsy type 1 and type 2 will be recruited by the Primary Investigators and their delegates at each study site. Dropouts (DO) will not be replaced unless if reaching >12.5% and only if joint agreement between investigator, study manager and sponsor can be met (for further details see Section 5.2 under *Withdrawal*). The target figure is 42 patients completing the study as per protocol. If DO rate is high (>13%) the maximum number of patients recruited can be up to 54 patients but decision to replace DO in this case will be left at discretion of investigators, study manager, and sponsor. Efforts will be made to achieve as many type 1 patients as possible in the overall population.

To be eligible for inclusion into this study, each patient must fulfill the following inclusion criteria and none of the exclusion criteria at Visit 0 and/or Visit 1.

4.2 Inclusion criteria

6. Patients with a diagnosis of narcolepsy type 1 (i.e. with cataplexy) or type 2 (without cataplexy) according to the International Classification of Sleep Disorders (ICSD-3) criteria (see Appendix A for criteria).
7. The patient is willing and able to fulfill study restrictions and to attend regularly scheduled clinic visits as specified in this protocol, and has signed the informed consent prior to study start.
8. Males or females, aged between 18 and 65-year-old.
9. Body mass index >18 kg/m2 and <35 kg/m2.
10. Patients treated with modafinil at stable dosage for at least 2 months and still complaining of excessive daily somnolence (EDS) despite the treatment
11. Epworth Sleepiness Scale (ESS) score should be ≥ 14/24 during the baseline period.
12. Patients with cataplexy are permitted to remain on their anticataplectic medications at stable doses (mainly sodium oxybate or venlafaxine). The authorized anticataplectic treatment should have been administered for at least 2 months prior to entry in the trial and the doses should not be changed throughout the trial.
13. Patients should have a transthoracic Doppler echocardiography considered as normal (left ventricular ejection fraction >55%, no significant morphological and/or no physiological anomaly, even if not symptomatic).
14. Women of childbearing potential (not surgically sterile or 2 years postmenopausal), must use a medically accepted method of contraception, and must continue one method for the duration of the study (and for 2 months after participation in the study). Acceptable methods of contraception include: abstinence, barrier method with spermicide, steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method, or intrauterine device (IUD).
15. Informed consent must be obtained for all subjects before enrollment in the study (including specific request for HIV serology and hepatitis as well as for urine screen for drug).

4.3 Exclusion criteria

The patients who present any of the following criteria will be excluded from the study:

1. Patients with an untreated sleep apnea syndrome (respiratory disorder index > 30/h) or who have any other cause of daytime sleepiness as assessed on patient history.
2. Patients working in an occupation requiring variable shift work or routine night shifts.
3. Patients with suicidal ideations or that has tried to commit suicide in the past 6 months.
4. Psychiatric and neurological disorders, other than narcolepsy/cataplexy, such as Parkinson's disease, Alzheimer's disease, Huntington's Chorea, multiple sclerosis, moderate or severe psychosis or dementia, bipolar illness, epilepsy, severe clinical anxiety or depression, BDI ≥ 21 or with suicidal risk (if item > 0), or other problem that in the investigator's opinion would preclude the patient's participation and completion of this trial or comprise reliable representation of subjective symptoms.
5. Patients currently under one of the following medications (CNS indication):
    a. Neuroleptic, anxiolytic, anticonvulsant, antiemetic (excepted domperidone), opioid, benzodiazepine (zolpidem/ zopiclone however authorized), psycho-stimulants (except modafinil).
    b. Antidepressants (selective serotonin reuptake inhibitor or modulators, tri- and tetracyclic antidepressants, monoamine oxydase inhibitors) may be given to patients with mild or moderate unipolar depression providing the treatment is maintained at stable dose for at least 6 weeks, is anticipated to remain stable during the study, is well tolerated and devoid of orthostatic hypotension and QTc prolongation as documented at Visit 2 (baseline).
6. Current or recent (within one year) history of a substance abuse or dependence disorder including alcohol abuse as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).
7. Other active clinically significant illness, including unstable cardiovascular, or neoplasic pathology which could interfere with the study conduct or counter-indicate the study treatments or place the patient at risk during the trial or compromise the study participation.
8. Contraindication to flecainide (2^{nd} or 3^{rd} grade atrioventricular block, chronic bifascicular block, complete right bundle branch block, sinus node dysfunction, auricular fibrillation, ventricular arrhythmias considered as medically significant, cardiac insufficiency, heart failure, documented Brugada syndrome, history of cardiogenic shock, and recent or previous myocardial infarction).
9. Patients currently treated or planned to be treated with antiarrhythmic drugs class I or with drugs eliciting bradycardia such as beta-blockers
10. Concomitant therapy which could elicit drug-drug interactions with flecainide as per SmPC, thus increasing or decreasing plasma concentrations
11. Patients with a known history of long QTc syndrome (e.g. syncope or arrhythmia) or presenting any significant serious abnormality of the ECG (e.g. recent myocardial infarction), or QTcf interval higher than 450 ms (electrocardiogram Fredericia's corrected QT interval).
12. Patients with Severe Hepatic or Renal Impairment, or with any other significant abnormality in the physical examination or clinical laboratory results.
13. Known hypersensitivity to the tested treatment including active substances and excipients for modafinil SmPC and excipients for flecainide capsules described in the Investigator Brochure.
14. Women of childbearing potential who intend to be pregnant during the next few months.
15. Patients without any medical care insurance, or protected by the law (curatelle/tutelle).
16. Patients participating in any other clinical trial within 60 days prior to entry in this study or still in the protected period imposed by a previous study.

Any deviation from these inclusion and exclusion criteria should be avoided. If considered minor and/or borderline and/or questionable, such a deviation should be justified and discussed with the study manager, whenever possible prior to enrolling the patient.

No patient will be allowed to enrol in the study more than once. No participation in another trial will be permitted until study completion and for the following two months (exclusion period).

Informed consent must be obtained for all patients before enrolment in the study.

5. STUDY TREATMENTS

5.1 Investigational Medicinal Product (IMP)

Investigational Medicinal Product (IMP) for this Study Protocol is constituted by THN102, a combination of modafinil and 2 doses of flecainide acetate and its placebo. Modafinil is the reference drug.

5.1.1 Test Drug Formulations

THN102 is a combination drug constituted by modafinil tablets (100 mg) from commercial source (TEVA) AND by flecainide acetate capsules (THN02 at 0, 1 mg, 9 mg).

Drug code:	**Modafinil (Provigil® Teva)**
Dosage form:	Tablet, 100 mg, packed in alu foil (commercial sourcing)
Storage:	15-25 °C (avoid exposure >25°C)
Route	Oral dose, D2 to D64
Dose:	300 mg per day, as 200 mg at 7:00 and 100 mg at 13:00

Drug code:	**Flecainide acetate (THN02 manufactured by PCA (Pharmacie Centrale des Armées)**
Dosage form:	Capsules made out of hypromellose (Capsugel Vcaps® Plus HPMC, size 2)
Storage:	15-25 °C
Route:	Oral dose
Vial:	Self-sealing white cylindric 30 mL HDPE (high density polyethylene) vials with HDPE snap-cap, containing 18 capsules per vial (for 6 days)
Dose:	1 mg per capsule, daily dose 3 mg, taken as 2 mg at 7:00 and 1 mg at13:00 9 mg per capsule, daily dose 27 mg, taken as 18 mg at 7:00 and 9 mg at13:00

Drug code:	**Placebo for flecainide acetate (THN02 manufactured by PCA)**
Dosage form:	Matched placebo capsule for flecainide acetate
Storage:	15-25 °C
Route	Oral dose
Vial:	Self-sealing white cylindric 30 mL HDPE (high density polyethylene) vials with HDPE snap-cap, containing 18 capsules per vial (for 6 days)
Dose:	0 mg per capsule, daily dose 0 mg, 2 capsules at 7:00 and 1 capsule at13:00

5.1.2 Reference Drug

Drug code:	**Modafinil (Provigil® Teva)**
Dosage form:	Tablet, 100mg, packed in alu foil (commercial sourcing)
Storage:	15-25 °C (avoid exposure >25°C)
Route	Oral, D2 to D64
Dose:	300 mg per day, as 200 mg at 7:00 and 100 mg at 13:00

5.2 Randomisation and Dosage Schedule

Packaging

Secondary clinical packaging will be made by Sodia, an external specialised CRO (Clinical Research Organisation), according to site, study allocation, subject number, period, and treatment.

Withdrawal

The target number is 48 patients to ensure that 42 patients complete the study as planned. Dropouts (DO) will not be replaced unless if representing more than 6 out of 48 recruited patients (12.5% or more taking into consideration all recruited patients). The decision to replace the dropouts will be taken jointly by sponsor, study manager and primary investigators. Thus a total between 42 and 48 patients may be recruited, with an unlikely possibility to go to as high as 54 patients if DO are frequent.

Randomisation

Allocation of a randomised patient number will be done by principal investigator or delegate at each site on Visit 1, using chronological entry. The subject numbers will be distributed in blocks of 6 for each site with reserve samples maintained at secondary clinical packaging CRO pending further distribution to achieve flexibility and coherence. A 3-digit number between #101 to #160 will be used.

Depending on date of re-test and on recruitment, secondary clinical packaging may be performed as one or two campaigns for flecainide capsules with one or two batches and may require adequate re-labelling for re-test date at CRO responsible for secondary packaging or by study site pharmacists. A cahier des charges will be prepared and a dedicated SOP will be followed.

5.2.1 Timing of Doses

Morning dose will be administered before meal with 150 mL tap water around 07:00 (within 1-hour range: 07:00 to 8:00), and early afternoon dose around 13:00 (within 1-hour range 13:00 to 14:00), trying to keep a similar pattern of drug intake daily for o'clock time and for hours between doses (target: 5 to 6 hours).

5.2.2 Drug storage and distribution

No specific drug preparation is required by the site pharmacists from the study site Hospital Pharmacies (PUI, Pharmacie pour Usage Intérieure) which are responsible for receipt, storage, distribution, and control on a patient by patient basis for all periods (site 1). Clinical supplies will be stored at study site for patients recruited if a locked, dedicated cupboard with temperature control and loging is available (sites 2 and 3).

The individual patient boxes contain 5 smaller boxes with corresponding treatment for each study period: stabilisation with modafinil (open); Period I, II and III with modafinil blisters (open) and flecainide vials (double blind) as per allocation schedule; and washout with modafinil alone (open). The boxes will be kept under lock until each small period box can be transmitted to the appropriate patient at his visit for treatment for the following 2 weeks (at V1 for stabilisation with modafinil, at V2 for Period I, at V3 for Period II, at V4 for Period III, and at V5 for the one-week washout period with only modafinil).

A manual describing storage, drug order by Principal Investigator (prescription), drug administration and control after return by the patient at each visit to assess compliance will be prepared prior to study start for each site to be in line with local situation. The returned intact, open and empty blisters for modafinil and the returned opened vials for flecainide will be controlled after each visit by site staff and returned to the patient large box.

After completion of patient treatment and control by monitor, the patient boxes will be returned to the PIU pharmacy for storage or kept under lock depending on specific agreement passed with site. After study completion and final review by monitor and written confirmation by study

manager, the clinical supplies will be returned to the CRO involved in secondary packaging for destruction.

5.2.3 Administration Procedures

Both study drugs will be administered at 7:00 and at 13:00 before breakfast and before lunch. Both capsules will be administered one after the other with 150 mL tap water. Precise time of drug intake will be recorded in the patient diary on a daily basis.

5.2.4 Diet

No special diet is imposed during the study and only general recommendations are proposed which will be captured at each visit for past period

- Maintain stable daily intake of xanthin-containing drinks (tea, coffee, coca-cola, power drinks etc.). Give mean daily number of cups or glasses
- Consume modest amount of alcohol containing drinks (such as 200 mL of beer or 100 mL wine per day). Give mean daily volume
- Avoid grapefruit consumption and quinine-containing drinks type Schweppes (Yes, no, occasions)

5.2.5 Washout between periods

No washout between periods is planned between stabilisation, Period I, II and III.

On Week 9 flecainide treatment will be washed out and modafinil treatment will be continued alone at 300 mg/day (200 mg morning and 100 mg at early afternoon). On Day 64, a final visit (V6) will be performed to assess evolution of efficacy after flecainide washout and to confirm safety at this end-of-study visit.

5.2.6 Precautions, antidotes

The patients will carry a card at all times stating their participation in a clinical trial and proving contact information (see *Section 5.6*).

If judged appropriate by the Primary Investigator as a consequence of narcolepsy and/or of AE (drowsiness, fatigue, dizziness, blurred vision...), the patients will be instructed to avoid driving any vehicle or machine exposing him/her to any risk. In such cases common transportation will be recommended.

The patients should be told to report any skin rash by phone and at visit if appropriate even if considered as benign.

5.3 Treatment Assignment and Emergency Envelopes

The study medication will be administered only to subjects included in this study, following the procedures set out in the study protocol.

Randomisation will be prepared by an independent statistician for the double-blind study part (Period I, II, and III). Patients will be randomised to receive all 3 treatments, according to 1 of the 6 possible sequences *(see Section 3, page 22*).

The Principal Investigator or the Central Pharmacy at each study site and the Pharmacovigilance representative will be provided with individual sealed emergency envelopes containing treatment code 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 monitor at the end of the study.

The allocation schedule will be transmitted electronically to the CRO in charge of secondary packaging and to the PK analyst in charge of plasma assays. 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 PUI pharmacists at study site are blinded to study treatment.

All other groups involved in study support will only have access to treatment code after delivering data planned as per protocol and after data freezing. Electronic transfer of allocation schedule to investigators, sponsor, study 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 Primary Investigators/Pharmacy at each study site and from Pharmacovigilance will be recovered at study completion, inspected for integrity by XXXXXX monitor, and destroyed. The integrity statements will be stored in the TMF.

5.4 Blinding, Packaging, and Labelling

Blinding

The investigators will receive a set of individual sealed envelopes containing the study medication code allocated to each scheduled patient for their site. These envelopes should remain intact throughout the study unless an emergency linked to a Serious Adverse Event (SAE) would occur in the event such information this knowledge would improve patient's care.

Packaging

The commercial clinical supplies for reference drug modafinil (tablets, Modiodal®, Teva) and the capsules for flecainide acetate manufactured and released by PCA will be packaged by the selected CRO according to allocation schedule, study site, patient number, period, and dose in smaller boxes by period and contained in a larger box for complete study. Individual smaller boxes for each period (stabilisation, Period I, Period II, Period III, washout) will be delivered to the appropriate patient at V1, V2, V3, V4, and V5, respectively. The individual boxes will contain commercial modafinil blisters (for all periods, open) and for Period I, II, and III only flecainide capsules (double blind as 0, 1 and 9 mg capsules).

All packages will be stored at study sites or at PUI sites until study completion, pending control by site pharmacist as appropriate and by XXXXXX monitor. Destruction will be performed by CRO involved in clinical packaging.

Labeling

The clinical supplies for modafinil tablets (open) and for flecainide (double blind) will be labeled individually according to allocation schedule, site, patient number, study period and content and according to applicable regulations, requirements and national laws in force.

For vials with flecainide capsules (0, 1, or 9 mg)
(re-test date according to batch and ongoing long term stability tests):

Etude THN102-201 Patient (#101-xxx) Pér. (I, II, III) Flacon 18 gélules de Flécaïnide de 1 mg ou 9 mg ou placebo Voie orale
Avaler 2 gélules vers 7 :00 et 1 gélule vers 13 :00 avec 150 mL d'eau
Médicament pour recherche biomédicale Conserver en dessous de 25°C
Tenir hors de la portée des enfants
Lot : SC0000 Date re-test: xx xxx 20xx

Investigateur : Dr. X. Xxxxxxxx Tel xxxxxxxxxx
Promoteur: Theranexus, 86 rue de Paris, F-91400 Orsay Tel :01-4654 8397

For modafinil blisters: (expiry date according to commercial batch):

Etude THN102-201 Pat. (#101-xxx) Pér. (Stab., I, II, III, Washout) Contient X Blisters 15 comprimés de Modafinil 100 mg Voie orale
Avaler 2 comprimés vers 7 :00 et 1 comprimé vers 13 :00 avec 150 mL d'eau
Médicament pour recherche biomédicale Conserver en dessous de 25°C
Tenir hors de la portée des enfants
Lot : SC0000 EXP : xx xxx 20xx

Investigateur : Dr. X. Xxxxxxxx Tel xxxxxxxxxx
Promoteur: Theranexus, 86 rue de Paris, F-91400 Orsay Tel :01-4654 8397

The labels for each period and for the patient boxes containing all 5 study periods will be adapted accordingly.

5.5 Supplies Preparation and Accountability

All clinical supplies will be initially delivered and stored at 15-25°C under lock at PIU sites. Access will be restricted to designated site pharmacists.

Prior to study start a Pharmaceutical Manual will be prepared by study manager to describe all steps required for drug distribution and control for each formulation and may differ depending on the site. This manual and a Sign-Off worksheet model if needed will be discussed and agreed with site investigators and PUI pharmacists involved prior to study start. Both documents will be filed in ISF and TMF. The information will be used to confirm compliance. Drug for a given patient and all periods will be distributed by pharmacists upon receipt of a dedicated and signed Prescription Form (Ordonnance) by Principal Investigator which should contain study code number, site, patient number and periods unless permission to store supplies at study site under lock and temperature control is available for a given site (such as for site 2) and in that case the individual patient boxes will be transmitted in blocks of 3 or 6 patients at a time or as jointly agreed. The individual box required to treat a patient for all periods and for all his subsequent visits will be transmitted to the Primary Investigator and kept at 15-25°C under lock until delivered to patient at each visit.

Drug dispensation logs prepared by Principal Investigator or delegate will be maintained throughout the study at each visit and for each patient by site staff. Comparison between tablet and capsule count against diary forms will be performed to obtain information to document compliance. A copy of these log forms, along with the filled Drug Accountability Form and the Reconciliation Form prepared by the monitor will be archived in respective ISF and TMF upon completion of the study and after locking the data base.

At the conclusion of the study, all used and unused study medication will be destroyed by CRO involved in secondary packaging after reconciliation of clinical supplies vs. CRF by monitor and after receiving written instruction from the study manager.

Monitoring of pharmaceutical activities will be described in the Monitoring Plan.

5.6 Compliance

The study medication will be administered at home by the patient and to ensure adequate drug compliance is consequently a key issue. Instructions will be provided to patient on respecting time schedule (between 7:00 and 8:00 before breakfast for the morning dose) and between 13:00 and 14:00 before lunch for the early afternoon dose), trying to maintain same time schedule throughout the study and a 5 to 6 h interval between daily doses. The precise time of drug intake will be recorded in the daily patient diary form.

Compliance will be carefully assessed during the study by comparing diary and theoretical drug intake. This information will be captured in the CRF.

Admission to the study

Admission to the study will be effected on Visit 1 when deciding to start the stabilisation period based on results of laboratory safety, maintained high ESS and willingness of patient to come every 2 weeks for a visit and to follow instructions.

Subject identification

During the run-in period, the subject will be identified by a dedicated code combining the site number (01, 02, 03) and the chronological sequence at a given site (01R06, 02R01, 03R04,...) This screening code will not be captured in the CRF but it is important for monitoring purposes. This screening number and the subject's initials will appear on all study documents, including on the screening and enrolment log form. **Screened subjects who do not enter the study will not have a CRF filled but their source documents will be maintained in the ISF.**

The reference to the full names will be made in the subject's identification list which must be kept strictly confidential. Initials may be used on source documents, worksheets, laboratory results, data printouts, ECG, and others. Only site number, study allocation number, period, day and date will appear in the CRFs and questionnaires. Birth year will be provided in CRF for demographics only. If source documents have to be used externally, full name if provided will be hidden and only allocation number, birth year, period, day, date and time will be transferred.

In the CRF the subject number after Visit 1 will use the randomised allocation patient number linked to clinical supplies.

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

6. PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

6.1 Prior and Concomitant Illnesses

This study is performed in male and female patients with narcolepsy and cataplexy (type 1) or with narcolepsy without narcolepsy (type 2) as defined under Appendix A.

Other concomitant illnesses may be present at initiation and patients may be included providing inclusion/exclusion criteria are respected and providing the disease will not impact on patient assessment for efficacy or compromise patient safety during the trial. Illnesses first occurring or detected during the study are to be regarded as adverse events and must be documented as such in the CRF (see Section 8.1 and 8.2, *Adverse events*).

6.2 Prior and Concomitant Treatments

Any treatment that might have to be given in addition to the study treatment during the study is regarded as a concomitant treatment and must be documented on the appropriate pages of the CRF, specifying drug taken, dose, route, time and reason for use.

All concomitant drugs must be known to and approved by the investigator and should be maintained stable during the study unless mandatory to increase or decrease the dose to ensure a better efficacy or a better safety for the patients. All changes in therapy or in doses must be documented in the CRF. The patient should mention all other drugs, including over the counter medication such as aspirin or vitamins as well as herbal teas.

7. STUDY PROCEDURES AND SCHEDULE

7.1 Overview of Data Collection

The schedule of tests performed is described in the Study Schedule (Page 9-10) and in Section 7.2 *Description of study days*. Methods of data collection and analysis of variables are described in Section 7.3 *Methods of data collection* and in the appropriate Appendices (see summary in Section 2.2 on page 23.

7.2 Description of Study Days

The Study Schedule on page 9-10 provides an overview of the key activities undertaken during the study. A total of 6 visits is planned after the run-in visit V0.

All medical devices used for vital signs and ECG possess an EC mark and are controlled at regular intervals by hospital maintenance service. If appropriate the relevant Declarations of Conformity and Instruction Manuals will be filed in the study ISF and TMF and these medical devices will be used according to their registered EC status.

7.2.1 Run-in visit (V0) and Screening Visit (V1)

Run-in visit V0

General discussion with potential patients will take place before the Run-In visit whenever possible. Sufficient time to read the information and sign the informed consent must be provided to the patient. The investigator will carefully explain background, study design, constraints, possible side effects, and objectives of this study. A transthoracic Doppler echocardiography must be performed within 3 months of screening.

The written informed consent will be collected on Visit 0 which may take place between Day -30 and D -1. In such a case the patient must have an adequate patient history, an ESS score ≥14 despite stable modafinil dose for 8 weeks at least and adverse event must be collected from that day onwards. Blood sampling for haematology, biochemistry and serology will be collected after collecting informed consent unless recently performed prior to study and considered as acceptable.

The patient will have during the run-in period a special code based on site number and chronological number (see Section 5.5, page 31).

Visit 0 and Visit 1 may be combined if recent patient history, patient commitment, convenience and recent data on laboratory safety parameters including serology, ECG and echocardiography are available.

Screening Visit V1 (Initiation Stabilisation Period)

The following examinations and tests will be carried out in each patient, before starting the 2-week stabilisation period with 300 mg modafinil:

- Sign informed consent and deliver signed copy and information for patient (unless obtained at V0)
- Compile medical history
- Collect AE if signature obtained on Visit 0
- Collect data on 6 patient questionnaires (5 for efficacy and 1 for safety)

- Check ESS ?14
- Assess as investigator the Clinical Global Impression for Severity (CGI-S)

- **Blood sampling for haematological status unless done at Visit 0** (see Appendix L)
  - Haematology and biochemistry
  - Serology: Hepatitis A antibody IgM, Hepatitis B surface antigen, Hepatitis C virus antibody, HIV antibodies
- **Urine sampling** at study site (see Appendix L)
  - Urinalysis (dipstick for pH, ketones, protein, glucose, blood, leukocytes, urobilinogen, bilirubin)
  - Street drug screen in urine (amphetamine/metamphetamine, benzodiazepines, cannabinoids, cocaine, and opiates)
  - Pregnancy test for female patients of child-bearing potential

- Record 12-lead site safety electrocardiogram
- Measure sitting vital sign and perform abbreviated physical examination

- **Provide to patient before his departure:**
  - Appointment for Visit 2
  - Patient diary and instructions for filling and for bringing back to next visit
  - Drug for stabilisation period (modafinil) and instructions
  - Instruction to bring back all drug supplies (intact, partly used, empty)

7.2.2 General Recommendations and Procedures

The BDI questionnaire for assessing depression and suicidal risk is a key safety parameter and will be evaluated at each visit. Patients presenting severe depression (BDI ? 21) and/or suicidal risk (item > 0) at Visit 0 or Visit 1 may not be included in the study. If at a subsequent visit a patient develops severe depression (BDI ? 21 with/or without suicidal risk >0), the patient must be immediately withdrawn from the study. If the BDI score increases during the study while remaining <21 and without any suicide risk, the patient will be maintained on antidepressants without changing the dose if perceived as feasible. It is left at the investigator judgment to decide continuing or withdrawing the patient from the study at this visit or at a later stage.

Special attention will be paid during the study to safety ECG performed at end of Period I, II, and III to rule out impact of flecainide treatment on conduction such as QRS prolongation (if ?25% vs. baseline, *ie.,* at Visit V2). A patient achieving such a threshold during the crossover periods will be excluded from the study.

If treatment with THN102 reveals a suspicion of a Brugada syndrome (ST segment elevation), the patient will also be excluded from the study.

The subjects will avoid taking any non-trial medication, including over-the-counter drugs throughout the study, unless specifically prescribed by the investigator or by a physician for an intercurrent illness. All concomitant drugs taken during the trial must be recorded in the CRF with name, dose, route, dates and reason. Drugs known to be relevant CYP450 inducers for modafinil and flecainide will be avoided if possible or at least maintained at same dose (see SmPC).

Visit day for Visit V2 (baseline), V3, V4, and V5 should be on target if possible (D29, D43, D57) with flexibility ±1day if necessary (or exceptionally 2 days), aiming at keeping 14 days between periods as much as possible. Other visits may have a ±2-day flexibility.

Diet recommendations can be found under Section 5.2.4.

Morning treatment can be taken between 07:00 and 08:00 and early afternoon treatment between 13:00 and 14:00, but keeping the pattern stable over the 8 week study (stabilisation, Period I, Period II, Period III) for a given patient and a 5 to 6h interval between morning and early afternoon doses. It is speculated that majority of patients will take drug around 7:00 before breakfast and around 13:00 before lunch.

In the event a visit is prolonged or if an additional visit at study site or at hospital is scheduled between Day 16 and Day 59 (Period I to 48 hours after end of Period III) for whatever reason, an additional plasma sample will be collected and precise time of last drug intake will be recorded.

Details for treatment distribution, storage and control are provided in Section 5.3 and Section

5.4. **7.2.3 Visit 2 (End of Stabilisation Period and Baseline)**

The following examinations and tests will be carried out in each patient, at completion of the 2 week stabilisation period with 300 mg modafinil:

- Collect patient diary for stabilisation period and assess readability and consistency
- Collect AE and concomitant drug information
- Ask patient to provide information on diet recommendations over past 2 weeks
- Request patient to fill out 6 questionnaires (5 for efficacy and 1 for safety)
- Check if ESS ≥14
- Assess as investigator the Clinical Global Impression for Severity (CGI-S)
- **Visit 2 data represent Baseline data**

- **Blood sampling** (see Appendix L)
  - Haematology and Abbreviated biochemistry
  - PK sample

- **Urine sampling (fresh)** at study site (see Appendix L)
  - Urinalysis
  - Street drug screen
  - Pregnancy test for female patients of child-bearing potential
- Record 12-lead site safety electrocardiogram
- Measure sitting vital signs and perform abbreviated physical examination
- **Decide if the patient may enter the double-blind part of the study (ESS, ECG)**
- **Provide to patient before his departure:**
  - Appointment for Visit 3
  - Patient diary and instructions for filling and for bring back to next visit
  - Drug for stabilisation period for both drugs and instructions
  - Instruction to bring back all drug supplies (intact, partly used, empty)

7.2.4 Double-blind periods with Visit 3, Visit 4, Visit 5

The following examinations and tests will be carried out in each patient at the completion of each period (I, II, and III) for Visit 3, 4, and 5, respectively:

- Collect patient diary from previous period and assess readability and consistency. Make sure all information is clear
- Collect drug supplies and check compliance
- Collect AE and concomitant drug information
- Ask patient to provide information on diet recommendations over past 2 weeks
- Request patient to fill out 7 questionnaires for visit (6 for efficacy and 1 for safety)
- Assess as investigator the Clinical Global Impression for Severity (CGI-S)
- Assess as investigator the CGI-C, vs. baseline (Visit 2)

- **Blood sampling** (see Appendix L)
  - Haematology and Abbreviated biochemistry
  - PK sample

- **Urine sampling (fresh)** at study site (see Appendix L)
  - Urinalysis
  - Street drug screen
  - Pregnancy test for female patients of child-bearing potential

- Record 12-lead site **safety electrocardiogram** and check vs. ECG at baseline
- Measure sitting vital signs and perform abbreviated physical examination

- **Provide to patient before his departure for his next visit:**
  - Appointment for next Visit
  - Patient diary and instructions for filling and for bringing back to next visit
  - Drug for stabilisation period and instructions (for site 1 over PUI)
  - Instruction to bring back all drug supplies (intact, partly used, empty)

7.2.5 End-of-Study visit (Visit 6)

On last day of the washout, a complete physical examination, safety ECG and safety profile (haematology, biochemistry, urinalysis) will take place and the patient will be discharged after this visit. This visit is considered as the End-of-Study visit.

In case of early termination the patient should be submitted to the examinations planned for Visit 6 on the visit day when it is decided to drop him from the study or the patient will be encouraged to report to the unit to have the investigations planned for that day (laboratory safety with haematology, chemistry, urinalysis) as well as a complete physical examination scheduled for end of study.

- Collect patient diary from previous period and assess readability and consistency. Make sure all information is clear
- Collect drug supplies and check compliance

- Collect AE and concomitant drug information
- Ask patient to provide information on diet recommendations over past 2 weeks
- Request patient to fill out 7 questionnaires for visit (6 for efficacy and 1 for safety)
- Assess as investigator the Clinical Global Impression for Severity (CGI-S)
- Assess as investigator the CGI-C, vs. baseline (Visit 2)

- **Blood sampling** (see Appendix L)
  - Complete haematology and biochemistry

- **Urine sampling (fresh)** at study site (see Appendix L)
  - Urinalysis
  - Street drug screen
  - Pregnancy test for female patients of child-bearing potential

- Record 12-lead site safety electrocardiogram
- Measure sitting vital signs and perform complete physical examination
- Discharge patient from study.

7.3 Methods of Evaluation

7.3.1 Pharmacokinetics

Modafinil and flecainide concentrations in plasma will be measured by XXX Europe (Saint-Benoît, France) using a validated LC-MS/MS method (low range validated in 2Q 2015). Assays will be performed under non-blinded conditions (only active periods). The individual subject code will not be disclosed to other parties and results will be distributed according to Period and not to treatment until the database has been frozen.

Details on collection times and procedures are provided in Table on page 40, in Appendix J, and in the following Section 7.3.2 to 7.3.3.

7.3.2 SOP and CRF

SOP

Standard operating procedures (SOPs) are available for all activities relevant to study monitoring and to process at study sites.

The clinical laboratories performing serology, haematology and biochemistry participate in quality assurance tests and fulfil the requirements of the quality assurance guidelines.

CRF and Database

A paper CRF master copy will be developed by XXX with support of study manager. Questionnaires filled by patient will be prepared by Theranexus, and adapted to site, period and patient to facilitate data collection and at later date transfer of key data into CRF by investigator or dedicated clinical staff. The questionnaires will be considered as source documents and filed in the ISF.

Clinical study data will be recorded for each subject, reviewed and later entered on CRF. The large majority of the questionnaires (5 or 6 for efficacy and 1 for safety) will be entered directly

by the patient at each site visit. The investigator or delegate must maintain adequate and precise source documents (lab safety, ECG, physical examination etc.), also including the questionnaires filled by patient and the CGI filled by investigator. The study data will be entered onto the CRF by dedicated site personnel. The XXX monitors responsible for source documents verification on behalf of the sponsor will generate queries and discuss them with investigator, local staff and study manager. Queries will be generated and submitted by XXX for resolution after double data entry. Additional data checks will be programmed to identify errors in the SAS dataset.

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 Data Management Plan (DMP) and in the pertinent SAPs.

7.3.4 Safety measurements

Pre-study examinations

Within 30 days prior to the study, subjects will undergo screening in order to verify inclusion criteria and rule out exclusion criteria.

Medical History

In a brief interview, medical and social histories including concomitant medication will be evaluated by a physician in order to determine whether the subject fulfils the inclusion criteria and meets none of the exclusion criteria.

Clinical Examination

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

Laboratory Testing (see Appendix L)

The laboratory tests described in Appendix L will be performed by the certified laboratory of each hospital for serology (screening only), haematology and biochemistry for all visits (selected parameters for biochemistry for V3, V4, and V5). Urine analysis, urine street drug and pregnancy test if needed will be performed by study site staff at each visit.

Reference ranges of the clinical laboratory will be provided by the 3 Central Laboratories prior to study screening for filing in respective ISF and TMF, for males and females. It is recommended to agree on a common laboratory normal range for haematology and biochemistry parameters which will be placed in the relevant CRF to be used as study references for all sites and patients (site 1). If consistent with other pathology diagnosed and if in agreement with inclusion/exclusion criteria some laboratory parameters may actually be outside normal range at study start. During the study the laboratory parameters which turn out to shift outside normal range or to deteriorate further will be rated by the investigator as clinically relevant or as not clinically relevant based on change from earlier findings, baseline, actual value measured, and clinical judgment.

Haematology and clinical chemistry will be carried out according to standard operating procedures of each Central Laboratory. Abnormal results will be verified to rule out laboratory error. Persistent relevant abnormal values must be followed up until the cause is determined or

until they return to the premedication value. Any abnormality detected post drug intake should be followed up until resolution or stabilisation.

All data printouts received daily by Fax or on paper from Hospital Central Laboratory to enable patient monitoring during study will be filed as source documents. Each printout will be signed and dated by investigator or his delegate. The laboratory data will be entered into the CRF.

Vital signs

Vitals signs (systolic, diastolic, heart rate) will be measured after 10 minutes sitting position at each visit.

Site safety 12-lead ECG

At each visit twelve-lead ECG will be recorded at a speed of 25mm/sec and calibrated at 1 cm/mV after 10 minutes in supine position. Automated analysis will be performed and all parameters will be recorded in the CRF, including heart rate and QT. If a QTc is prolonged (>450ms) or if markedly increased over baseline (>30msec), manual checking of QT and calculation of QTcf with Fridericia's formula will be performed for both pre-drug and post drug ECGs recorded on that day for safety purposes. Safety ECG will be recorded on 6 occasions (screening for V1, V2 to V5).

The investigator will provide:

- ECG measured parameters as Intervals (PR, QRS, QT)
- Check pattern of change for PR, QRS and QT vs. ECG from baseline (see Section 7.1.1)
- ECG derived ECG parameters (QTc corrected by Bazett's formula, heart rate)

Adverse events

Adverse events spontaneously reported by subjects or observed by the investigator will be assessed and recorded as described under Section 8.2.

Adverse events (AE) will be described in the CRF by event, time of onset, duration, and intensity, and their relationship to the test drug will be assessed. Outcome, therapy for treatment including route and dose if given, as well as additional follow-up procedures will be documented. If the subject drops out of the study as a consequence of an adverse event this must be recorded in the worksheet.

All adverse events, including intercurrent illnesses, must be reported and documented in the CRF. Definitions on adverse or serious adverse events are given under Section 8.2. and 8.3, respectively.

Beck's Depression Inventory (21-item BDI)

The BDI questionnaire for assessing depression and suicidal risk is a key safety document and will be evaluated at each visit**.** Patients presenting severe depression (BDI ≥ 21) and/or suicidal risk (BDI item > 0) at Visit 0 or Visit 1 may not be included in the study or must be excluded from the study if occurring during the trial.

Safety review

The safety parameters generated at each visit will be based on the profile of adverse events since last visit, daily patient sleep diary from previous 2 weeks, BDI 16-item score, questionnaires filled during visit vital signs, ECG, abbreviated physical examination and laboratory tests performed at each visit.

7.3.5 Special

Patients discovering a skin rash of any type during the study should call the investigator for medical advice.

7.3.6 Blood collection

A summary of collection schedule for blood for PK (plasma) and safety as well as number of samples and volume of blood by subject has been provided in table in Section 7.3.7 on page 40. The grand volume calculated for the complete study adds up to 120 mL of blood when including 30mL in reserve in case of need for additional laboratory tests and/or PK samples. Additional plasma samples for PK may occur for non-scheduled visit to study site during Period I, II, III or within 48 h after completion of Period III at any time post drug or for any reason. The maximum blood volume declared in the information document for 9 weeks is thus 120 mL.

7.3.7 Blood, Plasma Sample Table

Sampling Visit	Plasma PK	Reserve	Serology	Biochemistry	Haematology
Tubes Blood volume	**Li Hep Sarstedt 5 mL**		**5 ml**	**5 mL**	**5 mL**
Screening Start Stabilisation, V1	X		X	X	X
End Stabilisation, V2	X			X	X
End Period I, V3	X			X°	X
End Period II, V4	X			X°	X
End Period III, V5	X			X°	X
Washout period, V6				X	X
Reserve (lab, PK)		30 mL			
Grand total blood permissible: 120 mL	25 mL	30 mL	5 mL	30 mL	30 mL

°: On visit V3, V4, and V5: only abbreviated biochemistry parameters (ALT, SPT, AP, LDH, creatinine, urea)

8. ASSESSMENT OF SAFETY

Comprehensive assessments of any apparent toxicity experienced by the subject will be performed throughout the course of the study from the time of subject's signature of the informed consent. Investigator (or the site staff) will report any adverse event (AE), whether observed by the investigator or reported by the subject.

The safety profile of treatments will be assessed throughout the study by reviewing adverse events, physical examination, sitting vital signs, 12-lead ECG for immediate safety management, and laboratory tests.

The AEs for flecainide acetate and for modafinil are listed by System Organ Class and by frequency (common 1 to 10%; uncommon 1% to 0.1%; rare 0.1 to 0.001%) in their respective SmPC which are both attached to the THN102 Investigator Brochure. It should be stressed that the majority of these adverse events have been reported under chronic therapy, at much higher doses for flecainide (approximately 10-fold), and occur frequently in patients under polytherapy.

In the following sections on Adverse Event (8.1, 8.2 and 8.3) IMP (Investigational Medicinal Product) means modafinil, modafinil + flecainide (THN102), and placebo.

8.1 Adverse Event (AE)

Definition of an adverse event

An adverse event is defined as any untoward medical occurrence that emerges or worsens in a subject relative to her/his baseline conditions (i.e. present at screening visit), during her/his participation to the clinical study.

An AE is reported regardless of causal relationship with IMP and even if no IMP has been administered. An AE can therefore be any unfavorable and unintended sign, abnormal laboratory finding, symptom, or disease temporally associated with the use of IMP, whether or not related to the IMP.

AE may consequently include suspected adverse drug reactions and this covers the large majority of the reported events.

However AE may also include other events:

- Other medical experiences regardless of their relationship with the IMP, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated diseases, significant abnormalities in clinical laboratory values, psychological testing or physical examination findings,
- Reactions from IMP overdose, abuse, withdrawal, sensitivity, toxicity or failure of the IMP's expected pharmacological action.

Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the IMP, are not considered as AEs. Thus they should not be recorded on the AE page of the CRF unless the event is considered possibly or probably related to the IMP (i.e. worsening is not consistent with the anticipated natural progression of the disease).

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

When reporting an abnormal laboratory results on the AE pages of the CRF, 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.

Severity assessment

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

- **Mild**: The AE requires minimal or no treatment. The AE does not interfere with the subject’s daily activities.
- **Moderate**: The AE results in a low level of inconvenience or concerns with the therapeutic measures. The AE may cause some interference with functioning or reduction with the usual level of activity of the subject.
- **Severe**: The AE may require systemic drug therapy or other treatment. The AE causes a significant impairment of functioning, interrupts a subject’s usual daily activity and is usually incapacitating.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AE characterised as intermittent require documentation of the onset and duration of each episode.

Relationship assessment

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

- **Probably:** A causal relationship is clinically/biologically highly plausible. The onset of the event occurs within a plausible time sequence to administration of the IMP. There is a reasonable response on withdrawal. That is unlikely to be attributed to concurrent disease or other drugs or chemicals.
- **Possibly:** A causal relationship is clinically/biologically plausible. The onset of the event occurs within a reasonable time sequence to administration of the IMP. However, the influence of other factors may have contributed to the event (e.g., the subject’s clinical condition, other concomitant events).
- **Unlikely:** A causal and temporal relationship is clinically/biologically improbable. Another documented cause of the AE is most plausible (e.g., the subject’s clinical condition, underlying disease, and other concomitant treatments).
- **Unrelated**: A causal relationship can be definitively excluded. The AE is completely independent of IMP administration. Another documented etiology of the AE is most plausible.

The relationship to IMP can be modified during the study 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.

Final reporting of relationship to study drug will be either unrelated or related (*i.e.* events with a probably, possibly and unlikely relationship to the IMP).

Procedures for reporting of adverse events

Assessing of adverse events

Data on AEs will be obtained at scheduled or unscheduled study 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 CRF.

If a subject is seen by a physician not involved in the study 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 not meeting the criteria for "serious adverse events" should be captured on the appropriate pages of the CRF.

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 other causality factors, any action taken (concerning the IMP or other) and its outcome.

AEs must be followed until adequate resolution (fully resolved, return to baseline level, or stabilisation in time).

AEs must be recorded on the CRF 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.
- When an AE occurs secondary to other events (e.g. sequelae or complications), it should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record in the CRF.

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 CRF.

The reporting period is the period during which the AEs are collected on an ongoing basis from the day of the signed informed consent by the subject. All new AEs must be recorded until 1 week after the last IMP administration *ie.,* on last-study-day visit (Day 8 Period III). New protocol related AEs (caused by any intervention required by the protocol) and updates on all AEs ongoing

or with an unknown outcome must be recorded until the last subject visit required by the protocol. A last batch of queries will be sent after the last study visit if remaining ongoing/unknown outcomes of reported AEs are pending. After the last batch of queries with all collected data have been fully processed, CRFs and database will no longer be updated.

SAEs occurring after a subject has taken the last dose of study drug will be collected for 8 days after the last dose of study drug, 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 to a protocol procedure.

Within a study, all subjects who take IMP, whether they complete the treatment period or not, should enter the period as defined above.

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 worksheets and study documents until the date the subject is determined to be a screening failure. Beyond this date, only SAEs will be followed up by XXXXPharmacovigilance representative. No CRF will be prepared for screening failures or for subjects changing their mind about participation before Visit 1 (start of stabilisation).

8.2 Serious adverse event

Definition of a serious adverse event (SAE)

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 least 24-hour 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 study 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. the AE that may not be immediately result in death, life threatening, or requiring 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 XXX Pharmacovigilance delegate regardless its relationship to the IMP.

Definitions of Suspected Unexpected Serious Adverse Reactions (SUSAR)

Suspected Unexpected Serious Adverse reactions (SUSARs) are serious events that are not listed in the IB or SMPC and that the XXX Pharmacovigilance delegate, the investigator, the sponsor, and/or the study manager identify as related to IMP or study procedure.

Procedures for reporting of SAEs and SUSARs

All serious adverse events must be recorded on XXX Pharmacovigilance Serious Adverse Event report (SAE report), followed through resolution by the investigator.

The investigator must complete the SAE report and notify XXXX 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:

- All deaths and immediately life-threatening events, whether related or unrelated to IMP, will be communicated within 24 hours of site awareness
- Adverse events other than death and immediately life-threatening events, that meet expedited reporting criteria, regardless of relationship with IMP, will be communicated by the site within 24 hours of becoming aware of the event
- Other supporting documentation of the event may be requested by XXX Pharmacovigilance delegate and should be provided as soon as possible
- All reportable AEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the subject to be stable.

The electronic template should be preferably filled and it must be sent directly to XXX Pharmacovigilance delegate by electronic mail or facsimile as specified below:

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

- Identification of the investigator with full contact information,
- Subject identification details (subject number, subject initials, gender, age or year of birth, weight and height)
- 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

- The relationship of the event with the IMP or with the study 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 or stabilisation, even if CRFs and database will no longer be updated. SAEs occurring after a subject has taken the last dose of study drug will be collected for 8 days after the last dose of study drug, 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

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 SMPC for Modafinil and the SMPC for Flecainide Acetate attached as Appendix 7 of the THN102 Investigator Brochure (IB) Version 2 edited in May 2015 as reference) and that are associated with IMP to the regulatory/health authorities (RA/HAs) in expedited reporting. Unblinding will be performed as described in Section 5.3 by opening individual sealed envelope for involved subject and for involved period which were made available before study start.

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 study necessitate an expedited reporting to the RA/HAs as well.

RA/HAs 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 XXXX Pharmacovigilance delegate who will issue a complete report within 8 additional calendar days, with copy to investigator, monitor, study manager, and sponsor. All other serious adverse events and SUSARs must be filed in writing within 15 calendar days after first knowledge by XXX Pharmacovigilance delegate.

All serious adverse events designed as “not related” to IMP, will be reported to the RA/HAs in the Development Safety Update Report (DSUR) annually, if appropriate.

In accordance with the ICH GCP guidelines, XXX 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 study, or alter the ERC’s approval/favourable opinion to continue the study.

In particular, sponsor or designee will inform the investigators of serious adverse events and SUSARs that are considered to be possibly or probably related to the administered IMP. The investigators will keep copies of these safety reports in the Investigator Study 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 are duly documented, the investigator will promptly notify the concerned ERC of any safety reports provided by the XXX Pharmacovigilance delegate and provide copies of all related correspondence to monitor and to study manager. Only when specifically required by regulations and if requested, XXX Pharmacovigilance delegate will provide appropriate safety reports directly to the concerned ERC and maintain records of these notifications.

8.3 Pregnancy exposure

Women of childbearing potential (defined as not surgically sterile or 2 years postmenopausal), must use a medically accepted method of contraception, and must continue one method for the duration of the study (and for 2 months after participation in the study). Acceptable methods of contraception include: abstinence, barrier method with spermicide, steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method, or intrauterine device (IUD).

Women of child-bearing potential will be followed by a sensitive urinary pregnancy test (hCG, human chorionic gonadotrophin) at each visit (V1 to V6).

If a female patient were to become pregnant during the study, treatment would be interrupted and the pregnancy would be followed until delivery.

9. WITHDRAWALS OF SUBJECTS

Subjects will be informed that they have the right to withdraw from the study 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 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 study continuation after consideration of all available clinical elements presumed to impact on the subject's safety. The criteria which would require exclusion of a patient from study in the crossover over periods are listed in Section 7.2.2 (suicidal risk in BDI scale, QRS prolongation ≥25% vs. baseline, suspicion of a Brugada syndrome (ST segment elevation)). A patient would not be excluded at end of Period III since treatment with flecainide will be stopped for the washout-period.

In all cases, the reason for withdrawal must be recorded in the CRF 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 Section 8.3.

As far as possible, all examinations scheduled for the final study day (End-of-Study planned after washout period) must be performed on all patients who receive study medication but do not complete the study according to protocol (see Section 7.2). The investigator must make every effort to contact patients lost to follow-up.

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

10. EMERGENCY PROCEDURES

10.1 Emergency Contact

In case of emergency situations, the investigator should contact the study manager by telephone at the number listed on the title page of the protocol.

10.2 Emergency Identification of Study Medication

Since this study is blinded for Period I, II, and III, two sets of individual sealed randomisation envelopes with treatment code for 60 patients (individual sealed envelopes with scratch labels for disclosure of treatment) will be prepared by an independent statistician. One set will be delivered to the Primary Investigator at each site by Theranexus study manager during the Initiation Visit and at later dates as may be required by site recruitment and one full set to the XXX Pharmacovigilance delegate prior to study 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 a SAE for which knowledge of exact treatment may be useful for medical decision or for treatment. Such an event must be documented by Investigator by signing and dating the envelope (including precise time) and indicating with a short hand written note the reason for breaking the code. Efforts must be made to reach the study manager before undertaking this step if at all possible. All envelopes must be retrieved at study completion from study site by the monitor and inspected for integrity. All envelopes from investigator, intact or opened, will be filed in the TMF.

10.3 Emergency Treatment

During and following a subject's participation in the trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed to treat an undercurrent illness the investigator has become aware of.

11. STATISTICAL PROCEDURES

11.1 Analysis Variables

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

The database for this study will be maintained by XXX.

Pharmacokinetic variables:

The PK analysis will be carried out by the PK unit of PhinC Development.

As soon as they are available but only after database has been frozen, analytical determinations will be sent by e-mail (Microsoft Excel® 2003 file) by the bioanalytical center of XXX Europe to the PK unit of PhinC Development (with copy to Theranexus, study manager and XXX monitor).

After completion of the bioanalytical part of the study, a quality checked and validated paper copy of the bioanalytical results will be provided by the bioanalytical center of XXX Europe to the PK Unit of PhinC Development with copy to Theranexus, study manager and XXX monitor.

Subsequently, plasma concentrations will be processed for PK data generation. The PK parameters will be calculated, using the Phoenix® WinNonLin® (Pharsight Corporation) running on a PC. However information will be very limited.

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 LOQ 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 (N.R.) will be excluded from the PK analysis.

It is anticipated that plasma concentrations at steady state will be often available 2 to 4 hours after morning or 2 to 3 hours after early afternoon doses. Steady state (Css) should be reached in 2 to 3 days but will fluctuate between morning and afternoon samples as a consequence of the different dosing regimen but accumulation achieved for modafinil and for both flecainide doses after 14 days of treatment should be assessable. The other classical PK parameters of modafinil and flecainide cannot be estimated directly with few exceptions with this limited sampling:

C_{max} The observed maximum concentration of modafinil or flecainide in plasma measured in a subject after dosing identified by inspection of the plasma drug concentration versus time data by WinNonlin. Not assessed in this study. Only approximation

C_{min} The minimum concentration of modafinil or flecainide in plasma measured before morning or early afternoon dose and identified by inspection of the plasma drug concentration versus time data by WinNonlin. Not assessed in this study unless some additional plasma samples can be collected just before early afternoon dose

Css The observed accumulation of modafinil or flecainide at steady state. Can be estimated in this study as a range within the limitation of the time window for each visit

t_{max} The time at which C_{max} was apparent, identified by inspection of the plasma drug concentration versus time data by WinNonlin. Not assessed in this study

$t_{1/2}$ The terminal plasma half-life. It might be possible to estimate it with a PopPK approach. If a few additional samples are collected between Day 56 and 58 it could improve this approximation

AUC_{0-t} The area under the concentration-time curve from time zero (pre-dose) to the time of last quantifiable concentration is estimated, using a linear trapezoidal method for all the doses. Not assessed in this study

More information might be gained in a few patients who may come to study site or to hospital for non-scheduled visits and who accept to have an additional plasma sample collected and to provide the precise date and time of their last drug intake. Visits can take place for any reasons and at any time but permission for taking blood for bioanalytical proposes must be described in the patient information.

11.2 Study Populations

- The Safety analysis Set (SS) set will include all patients who have received study drug at least once.
- The Intent-To-Treat (ITT) set includes all patients who received treatment for at least one study period and who present no major protocol deviations for relevant parameters measured. The efficacy analyses will be conducted on ITT set.
- The Per Protocol (PP) set includes all patients who have completed the study without major protocol deviation. The primary endpoint ESS will be analysed with the PP set to demonstrate robustness of the primary analysis. If deviating at least by more than 4 patients from the ITT set, the other key secondary endpoints might also be analysed on the PP set.
- The PK analysis set will include all subjects who have received treatment as per protocol (even if study not completed) and who present no major protocol deviations with an impact on PK.

More details will be provided in the SAP.

11.3 Statistical Methods

Details of the planned analyses will be described in the SAP and 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.
- Data will be summarized according to the treatment as randomised.

- 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.

Efficacy

Endpoint for Primary Endpoint ESS

The primary efficacy parameter being the ESS total score at each key visit (end Period I, end Period II, end Period III) will be analysed in the ITT set with a mixed-effect analysis of variance model suited to the cross-over design. The model will include the treatment, period and sequence 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 the THN102 high dose (Modafinil 300mg/27mg) and modafinil alone will be assessed with a contrast t-test at the two-sided 5% level. The THN102 low-dose treatment (Modafinil 300mg/3mg) will be analysed in a similar fashion.

This is a pilot phase IIa trial exploring 2 dose levels of THN102 versus modafinil alone. As the trial is originally intended to remain exploratory, each comparison will be made at the 2-sided 5% level, without adjustment for multiplicity.

Should the trial be considered as a confirmatory study for regulatory purposes, each of the two THN102 dose comparisons to modafinil on the primary endpoint will be assessed at the two-sided 2.5% level of significance, so that the overall type I error rate remains below 5% (Bonferroni correction).

Handling of missing values/censoring/discontinuations

Subjects who change their planned treatments or doses or have missing outcome measurements will not be excluded from the primary analysis in the ITT set unless considered as major violations. Major and minor violations will be defined in the SAP. 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. So missing data will not be imputed or replaced prior to the analysis.

Supportive analysis

The same analysis will be repeated in the PP set, to assess robustness of the primary analysis (ESS) and possibly on key secondary results.

Subgroup analyses may be performed to investigate the effect of the main demographics (age, gender,...) and disease (narcolepsy type, ...) characteristics on the efficacy outcomes.

Secondary efficacy analyses

The continuous secondary efficacy parameters, including the modified ESS for daily pattern at each day separately, the PGI score, the CGI-S and CGI-C scores for sleepiness and cataplexy, the EQ-5D VAS, the 14-item fatigue score, and the derived endpoints from the patient diaries will be analysed in the ITT set using the same method as for the primary endpoint.

For categorical data, including the Good Response on ESS and the ESS absence of residual somnolence as rates of responders will be compared in the ITT set between the each THN102 dose group and modafinil alone using a Mc-Nemar test at the 2-sided 5% level. The EQ-5D categorical responses will be similarly compared using the Wilcoxon signed-rank test for paired ordinal data.

Endpoints for Safety Parameters

Safety parameters as per list under Section 2.2 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. Summary statistics will be provided by treatment and visit/time. It will be decided later

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 QTc change and distribution vs. baseline.

BDI
BDI score data will be listed by treatment, subject, and visit/time. Summary statistics 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.

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 Treatment 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, including all concomitant therapies leading to dose reduction, will be coded by WHO version and listed by treatment group and subject.

Pharmacokinetics

Plasma concentrations reached at steady state will be presented for modafinil and for flecainide for each visit (V1 to V5), considering time after last drug intake.

Concentration-time data will be listed per treatment and subject for modafinil and for flecainide. Plasma concentrations and time post drug intake will also be plotted to assess range of exposure at steady state for each treatment (*i.e.*, post morning and post early afternoon dose) and to assess reliability of prediction made by extrapolation from Phase I studies for flecainide. This may also

in the future help constitute background information for Population PK (PopPK) and for PK/PD correlations.

SAP
Details will be provided in the relevant SAP.

11.4 Interim Analysis

No formal interim analysis is planned.

In case of an unplanned interim analysis, a Data Monitoring Committee (DMC) will be established to control the propagation of results. Blinded data may be reviewed during the course of the study for safety or other purposes.

11.5 Sample Size Justification

It was recommended to size the present study considering a mean difference not greater than 3, since the magnitude of the effect seen will probably not be as large as the effect of modafinil versus placebo. If we assume a difference in ESS between THN102 and modafinil between 2 to 2.5 we would need between 140 and 200 patients with a parallel design, numbers too large for a Phase IIa trial. The sample size required for a cross-over design is approximately one third of the size required in a parallel study. The cross-over option is a viable alternative design, since sample size remains below 60 patients in this condition.

The same assumptions as Dauvilliers et al. in their study with pitolisant, modafinil and placebo (Lancet Neurol. 2013) were applied for power evaluation, for mean difference in ESS, namely, a SD of the change equal to 5, a within-subject coefficient of correlation of 0.65 (i.e., the within subject SD = 3.8), a 80% power for a 2-sided comparison at the 5% significance level. The mean difference between modafinil vs. placebo was 3 in the Lancet study and we chose to decrease it to 2.4, as the magnitude of the effect is expected to be lower when comparing THN102 to modafinil. The patient population recruited was a combination of type 1 and type 2 narcoleptics.

Forty-eight (48) patients will be enrolled in this 3-site study to ensure that at least 42 subjects are evaluable for the primary analysis. With this sample size (42), the study will have at least 80% power to detect a mean difference in ESS between either modafinil + flecainide (THN102) dose and modafinil alone at the two-sided 5% level of significance. This sample size assumes a mean difference of 2.4, and an intra-subject standard deviation of 3.8. With this approach it is also expected that the drop-out rate would not be larger than 12.5%. If more than 6 patients were to drop-out during the trial however, up to 6 additional narcoleptics may be enrolled at the discretion of the investigators and sponsor. No more than 54 patients may be entered into the study trial.

12. ETHICAL AND LEGAL ASPECTS

12.1 Good Clinical Practice

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that investigator, XXX pharmacovigilance delegate, XXX monitor and study manager all abide by the principles of the good clinical practice (GCP), ICH guidelines and national regulations as well as the ethical principles laid down in the current revision of the Declaration of Helsinki.

12.2 Delegation of Investigator Responsibilities

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

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

Training schedules will be provided on request.

12.3 Subject Information and Informed Consent

Before being admitted to the clinical study, the subject must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a form understandable to him. An informed consent document that includes both information about the study and the consent form will be prepared and given to the subject. This document will contain all elements required by local law and Sponsor's requirements. The document must be in a language understandable to the subject and must specify who informed the subject. The investigator is ultimately responsible for ensuring the EC-approved informed consent is appropriately signed and dated by each subject prior to the performance of any study procedures.

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 not competent legally to enter such a Phase II study under the coverage of the subject's legally authorised representative[1].

A copy of the signed consent document must be given to the subject or the subject's legally authorized representative.

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

12.4 Confidentiality

Only the subject number and birthdate will be recorded in the CRF and transfer documents (no initials), and if the subject name appears on any other document (e.g., ECG, laboratory report,

1 *"Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.*

pathologist report), it must be obliterated before a copy of the document is supplied to Data Management. Study findings stored on a computer will be filed in accordance with the applicable law concerning computerised data. The subjects will be told that Principal Investigator and his staff, XXX staff, study manager, ERC, regulatory authorities, and representative of 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 local data protection laws.

Biological samples collected during the study will be used for assays specifically described in the protocol and assayed in France. The samples will be destroyed after approval of CSR upon written request by study manager.

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

12.5 Protocol Amendments

No signee of this protocol (Principal Investigator, sponsor, or study manager) will alter this study protocol without obtaining the written agreement of the other parties. Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol and request a Protocol Amendment.

12.6 Approval of the Study Protocol and Amendments

Before the start of the study, the sponsor will submit to the ERC the English study protocol, , the informed consent document as informed consent and subject's information with date), a Certificate for insurance coverage, the CV of the three Principal Investigators and of their key co-investigators, pertinent Regulatory Documents as well as the Investigator Brochure for THN102 with a cover letter and a list of documents submitted and their precise dates of issue. CRF may also be submitted if applicable.

The sponsor and the study manager will notify ANSM with the appropriate documentation, including a submission form, protocol, Investigator Brochure, SmPC for both products, the letter of submission to the ERC (with update of correspondence and update at later stage). The study will not start until authorisation by ANSM and by ERC have been received in writing and until the administrative requirements and workload (grid costs) have been discussed with the hospital administrations and the agreements signed.

Study medication can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the study has been received by study monitor. This documentation must also include a list of the members of the ERC and their occupation and qualifications. The opinion given by the ERC should specify the study title, study code, study 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 study, all ethical and legal requirements must be met.

The ERC and, if applicable, the authorities must be informed of all subsequent protocol amendments, in accordance with country 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 ERC. This also applies to any communication between the investigator and the Authorities.

12.7 Ongoing Information for the Ethical Review Committee

The investigator must submit to the ERC (Ethical Review Committee):

- Information on serious adverse events (SAE). However suspected unexpected adverse event reactions (SUSAR) if any will be declared by XXX Pharmacovigilance delegate.
- Periodic reports on the progress of the study if it is specifically requested in the initial reply by the ERC.

12.8 Premature Closure of the Study

The Coordinating Investigator and the sponsor (Theranexus) have the right to close this study 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 3 study sites. The ERC and the local Agency (ANSM) must be promptly informed.

Should the study be closed prematurely, all study materials (completed, partially completed, study medication, etc.) must be returned to Theranexus or be destroyed locally, as if the study had been completed.

12.9 Archiving and Record Retention

The following records must be retained by the Principal Investigator as Investigator Study File (ISF) for a **minimum of 15 years** after the completion or termination of the study:

- Signed informed consent documents for all subjects
- Subject identification code list, screening log (if applicable), and enrolment log
- Record of all communications between the investigator and the ERC
- Composition of the ERC
- Record of all 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 study 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.

12.10 Liability and Insurance

In accordance with GCP and ICH guidelines, 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 following information will be included in the information for the patient as requested by the Insurance Company:

> "The following adverse events have been frequently observed after modafinil use: headache, dizziness and somnolence, paraesthesia (corresponding to skin tingling or formication), appetite decrease, nausea, nervousness, insomnia, depression, confusion, blurred vision, palpitations, abdominal pain, nausea, dry mouth, diarrhoea or constipation, chest pain and asthenia (corresponding to physical fatigue).
>
> The following adverse events have been frequently observed after flecainide use**:** headache, asthenia, nausea, gastric upset, dizziness and blurred vision.
>
> In addition, like with any other drug, an allergic reaction represents a potential risk and may occur."

13. STUDY MONITORING AND AUDITING

13.1 Study Monitoring

The investigator is responsible for the validity of all data collected at the site. The sponsor is responsible for monitoring these data to verify that the rights and wellbeing of subjects are protected, study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and regulatory requirements. Before the study initiation visit, the sponsor-assigned study monitor will write a monitoring plan indicating the monitoring procedures and at which occasions during the study monitoring visits will be performed. Periodic visits will be made to the study site throughout the study at mutually agreeable times. Any appropriate communication tools will be set up to ensure the sponsor and/or its representative is/are available for consultation, so they can stay in contact with the study site personnel. Adequate time and space for monitoring visits should be made available by the investigator.

The investigator will allow direct access to all relevant files (for all subjects) and clinical study supplies (dispensing and storage areas), for the purpose of verifying entries made in the CRF, and assist with the monitor's activities, if requested.

After trial completion, used and unused study test drug will be verified, reconciled with CRF and log forms. Intact and used clinical supplies will be returned to CRO involved with clinical packaging after reconciliation of clinical supplies by monitor and after written instruction by the study manager.

13.2 Source Data Verification and On-Site Audits

The local ERC, and/or a clinical quality assurance group delegated by the sponsor (Theranexus), or the National Agency acting on its own or at specific request of EMA or FDA (Food and Drug Administration) may request access to all source documents, CRF, and other study 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.

14. DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 Documentation of Study Findings

A case report form (CRF) will be prepared by XXX team and will be reviewed by the sponsor's representative for adequacy and completeness. Details on monitoring process by XXX monitor will be included in the Monitoring Plan.

The plasma concentrations data will be transmitted by XXX Europe to Data Management for inclusion into the study database. The format and the details however will be provided in the analytical protocol to be prepared by XXX and in the SAP.

The investigator, or designated representative, should complete the worksheet pages or source documents immediately after information is collected, when a study subject is seen for an examination, treatment, or any other study 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, updated during each study period, and all versions will be filed in both the Trial Master File (TMF) and the Investigator Study File (ISF).

A Data Management Plan will be prepared by XXX before study start and circulated to the clinical team for review and comments.

The completed CRF as well as appropriate tables and calculated data must be reviewed and signed by the investigator named in the study protocol or by a designated sub-investigator prior to transmission to statistician for data entry.

14.2 Use of Study 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 study and for no other purpose unless prior written permission from Theranexus is obtained.

By signing the study protocol, the Principal Investigator agrees that the results of the study 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 Study File (ISF). The authorities will be notified of the investigator's name, address, qualifications, and extent of his involvement. The Trial Master File (TMF) will be maintained by XXX's monitor and transferred to sponsor after study completion.

The study manager will be responsible for preparing the CSR. The primary investigator will be required to sign a statement that he has read the report and that he confirms that, to the best of his knowledge, it accurately describes the conduct and results of the study.

Theranexus shall have the right to present and to publish the scientific findings from this Phase I trial within reasonable time after termination of the study and availability of the CSR, providing appropriate circulation of the manuscript among involved partners at least 60 days in advance. Co-authorship will reflect scientific involvement in study design, study 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.

15. AGREEMENT - SIGNATURE PAGE

Protocol Title

SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS

Protocol version 6.0 dated on 11 May 2018

By signing below, I hereby confirm that I have read, discussed and understood the above-mentioned version of the protocol and the background information concerning the study drug.

I attest that I will carry out the study according to this protocol.

I also agree that the work will be performed according to Good Clinical Practice (GCP) guidelines, the ethical principles, as referenced in Section 13, and all currently applicable laws and regulations of the country(ies) where the study will be conducted.

Date: _____

Medical Director's signature
Theranexus SA
Dr Werner Rein

Date: _____

Coordinating Investigator's signature
Pr. Yves Dauvilliers

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17. APPENDIX

17.1 Appendix A - Diagnostic Criteria for Patients with Narcolepsy Type 1 and Type 2

To be diagnosed as a patient type 1 the following Criteria A and B must be met:

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. The presence of one or both of the following:

16. Cataplexy and a mean sleep latency of ≤8 minutes and two or more SOREMPS on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.

17. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.

To be diagnosed as a narcoleptic patient type 2 the Criteria A through E must be met:

C. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

D. A mean sleep latency of mean sleep latency of ≤8 minutes and two or more SOREMPS on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal PSG may replace one of the SOREMPs on the MSLT.

E. Cataplexy is absent.

F. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.*

G. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

*: If the CSF hypocretin-1 concentration is tested at a later stage and found to be either ≤110pg/mL or <1/3 of mean values obtained in normal subjects with the same assay, then the disorder must be reclassified as narcolepsy type 1.

Source: International Classification of Sleep Disorders, 3rd ed, American Academy of Sleep Medicine, Darien, IL 2014, American Academy of Sleep Medicine

Abbreviations:
ICSD-3: International Classification of Sleep Disorders, 3rd ed, 2014
CSF: Cerebrospinal Fluid
MSLT: Multiple sleep latency test
PSG: Polysomnography
SOREMPs: Sleep-onset rapid eye movement periods

17.2 Appendix B - Epworth Sleepiness Scale (ESS)

- **How likely are you to doze off or to fall asleep in the following situations, in contrast to feeling just tired?**
- **This refers to your usual way of life in recent time (last week).**
- **Even if you have not done some of these things recently, try to work out how they would have affected you.**

Use the following scale to choose the most appropriate number of each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situations	**Chance of dozing (0-3)**
Sitting and reading	
Watching television	
Sitting inactive in a public place (*e.g. a theatre or meeting...*)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car while stopped for a few minutes in the traffic	
Total score	

To be captured in CRF as per table above

17.3 Appendix C - Modified ESS for Daily Pattern

- **How likely are you to doze off or to fall asleep in the following situations, in contrast to feeling just tired? Circle the figure corresponding**
- **This refers to your usual way of life in recent time (last week).**
- **Even if you have not done some of these things recently, try to work out how they would have affected you.**

Use the following scale to choose by circling the most appropriate number of each situation: 0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situations	Risk dozing off 7H to Noon				Risk dozing off Noon to 17H				Risk dozing off 17h to 22H			
Sitting and reading	0	1	2	3	0	1	2	3	0	1	2	3
Watching television	0	1	2	3	0	1	2	3	0	1	2	3
Sitting inactive in a public place (*e.g. a **theatre or meeting...***)	0	1	2	3	0	1	2	3	0	1	2	3
As a passenger in a car for an hour without a break	0	1	2	3	0	1	2	3	0	1	2	3
Lying down to rest in the afternoon when circumstances permit	0	1	2	3	0	1	2	3	0	1	2	3
Sitting and talking to someone	0	1	2	3	0	1	2	3	0	1	2	3
Sitting quietly after a meal without alcohol	0	1	2	3	0	1	2	3	0	1	2	3
In a car while stopped for a few minutes in the traffic	0	1	2	3	0	1	2	3	0	1	2	3
On the road when driving	0	1	2	3	0	1	2	3	0	1	2	3
Sitting for a meal and eating	0	1	2	3	0	1	2	3	0	1	2	3
When working	0	1	2	3	0	1	2	3	0	1	2	3
When performing a routine activity (*cleaning, gardening...*)	0	1	2	3	0	1	2	3	0	1	2	3

To be captured in CRF as per table below:

Daily Pattern	07:00 à 22:00 (out of 108)	07:00 à midi (out of 36)	Midi à 17:00 (out of 36)	17:00 à 22:00 (out of 36)
Score				

17.4 Appendix D - Fatigue Scale (14-points)

Please tick off all questions below for the past week and including today:

Physical symptoms	***Yes***	***No***
1. Do you have problems with tiredness?	❑	❑
2. Do you need to rest more?	❑	❑
3. Do you feel sleepy or drowsy?	❑	❑
4. Do you have problems starting things?	❑	❑
5. Do you start things without difficulty but get weak as you go on?	❑	❑
6. Are you lacking in energy?	❑	❑
7. Do you have less strength in your muscles?	❑	❑
8. Do you feel weak?	❑	❑
Mental symptoms		
9. Do you have difficulty concentrating?	❑	❑
10. Do you have problems thinking clearly?	❑	❑
11. D you make slips of the tongue when speaking?	❑	❑
12. Do you find it more difficult to find the correct word?	❑	❑
13. How is your memory?	❑	❑
14. Have you lost interest in the things you used to do?	❑	❑

Filled by patient at each visit

To be captured in CRF as per table

Fatigue Symptoms	Yes
Physical fatigue symptoms	
Mental fatigue symptoms	
Grand total for fatigue symptoms	

17.5 Appendix E - European Quality of Life EQ-5D and VAS

Instructions
For each group, please indicate which statement best describes your own health state today. Please tick off only one statement for each group.

Mobility

- I have no problem in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-care

- I have no problems with self-care ☐
- I have some problems with washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual activities (eg. work, study, housework, family or leisure activities)

- I have no problems doing my usual activities ☐
- I have some problems doing my actual activities ☐
- I am unable to do my actual activities ☐

Pain / Discomfort

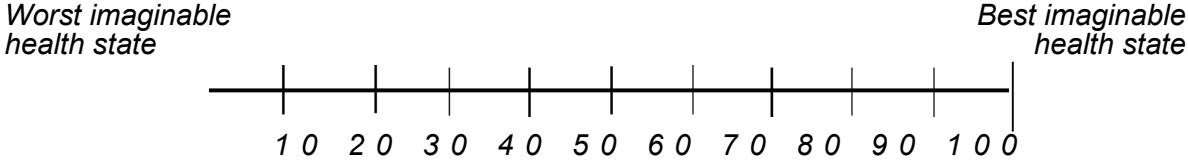
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety /Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

Scale for recording your health state today (*note: to be vertical in the questionnaire***)**
To help people say how good or bad a health state is, we have drawn a scale (rather looking a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.
We would like you to indicate on this scale how good or how bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



17.6 Appendix F - Beck Depression Inventory (BDI)

Instructions :

- *This questionnaire is a collection of 21 items corresponding to your mood and feelings*
- *Please read carefully all definitions for each category and select the one closest to what you have been experiencing over the past 2 weeks, including today*
- *Circle the figure placed before the definition you have selected. If you hesitate between 2 statements, please select the highest figure and circle this number.*
- *Please ensure you select only one definition in each group, including for group n°16 (modification in sleeping habits) and in group n°18 (changes in appetite).*

1. Sadness

0 I do not feel sad.
1 I feel sad much of the time.
2 I am sad all of the time.
3 I am so sad or unhappy that I can't stand it.

2. Pessimism

0 I am not discouraged about my future.
1 I feel more discouraged about my future than I used to be.
2 I do not expect things to work out for me.
3 I feel my fortune is hopeless and will get only worse.

3. Past Failure

0 I do not feel like a failure.
1 I have failed more than I should have.
2 As I look back I see a lot of failures.
2 I feel I am a total failure as a person.

4. Loss of Pleasure

0 I get as much pleasure as I ever did from the things I enjoy.
1 I don't enjoy things as much as I used to.
2 I get very little pleasure from the things I used to enjoy.
3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings

0 I don't feel particularly guilty.
1 I feel guilty over many things I have done or should have done.
2 I feel quite guilty most of the time.
3 I feel guilty most of the time.

6. Punishment Feelings

0 I don't feel I am being punished.
1 I feel I may be punished.
2 I expect to be punished.
3 I feel I am being punished.

7. Self-Dislike

0 I feel the same about myself as ever.
1 I have lost confidence in myself.
2 I am disappointed in myself.
3 I dislike myself.

8. Self-Criticisms
0 I don't criticize or blame myself more than usual.
1 I am more critical of myself than I used to be.
2 I criticize myself for all of my faults.
3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0 I don't have any thoughts of killing myself.
1 I have thoughts of killing myself, but I would not carry them out.
2 I would like to kill myself.
3 I would kill myself if I had the chance.

10. Crying
0 I don't cry anymore than I used to.
1 I cry more than I used to.
2 I cry over every little thing.
3 I feel like crying, but I can't.

11. Agitation
0 I am no more restless or would up than usual.
1 I feel more restless or would up than usual.
2 I am so restless or agitated that it's hard to stay still.
3 I am so restless that I have to keep moving or doing something.

12. Loss of Interest
0 I have not lost interest in other people or activities.
1 I am less interested in other people or things than before.
2 I have lost most of my interest in other people or things.
3 It's hard to get interested in anything.

13. Indecisiveness
0 I make decisions about as well as ever.
1 I find it more difficult to make decisions than usual.
2 I have much greater difficulty in making decisions than usual.
3 I have trouble making any decision.

14. Worthlessness
0 I do not feel I am worthless.
1 I don't consider myself as worthwhile and useful as I used to.
2 I feel more worthless as compared to other people.
3 I feel utterly worthless.

15. Loss of Energy
0 I have as much energy as ever.
1 I have less energy than I used to have.
2 I don't have enough energy to do very much.
3 I don't have enough energy to do anything.

16. Changes in Sleeping Patterns
0 I have not experienced any change in my sleeping pattern.
1 I sleep somewhat more/less than usual.
2 I sleep a lot more/less than usual.
3 I sleep most of the day.
I wake up 1-2 hours early and can't get back to sleep.

17. Irritability
0 I am no more irritable than usual.
1 I am more irritable than usual.
2 I am much more irritable than usual.
3 I am irritable all the time.

18. Changes in Appetite
0 I have not experienced any change in my appetite.
1 My appetite is somewhat greater/lesser than usual.
2 My appetite is much greater/lesser than usual.
3 I crave for food all the time or I have no appetite at all.

19. Concentration Difficulty
0 I can concentrate as well as ever.
1 I can't concentrate as well as usual.
2 It's hard to keep my mind on anything for very long.
3 I find I can't concentrate on anything.

20. Tiredness or Fatigue
0 I am no more tired or fatigued than usual.
1 I get more tired or fatigued more easily than usual.
2 I am too tired or fatigued to do a lot of the things I used to do.
3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex
0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

Total score: _____Score for suicidal thoughts:_____

Filled by patient at each visit (assessment over previous 2 weeks)

To be captured in CRF as global score (maximum is 63 and global depression score should not be >21) and as score for suicide ideation (item 9 which must be zero)

17.7 Appendix G - Patient Diary (Agenda)

Period: **Stabilisation E** **Period I E** **Period II E** **Period III E** **Washout E**

Site 1 E **Site 2 E** **Site 3 E** **Date from ..... to .....**

Number patient : I_I_I_I **Date for your next visit (next period) : .....**

A study start around 7:00 when getting out of bed and is completed 24 hours later after a night of sleep.

Data should be entered before going to bed and after getting up.

Day (2-15, 16-29, 30-43, 44-57,58-64) **Date**							
Get up (= start study day)	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I
Drug intake Morning (7:00 - 8:00) Early afternoon (13:00 -14:00)	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I	 I_LI : I_I_I I_LI : I_I_I
Day Period (7:00 à 22 :00)							
Somnolence episodes: Number	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I
Sleep attacks: Number	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I
Voluntary Naps: Number	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I	I_I_I
Total duration naps (hr nin)	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min
Cataplexy episodes Number complete Number partial	 I_I_I I_I_I	 I_I_I I_I_I	 I_I_I I_I_I	 I_I_I I_I_I	 I_I_I I_I_I	 I_I_I I_I_I	 I_I_I I_I_I
Going to bed	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I	I_LI : I_I_I

Day (2-15, 16-29, 30-43, 44-57,58-64) **Date**							
Wake up periods during sleep Number* Total duration* (hr nin) **Hypnagogic hallucinations** **Sleep paralysis**	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □	I_I_I I_LI h I_I_I min Yes □ No □ Yes □
Duration of sleep** (until next day)	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min	I_LI h I_I_I min
Comments							
Averse Events							

***Enter estimations for number and total duration and do not try to be precise when awakening at night.**

***To be recorded and calculated by investigator only in CRF.*

The visit day terminates the period. On that day you should record drug intake morning and noon and time of getting out of bed.

Take along the pages of your daily diary for the next visit and take all drug left from the period for blisters and vials even if empty or partly used.

17.8 Appendix H - Patient Global PGI-S and PGI-C

Patient Global Impression for Severity (PGI-S) will be filled by patient at each visit for assessing his health status over previous week as follows:

1	Normal, not ill at all	You have no somnolence episodes during day time and no sleep problems
2	Borderline ill	You have a few somnolence episodes during day time and few or no sleep problems
3	Mildly ill	You have occasional somnolence episodes during day time and a few sleep problems
4	Moderately ill	You have frequent somnolence episodes and occasional sleep attacks during day time and sleep problems
5	Markedly ill	You have frequent somnolence episodes and sleep attacks during day time and sleep problems. Your life pattern is disturbed
6	Severely ill	You have numerous somnolence episodes and sleep attacks during day time and poor sleep. You have major problems working and functioning
7	Among the most extremely ill patients	Somnolence episodes and sleep attacks prevent you from working

Patient Global Impression for Change (PGI-C) will be filled by patient at Visit V3, V4, V5 and V6 vs. Baseline (Visit V2 at end of stabilisation period) to assess his health status in response to treatment over previous week as follows:

1	Very much improved	Complete or nearly complete remission of your diurnal symptoms (somnolence episodes, sleep attacks...)
2	Much improved	Partial remission of your diurnal symptoms (somnolence episodes, sleep attacks...)
3	Minimally improved	Slight improvement of your diurnal symptoms (somnolence episodes, sleep attacks...), but with limited impact on your daily life
4	No change	Your diurnal symptoms remain essentially unchanged
5	Minimally worse	Slight increase of your diurnal symptoms (somnolence episodes, sleep attacks...)
6	Much worse	Substantial worsening of your diurnal symptoms (somnolence episodes, sleep attacks...)
7	Very much worse	Severe exacerbation of your diurnal symptoms (somnolence episodes, sleep attacks...)

Filled by patient at each visit

To be captured in CRF as global score for severity for all visits and for change at V3, V4, V5 and V6

17.9 Appendix I - CGI-S and SGI-C for Sleepiness and Cataplexy

Clinical Global Impression for Severity (CGI-S) must be filled by investigator at each visit for Global Assessment, for Sleepiness and for Cataplexy as follows:

Score	Status	Global	Sleepiness	Cataplexy*
1	Normal, not ill at all			
2	Borderline ill			
3	Mildly ill			
4	Moderately ill			
5	Marked ill			
6	Severely ill			
7	Among the most extremely ill patients			

*: NA for type 2 patient

Clinical Global Impression for Change (CGI-C) must be filled by investigator at Visit V3, V4, V5 and V6 vs. Baseline (Visit V2 at end of stabilisation period) to assess changes linked to treatment for Global Assessment, for Sleepiness and for Cataplexy as follows:

Score	Status	Global	Sleepiness	Cataplexy*
1	Very much improved			
2	Much improved			
3	Minimally improved			
4	No change			
5	Minimally worse			
6	Much worse			
7	Very much worse			

*: NA for type 2 patient

Filled by investigator at each visit for severity and at V3, V4, V5 and V6 for change

To be captured in CRF as global score, sleepiness score and cataplexy score for patients type 1.

17.10 Appendix J - Plasma Collection and Processing for PK Assay

Material	Provided by
S-Monovette® Li heparine on beads (4.5 mL, Sarstedt, Ref. 05.1106)	Site
Disposable plastic Pasteur pipettes	Site
Labels (blood tubes) for collection as needed	Site
Labels for plasma PK samples	Sponsor
Refrigerated centrifuge	Site
Nunc cryotubes, 1.2 mL, conic, internal screw-cap, star foot, Ref 479-6842	Sponsor
Nunc cryotube storage boxes with dividers (10x10) and grid	Sponsor
Precision automated pipets, exchangeable tips (Eppendorf)	Site

Note: material used for safety not listed

Specifications for tube labels

Labels for blood (as needed) and for plasma collection tubes at clinical site will contain the following printed information: study code (*THN102-201*), site number, patient number, visit (*V1, V2, V3, V4, V5, additional*), matrix (*plasma*). Date will be entered by hand

Collection of PK plasma samples at study site

Time 0 is the time of last drug intake and all time-points are calculated on that basis. Date and precise time of last drug intake prior to visit must be carefully recorded on worksheet and on CRF. Samples are collected at study state but time spent since last drug intake can fluctuate.

18. At visit V2, V3, V4, and V5 collect blood for safety and for PK sample.
19. After blood collection, each Monovette tube intended for PK should be inversed gently at least 5 times and stored at 4°C pending centrifugation.
20. Centrifugation should occur within 60 minutes of collection, preferably within 30 minutes.
21. Tubes should be centrifuged at 2200 g, for 15 min, at 4°C.
22. After centrifugation transfer 2 x 800µL plasma with an Eppendorf pipet to pre-labelled Nunc tubes and store at -24°C ± 6°C, pending assay (1 assay tube, 1 reserve).
23. Change tip of automated pipet for each new plasma sample.
24. **The cryotubes filled with plasma will be stored in the appropriate Nunc storage box with dividers (10 x 10) and printed grid, using chronological order per visit and per subject (from front to back for samples and from left to right for subjects, 1 lane per patient).** This leads to 1 storage box for 10 patients if 1 lane per patient. Depending on number of patients and shipment the actual number of patients per box may be adapted.
25. The basic cryotubes intended for shipment and assay should be stored in different boxes than reserve samples. If preferred, the reserve plasma tubes may be stored in plastic bags by subject and period.
26. Record the exact time and date of each blood collection in the CRF.

XXX Europe

1. Plasma samples will be analysed in singulate (volume 100µL) by XXX with their validated analytical method consisting of protein precipitation followed by LC-MS/MS. The LLOQ (Lower Limit of Quantification) with the new validated method with lower range is 10ng/mL

for modafinil and 1.0 ng/mL for flecainide acetate. The linear range of the assay (calibration range) is thus 10 to 10'000 ng/mL for the former and 1.0 to 1'000 ng/mL for the latter. Sample dilution will be performed if concentration initially measured in plasma is ALQ (Above Limit of Quantification).

2. Shipment of plasma samples to XXX will be performed tentatively on 2 occasions with completed patients mid-study and after study completion (see shipment instructions in Appendix K).

28. The actual treatments provided to the subjects will be provided to XXX Europe in a sealed envelope containing the randomisation study code or by electronic transfer (see additional information under Section 5.3). A secrecy agreement will also be signed to indicate restrictions for data distribution.

29. An analytical protocol will be prepared by XXX and agreed by study manager and by sponsor before undertaking the assays in study plasma samples.

30. The plasma concentrations data will be transmitted to Phinc with copy to Theranexus, study manager and XXX monitor according to Section 11.1. The detailed format will be provided in the analytical protocol prepared by XXX.

17.11 Appendix K - Shipment of Biological Samples for PK

Transfer of biological specimens for plasma samples

1. Plasma cryotubes stored on study site at -24°C ± 6°C will be organised by visit and by patient, in chronological fashion in dedicated Nunc storage card boxes (as indicated in Appendix J). Plasma reserve samples will be stored separately in dedicated boxes but will remain at study site unless required by XXX.
2. At period or at study completion the dedicated storage boxes with Nunc cryotubes will be checked for completeness by site technician and by monitor against grid and CRF.
3. Prior to shipment the Nunc storage boxes will be carefully sealed, limiting any empty space with paper to limit shifting of samples during transport.
4. A Proforma Invoice and an Acknowledgement Form will be prepared by a site technician. A Sample Transfer Form for plasma will be prepared by site staff as agreed with the study manager and with XXX to accompany the shipment. This Sample Transfer Form should contain for each subject and each period the basic information, including study code, period, subject number, matrix, nominal time, actual time for all samples, a column for comments and if possible time of drug intake. This may be paper copies of pertinent pages of CRF or an adapted extract of study database.
5. The day of transfer will be agreed in advance with XXX and confirmed by electronic mail with copy to study manager and to XXX monitor.
6. A reliable courier (World Courier or similar) will be used for transport and large amount of dry ice (preferably in slates) will be used in each insulated box to ensure at least 72 hours of temperature control for the Nunc storage boxes.
7. XXX staff will sign the enclosed Acknowledgment Receipt Form to confirm shipment and sample condition and forward to investigator, sending a copy to study manager and to monitor by electronic mail (scan) or by Fax.
8. Two shipments (1 mid-study and 1 at study completion) are presently planned but this can be adapted if preferable for logistical reasons.
9. The reserve plasma samples will be stored at study site and destroyed locally when the Clinical Study Report has been approved and upon written request by the study manager.

The insulated box with storage boxes containing plasma samples and documents will be sent to:

XXX

17.12 Appendix L - Laboratory Safety

Haematology (6 times, V0 or V1, V2 to V6)

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

Serology (at V1 only)

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

Biochemistry (V0 or V1, V2, V6, with abbreviated list° for V3, V4, V5)

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

Urinalysis (V1 to V6, performed at study site on fresh urine)

- Dipstick for pH, protein, glucose, blood, ketones, leukocytes, blood, urobilinogen, bilirubin
- Street drug screening such as amphetamines/methamphetamine, benzodiazepines, cocaine, cannabinoids, opiates, barbiturates
- Pregnancy test (h-CG) for patients with child-bearing potential

All safety parameters are performed at the hospital laboratory of each study site except for urine analysis, urine street drug screen, and urine pregnancy test which are performed by site staff at each visit.

All urinalysis dipsticks will be made available by the sponsor.

17.13 Appendix M - Changes Made to Protocol Version V5 to Generate Version 6.0

All additions have been identified by the use of **underline** and all deletions by strikethroughs.

4.2 Inclusion criteria

9. Women of childbearing potential (not surgically sterile or 2 years postmenopausal), must use a medically accepted method of contraception, and must continue one method for the duration of the study (and for 30 days 2 months after participation in the study). Acceptable methods of contraception include: abstinence, barrier method with spermicide, steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method, or intrauterine device (IUD).

8.4 Pregnancy exposure

Women of childbearing potential (defined as not surgically sterile or 2 years postmenopausal), must use a medically accepted method of contraception, and must continue one method for the duration of the study (and for 30 days 2 months after participation in the study). Acceptable methods of contraception include: abstinence, barrier method with spermicide, steroidal contraceptive (oral, transdermal, implanted, and injected) in conjunction with a barrier method, or intrauterine device (IUD).