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

Sponsor Project Code: THN102-202

[redacted]

STATISTICAL ANALYSIS PLAN

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Version: Final 1.0 (21-FEB-2020)

DOCUMENT REVISION HISTORY

Version Draft 0.1 (10-DEC-2018): Document was created.
Version Draft 0.2 (22-MAY-2019): The following changes were made:

- Incorporated Protocol versions Final 6.0/Final 8.0 France
- Added description of objective activity measure analysis in Section 5.6.7
- Added description of pharmacokinetic analysis to Section 5.7
- Compliance now calculated for modafinil and flecainide tablets separately and overall
- Subject diary data now summarised using the last 3 days before visit (from 7)
- Added adjusted total time slept (hours) to the analysis of diary data
- Statistical output has been re-numbered

Version Draft 0.3 (16-JAN-2020): The following changes were made:

- Added definition of treatment duration based on IMP exposure data
- Re-evaluated the severity of some protocol deviations and added 2 new protocol deviations
- Added the 'ethnicity' demographics variable (previously missed)
- Added rule that PK samples below the LLOQ will be set to 0 for summaries.
- Adjusted the statistics displayed in the pharmacokinetics summaries

Version Draft 0.4 (31-JAN-2020): Updated analysis of activity measures (Section 5.6.7):

- Added AX3 Analysis Plan to the list of appendices
- Changed the list of activity variables included in the efficacy analysis
- The mean value corresponding to the collection visit will be used in summaries and analyses

Version Draft 0.5 (20-FEB-2020): The following changes were made after the BDRM:

- Changed the definition of the Per Protocol set to include all subjects in the FAS with at least one treatment period not affected by a major protocol deviation
- Protocol deviations #11, #18, #20 changed to "case by case" according to Sponsor's comments on 06-FEB-2020 (before the blind data review meeting held on 10-FEB-2020).
- Decisions made during the BDRM regarding protocol deviations affecting efficacy and pharmacokinetic analyses are described in Sections 5.1.2, 5.6, 5.7.
- Tables and listings for protocol deviations now show the trial periods affected by the major protocol deviations
- Added Table 15.1.4.1 Number of Subjects by Country and Site – Enrolled
- Compliance is now calculated using the treatment duration rather than the treatment period duration

Version Final 1.0 (21-FEB-2020): The following changes were made:

- Added the titles and filenames of all TLFs to Appendices
- Removed the estimation of carryover effects in Section 5.6.2

SIGNATURES

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviations	Description of abbreviations
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BDR	Blind Data Review
BMI	Body mass index = body weight (kg) / height^2 (m^2)
CNS	Central nervous system
CRO	Contract research organisation
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
DMP	Data management plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	Early discontinuation visit
EOT	End-of-treatment
ESS	Epworth Sleepiness Scale
FAS	Full Analysis Set
GFR	Glomerular filtration rate
GLM	Generalised linear model
GLMM	Generalised linear mixed model
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HLGT	High level group term
HLT	High level term
ICD	Impulse control disorder
IMP	Investigational medicinal product
IS	Interdaily Stability
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intradaily Variability
KDIGO	Kidney Disease Improving Outcomes
LLT	Lowest level term
LNH	Lower than (L), within (N) or higher than (H) the reference range
MAR	Missing at random
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MDS-UPDRS	Movement Disorder Society-sponsored version of Unified Parkinson's Disease Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed models for repeated measures
MoCA	Montreal Cognitive Assessment
n	Number of observations/ frequency count
PCA	Pharmacie Centrale des Armées (Central Army Pharmacy)
PD	Parkinson's disease
PK	Pharmacokinetics
PP set	Per Protocol set
PT	Preferred term
PT	Prothrombin time

PVT	Psychomotor Vigilance Test
RA	Relative Amplitude
Q1	First quartile
Q3	Third quartile
QRS	Combination of three of the graphical deflections on an electrocardiogram
QT	Duration between Q wave and T wave on the ECG (expressed in ms)
QTcF	Corrected QT-interval (Fridericia's formula) in ECG (expressed in ms)
QUIP-RS	Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedure
SS	Safety Set
THN102	Theranexus internal code for the combination modafinil and flecainide
TLF	Tables, listings, figures
TNF	Tumour Necrosis Factor
WHO	World Health Organization
WHO-DDE	World Health Organization-Drug Dictionary Enhanced

INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical trial protocol versions:

Document, Version	Date
Protocol, Final 1.0	11-JAN-2018
Protocol, Final 4.0	30-MAY-2018
Erratum to Protocol Final 4.0, Final 1.0	14-JUN-2018
Protocol, Final 5.0 France	16-JUL-2018
Protocol, Final 5.0	19-OCT-2018
Protocol, Final 6.0 France	19-OCT-2018
Protocol, Final 6.0	27-FEB-2019
Protocol, Final 8.0 France	12-APR-2019

Due to non-substantial changes in the data collected and no changes in the statistical methodology described by the protocol, this SAP is written assuming the latest protocol version (**Final 6.0** or **Final 8.0 France**). Differences between the protocol versions will be listed in the relevant subsections of the SAP.

The SAP includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data, and it is structured according to different data types. The SAP is finalised and signed-off prior to unblinding the trial.

Actigraphy data collected over the course of the trial will be evaluated by a research team from [redacted] The corresponding AX3 Analysis Plan is included as an appendix (see Section 9). The resulting derived data will be transferred to [redacted] for efficacy analysis, which is described in Section 5.6.7.

All analysis data sets and statistical output will be produced by the statistics department at [redacted] using the SAS system version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) [1].

1. FLOW CHART AND VISIT SCHEDULE

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

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

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

1. There is no Day 0 (D0), i.e. the day after D-1 is D1. First IMP intake will be on Day 1. (On the day after V1C for treatment period II, on the day after V2C for treatment period III).
2. Safety laboratory will include haematology, biochemistry and urinalysis. At VS1 also serology and blood coagulation.
3. Urine pregnancy tests will be done in women of childbearing potential only. They may be performed more frequently to meet country-specific requirements.

4. Vital signs: Systolic and diastolic blood pressure as well as heart rate will be measured twice: after 5 minutes of supine rest and after 2 minutes in standing position (one set). At VR, V1C and V2C three sets of supine and standing vital signs will be measured 15-20 min apart.
5. Weight will be measured in street clothes without shoes.
6. At VS1 the C-SSRS Screening version will be completed. At other visits, the C-SSRS Since Last Visit version will be completed.
7. PVT will be done at 10:00 h, 12:00 h, 14:00 h and 16:00 h (± 0:15 h each). If this PVT assessment schedule is too burdensome for the subject, it may be individually adapted to at least 3 assessments, with a time window of not less than 1 h between two PVT assessments. Once chosen, the timeframe should remain constant during the trial for each subject.
8. The subject diary will be used continuously (i.e. also during washout periods) to record get-up time, total time (hours) slept last night, wake-up periods during night sleep, time of drug intake and number of capsules taken (except screening phase diary issued at VS1), somnolence episodes, diurnal involuntary sleep attacks, voluntary naps, number of caffeinated drinks and going-to-bed time.
9. Visits V1A and V1B should be scheduled so that 3 days of actigraphy data can be collected. (The same for VS2 and VR, V2A and V2B, as well as V3A and V3B.) Actigraphy will be assessed using an actigraphy wrist band.
10. MoCA should be performed in the morning.
11. In case of early discontinuation, the same procedures as required for V3B will be performed.
12. One PK blood sample will be taken when the subject arrives on the site. The times of blood withdrawal must be recorded.
13. Starting from Day 21, the visit day numbers are theoretical, as the washout period is flexible and can be extended to up to 14 days. The 2-week duration of the treatment period is fixed.

2. OBJECTIVES AND DESIGN

2.1 Trial Objectives

2.1.1 Primary Objective

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

2.1.2 Secondary Objectives

The secondary objectives of this trial are

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

2.2 Trial Endpoints

2.2.1 Safety Endpoints

The safety endpoints of this trial are

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

2.2.2 Key Efficacy Endpoint

The key efficacy endpoint for this trial is

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

2.2.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints of this trial are

9. ESS score responder rate, defined as the proportion of subjects with at least 25% ESS improvement from baseline, at the end of each treatment period
10. Absence of residual somnolence, i.e. ESS < 11 at the end of each treatment period
11. Psychomotor Vigilance Test (PVT) variables change from baseline at the end of each treatment period
12. MoCA score change from baseline at the end of each treatment period
13. Actimetry change (inactivity) from baseline at the end of each treatment period
14. Number and duration of diurnal involuntary sleep attacks (subject diaries) change from baseline at the end of each treatment period
15. Episodes of somnolence (subject diaries) change from baseline at the end of each treatment period

2.3 Overall Trial Design

This is a prospective, double-blind, randomised, placebo-controlled trial using a complete 3-way cross-over design. Subjects will be assessed during twelve visits (seven on site and five by phone call). The seven trial periods are depicted in Table 1.

Table 1: Trial design

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

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

The trial procedures by visit are presented in the flow chart in Section 1.

At visit VR the subjects will be equally randomised (1:1:1:1:1:1) double-blind to a treatment sequence containing three periods (shown in Table 2).

Table 2: Treatment sequences

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

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

2.4 Randomisation

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

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

2.5 Treatments

2.5.1 Test drug formulations

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

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

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

2.5.2 Reference drug formulations

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

Drug code:	**Modafinil placebo**
Dosage form:	1 tablet of 0 mg, over-encapsulated (orange capsule)
Excipients:	Tablet: Lactose monohydrate, pregelatinised starch (maize), microcrystalline cellulose, croscarmellose sodium, Povidone K29/32, magnesium stearate. Capsule, filler: Gelatine, Swedish Orange, microcrystalline cellulose.
Vials:	Capsules will be provided into HDPE snap-cap vials containing 18 capsules each.
Storage:	15-25 °C (avoid exposure >25°C)
Route:	Oral
Dose:	2 capsules containing 0 mg each, at 8:00 h (± 1:00 h) in the morning A 24-hour (± 1:00 h) interval between two consecutive doses is required.

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

2.6 Sample Size

For sample size planning ESS was considered to be the key efficacy endpoint. Solid information on the expected difference between placebo and THN102 dose and the associated intrasubject variance were not available. Using results reported in Adler et al. [4] as a rough orientation an effect size of 0.40 may constitute a conservative estimation for the comparison of the high THN102 dose with placebo. A sample size of 54 subjects will have a power of 82% to detect this effect size based on a paired t-test with a 0.05 two-sided significance level. To account for drop outs 60 subjects will be randomised.

In this exploratory phase 2a study, no adjustment for multiple testing will be applied.

2.7 Blinding

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

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

During the trial, the subject and all personnel involved with the conduct and the interpretation of the trial, including the investigators, site personnel, and the sponsor's staff, are blinded to the treatment assignment. The randomisation schedule is filed securely by the clinical CRO, in a manner such that blinding is properly maintained throughout the trial. Treatment assignment will not be available until the completion of the trial and until after final data review (clinical data base lock), except in the case of emergency.

3. ANALYSIS SETS AND SUBGROUPS

3.1 Analysis sets

The **Enrolled Set (**ES) includes all subjects who have signed the informed consent form.

The **Randomised Set** (RS) includes all subjects randomised at visit VR.

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

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

The **Per Protocol** (PP) set includes all subjects in the FAS who have at least one treatment period without a major protocol deviation. Major and minor violations are defined in Sections 5.1.2 and 5.6. The main secondary endpoints (ESS, PVT and cognition) will be analysed with the PP set to demonstrate robustness of the primary analysis.

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

3.2 Subgroups

No subgroups are defined for the primary analysis of this study.

4. GENERAL DEFINITIONS AND NAMING CONVENTIONS

To avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of subjects (n),
- mean,
- standard deviation (SD),
- median,
- first quartile (Q1) and third quartile (Q3)
- minimum (min) and maximum (max)

for subjects with data. Additionally, the geometric mean (GeoMean), geometric standard deviation (GSD), and geometric coefficient of variation (GCV) will be displayed for certain variables. Values of '0' will be removed from the calculation of the geometric mean, GSD, and GCV.

Mean, geometric mean, median, and the quartiles will be presented to one more decimal place than the raw value. The minimum and maximum values will be presented with the same decimal precision as the raw value. SD, GSD, and GCV will be reported to two decimal places greater than the original value.

For qualitative (categorical) variables, the frequency count (n) and percentage (%) of subjects with non-missing data per category will be the default frequency tabulations. Where appropriate and present, the number of missing values will be displayed as "Missing" category.

Percentage values are to be presented to one decimal place, for example, 52.3%.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalised; articles, prepositions, and conjunctions, and "To" in infinitives will not be capitalised, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline and endpoint value will be described in a footnote in every TLF where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: yyyy-mm-dd (e.g. 2003-11-20). Times will be listed in the format: hh:mm (e.g. 09:15) or in the format hh:mm:ss if seconds are collected. When the date and time are collected, these are listed in the format: yyyy-mm-ddThh:mm (e.g. 2003-11-20T09:15), yyyy-mm-ddThh, or yyyy-mm-ddThh:mm:ss.

Partially missing dates will be listed in the format yyyy-mm (e.g. 2013-11) if only day is missing or in the format yyyy (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by subject's number and visit number where applicable, unless specified otherwise.

4.3 Treatment Group Names and Labels

Statistical output will be presented by treatment sequence or treatment. Tables and figures that are displayed by treatment sequence or by treatment will be labelled with an S or T respectively. The labels used for treatment sequences and pooled treatment groups can be seen below (Table 3 and Table 4 respectively). For more details data pooling by treatment, see Sections 4.6-4.8.

Table 3: Sequence Labels

Description	Label in Statistical Output
Sequence 1: Dose A – Dose B – Dose C	ABC
Sequence 2: Dose B – Dose C – Dose A	BCA
Sequence 3: Dose C – Dose A – Dose B	CAB
Sequence 4: Dose A – Dose C – Dose B	ACB
Sequence 5: Dose C – Dose B – Dose A	CBA
Sequence 6: Dose B – Dose A – Dose C	BAC

Table 4: Treatment Labels

Description	Label in Statistical Output
Placebo	Placebo or A
THN102 200 mg/2 mg	Test 200/2 or B
THN102 200 mg/18 mg	Test 200/18 or C

4.4 Visit Numbering and Labels

The numbers to be used in the analysis datasets and the labels to be used in the tables, listings and figures for the different trial visits are defined in Table 5.

Table 5: Visit Numbering and Labels

Visit number	Visit name	Label in Statistical Output
10	Screening – VS1	VS1
20	Actigraphy – VS2	VS2
30	Baseline – VR	VR
40	Actigraphy – V1A	V1A
50	End of treatment I – V1B	V1B
60	End of washout I – V1C	V1C
70	Actigraphy – V2A	V2A
80	End of treatment II – V2B	V2B
90	End of washout II – V2C	V2C
100	Actigraphy – V3A	V3A
110	End of treatment III – V3B	V3B
120	Early Discontinuation Visit – EDV	EDV
130	Follow-up – V3C	V3C

The values collected at the EDV will be slotted according to date of EDV occurrence (see Section 4.6).

4.5 Treatment Day Numbering

All assessment dates will be related to the first day of IMP intake during the first treatment period. This first day of IMP intake is referred to as Day 1. Day –1 is the day that is preceding Day 1 and Day 0 will not be defined.

Treatment days may alternatively be numbered in listings with reference to the ongoing treatment period using the following rules:

- Dates prior to or during the first treatment period will be numbered with reference to the date of first IMP intake as described above.
- Dates belonging to the second and third treatment periods will be numbered with reference to the day after visit V1C or V2C respectively.
- Treatment days during any treatment period will be labelled according to the planned treatment sequence of the subject (e.g. A-11 for day 11 of the first treatment period in the sequence ABC). Treatment days prior up to visit VR will be labelled without reference to treatment sequence.

4.6 Trial Periods

Baseline period

The baseline period will be defined as the period from informed consent signature date to the date of visit VR.

Treatment periods

The periods from the day after visits VR, V1C, and V2C, to the dates of visits V1B, V2B, and V3B respectively, will be defined as the three treatment periods of this trial.

Data collected at visits V1B, V2B, and V3B will be considered as end-of-treatment values for their respective treatment periods.

If an early discontinuation visit (EDV) occurs after 7 or more IMP intakes, and not more than 3 days after the last IMP intake, the data collected at the EDV will be assigned to the end of the ongoing treatment period for statistical analyses.

Washout periods

The periods from the day after visits V1B and V2B, to the dates of visits V1C and V2C respectively will be defined as the two washout periods of this trial.

Data collected at visits V1C and V2C will be considered as end-of-washout values for the first and second treatment periods respectively and will be summarised within the same treatment as the end-of-treatment values of the respective treatment period.

If an EDV occurs 6 or more days after the last IMP intake of the preceding treatment period, the data collected at the EDV will be assigned to the end of the ongoing washout period for statistical analyses.

Follow-up period

The follow-up period is a trial period starting with the day after visit V3B/EDV until the trial termination date.

4.7 Baseline and Endpoint Values

Baseline value

The baseline value for a variable is defined as the last non-missing value collected before or during visit VR.

For diary data, the baseline value will be the value standardised as described in Section 5.6.8 over the baseline period.

Endpoint value

The endpoint value for a variable is defined as the last non-missing value collected during any end-of-treatment visit (V1B, V2B, or V3B).

For diary data, the endpoint value will be the value standardized as described in Section 5.6.8 over any treatment period corresponding to a given treatment.

Absolute change from baseline will be calculated as

$$Absolute\ Change\ from\ Baseline\ at\ Visit\ X = Value\ at\ Visit\ X - Baseline\ Value$$

Relative change from baseline (%) will be calculated as

$$Relative\ Change\ from\ Baseline\ at\ Visit\ X = \frac{Value\ at\ Visit\ X - Baseline\ Value}{Baseline\ Value} \times 100$$

Note: Subjects with a baseline value of '0' will be excluded from the calculation of relative change.

4.8 Treatment Assignment

In summaries and analyses where data is pooled by treatment, assignment to treatments will be performed as follows:

- Data collected up to and including visit VR (baseline) will be assigned to all treatments.
- Data collected at visits V1A-V1C, V2A-V2C, V3A-V3B, will be assigned to the treatment corresponding to the first, second and third treatment period respectively
- Data collected at the EDV visit will be assigned to treatment periods according to the rules in Section 4.6
- Efficacy analyses will be performed according to treatment **as randomised**. Data will be assigned to treatments based on the combination of planned treatment sequence and treatment period.
- Safety analyses will be performed according to treatment **as treated**. Data will be assigned to treatments based on the treatment actually received during the corresponding treatment period.

Other features of or deviations from the rules of treatment assignment are discussed in the relevant sub-sections of Section 5.

4.9 Coding Systems and Conventions

4.9.1 Coding of adverse events and medical history

Adverse event and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.0 [2].

4.9.2 Coding of medications

Medications are classified according to active drug substance using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE), 2018 March version [3]. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this trial, ATC codes are defined to the 4th level.

4.10 Handling of Missing Data

Data imputation methods will not be used in the analysis of efficacy or safety data. Efficacy data will be assumed to be missing at random (MAR), and likelihood-based estimation methods robust to this form of missingness will be used in efficacy analysis. Other details of handling of missing data, where applicable, are discussed in the relevant sub-sections of Section 5 (*STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY)*.

5. STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

5.1 Subjects Disposition

5.1.1 Disposition and Withdrawals

The following disposition data will be collected:

- date of informed consent
- date of trial termination
- did the subject complete the trial as scheduled (yes, no)
- reason for premature trial termination (at their own request (specified), investigator's opinion, major protocol deviations, treatment incompliance, prohibited concomitant therapy, adverse event, at the specific request of the sponsor, other (specified))

Screening failures will be all subjects discontinuing the trial due to any reason prior to randomisation at visit VR.

Withdrawals will be all subjects randomised at visit VR who do not complete the trial (visits V1A-V3B) as scheduled.

The following tables and listings will be presented:

Table 15.1.1.1.S Analysis Sets – Enrolled
Table 15.1.1.2.T Analysis Sets – Enrolled
Number and percentage of subjects included into the enrolled, randomised, safety, full analysis, per protocol, and PK analysis sets will be provided. Percentage will be based on the number of subjects in the enrolled set.

Table 15.1.1.3 Reasons for Exclusions from Analysis Sets – Enrolled
Number and percentage of subjects excluded from the randomised, safety, full analysis, per protocol, and PK analysis sets will be provided. Percentage will be based on the number of subjects in the enrolled set. The reasons of exclusion from the analysis sets will be incorporated into the table.

Table 15.1.2 Screening Failures – Enrolled
Counts and percentages of subjects who discontinued the trial prior to randomisation at visit VR will be summarised by reasons associated with the discontinuation. Percentage will be based on the number of subjects in the enrolled set.

Table 15.1.3.1.S Subject Disposition – Randomised
Table 15.1.3.2.S Subject Disposition – Safety
Counts and percentages of subjects who completed the treatment phase as scheduled, drop-outs during the treatment phase will be summarised separately in each period and overall. Reasons associated with the termination will be included. Percentage will be based on the number of subjects in the safety set.

Table 15.1.4.1 Number of Subjects by Country and Site – Enrolled
Table 15.1.4.2 Number of Subjects by Country and Site – Randomised
Table 15.1.4.3 Number of Subjects by Country and Site – Safety
Counts and percentages of subjects will be presented by site. Percentage will be based on the number of subjects in the safety set.

Table 15.1.5.S Number of Subjects by Visit – Safety
Counts and percentages of subjects who continue in the trial will be presented by visit. Percentage will be based on the number of subjects in the safety set.

Listing 16.2.1.1 Screening Failures – Enrolled
Subjects who discontinued the trial prior to randomisation at visit VR will be listed. Reasons associated with the discontinuation will be displayed.

Listing 16.2.1.2 Subject Disposition – Randomised
Listing 16.2.1.3 Subject Disposition – Safety
Subjects who complete the trial as scheduled or as withdrawals will be listed. Reasons for premature trial termination will be displayed for drop-outs.

Listing 16.2.1.4 Subject Visits – Enrolled
All visits' dates will be listed by subject.

Listing 16.2.3 Exclusions from Analysis Sets – Enrolled
Subjects excluded from any analysis set and corresponding reasons for exclusion will be listed.

Figure 15.1.1.S Flow Chart of Subject Disposition – Enrolled
Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled

5.1.2 Protocol Deviations

All analysis sets are defined in Section **Error! Reference source not found.**. The per protocol (PP) set is defined as all subjects who have completed the trial without major protocol deviation.

During the Blind Data Review (BDR) the eligibility of subjects for the PP set will be assessed. The BDR will be performed after data entry, prior to locking the database. All decisions made during the BDR will be documented in the BDR report before the closure of the database.

Protocol deviations are deviations from the procedures outlined in the clinical trial protocol or from subsequent protocol-related instructions like missed evaluations, incorrect timing of evaluations, non-compliance with the IMP, intake of prohibited medications or any non-adherence to the clinical trial protocol that impacts subject's rights, safety or welfare. Protocol deviations that may affect the efficacy or PK outcome will be discussed during the BDR.

An appropriate clinical trial team, including a physician, will review potential protocol deviations and relevant information regarding those deviations to determine a possible impact on safety or efficacy endpoints. A decision will be made as to the effect of the possible deviations to determine if it is considered major or minor. The status, major or minor, of each protocol deviation will be documented in the BDR report. A subject may have one or more major protocol deviations resulting in the exclusion of that subject from the per protocol analysis set.

Reference listings will also be made available to help with the review of the protocol deviations.

Note: Protocol deviations will, if possible, be validated against data recorded in the eCRF. Note where an answer for an inclusion/exclusion tick box differs from the algorithmic check of the criteria, the algorithmic check will overrule the tick box.

Protocol deviations of the following categories and respective data listings will be reviewed during the BDR.

Inclusion Criteria

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#01.	1. Subjects with a diagnosis of idiopathic Parkinson's disease as defined by the Movement Disorders Society (MDS).	major
PD#02.	2. Subjects with Hoehn and Yahr scale score ≤ 4.	case by case
PD#03.	3. Males or females, aged between 18 and 75 years. *Since Protocol Version 6.0 (or 8.0 France)*: 3. Males or females, aged between 18 and 80 years.	case by case

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#04.	4. Body mass index > 18 kg/m^2 and < 30 kg/m^2. *Since Protocol Version 6.0*: 4. Body mass index > 18 kg/m^2 and < 35 kg/m^2. *For Protocol Version 8.0 France*: 4. Body mass index > 18 kg/m^2 and < 30 kg/m^2.	case by case
PD#05.	5. Subjects should have a complaint of daytime sleepiness impacting their quality of life and/or daytime functioning (e.g. falling asleep while reading or watching TV, while eating or talking with other people).	major
PD#06.	6. Epworth Sleepiness Scale (ESS) score ≥ 14.	major
PD#07.	7. Women of childbearing potential (not surgically sterile or < 2 years postmenopausal), must use a highly effective method of contraception, and must continue for the duration of the trial (and for 2 months after participation in the trial). Highly effective methods of contraception include hormonal contraception associated with inhibition of ovulation (combined estrogen/progestogen: oral, intravaginal, transdermal; progestogen-only: oral, implanted, and injected) in conjunction with a barrier method (preferably male condom). Highly effective methods further include intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner (provided that the partner is the sole sexual partner of the subject and the vasectomised partner has received medical assessment of the surgical success) and sexual abstinence, i.e. when this is in line with the preferred and usual lifestyle of the subject.	minor
PD#08.	8. Subjects willing and able to follow trial procedures (including to swallow IMP capsules) and to regularly attend scheduled clinic visits as specified in the protocol, and who have signed the informed consent prior to any screening procedure.	minor

Exclusion Criteria

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#09.	1. Subjects with known or with a suspected sleep apnea syndrome or who have any other cause of excessive daytime sleepiness, such as shift work sleep disorder.	major
PD#10.	2. Psychiatric and neurological disorders (other than Parkinson's disease), such as idiopathic narcolepsy, Alzheimer's disease, Huntington's Chorea, multiple sclerosis, epilepsy, psychosis, bipolar disorder, severe clinical anxiety or depression, multiple system atrophy (Shy-Drager syndrome) or other problem that in the investigator's opinion would preclude the subject's participation and completion of this trial or comprise reliable representation of subjective symptoms.	case by case
PD#11.	3. Cardiovascular disorders such as a. Uncontrolled moderate to severe hypertension b. ECG QTcF duration ≥ 450 ms (men) or ≥ 470 (women)	case by case

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review

c. ECG signs of left ventricular hypertrophy (exclusion if at least one of the three indices is abnormal):
   - Sokolow-Lyon voltage (sum of amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 ≥ 3.5 mV), or
   - Cornell voltage (S wave in V3 + R wave in aVL > 2.8 mV in men or > 2.0 mV in women), or
   - Modified Cornell (R wave in aVL > 1.1 mV)

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

For France only:

3. Cardiovascular disorders such as
   a. Uncontrolled moderate to severe hypertension
   b. ECG QTcF duration ≥ 450 ms (men) or ≥ 470 (women)
   c. ECG signs of left ventricular hypertrophy (exclusion if at least one of the three indices is abnormal):
      - Sokolow-Lyon voltage (sum of amplitude of the S wave in lead V1 and the R wave in lead V5 or V6 ≥ 3.5 mV), or
      - Cornell voltage (S wave in V3 + R wave in aVL > 2.8 mV in men or > 2.0 mV in women), or
      - Modified Cornell (R wave in aVL > 1.1 mV)
   d. Recent (less than three months before screening visit VS1) myocardial infarction
   e. Stable or unstable angina pectoris
   f. Cardiac insufficiency
   g. Previous history of heart failure
   h. Previous history of cardiac valvular surgery
   i. Ventricular arrhythmias
   j. Atrial fibrillation unless it is stable and controlled by stable doses of amiodarone, calcium channel blocker or beta-blocker
   k. 2nd or 3rd grade atrioventricular block or chronic bifascicular block, unless an adequate pacemaker is present
   l. Sinus node dysfunction
   m. Documented Brugada syndrome
   n. Cardiogenic shock, severe bradycardia (less than 50 bpm), severe hypotension, hemodynamically significant valvular heart disease

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
	o. Mitral valve prolapse in subjects who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants.	
PD#12.	4. Subjects with current impulse control disorder.	minor
PD#13.	5. Subjects showing dementia or with MoCA < 23.	case by case
PD#14.	6. Subjects with current suicidal risk, based on investigator's clinical judgement or with a "yes" answer to item 4 and/or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at VS1, referring to the last month before screening.	minor
PD#15.	7. Current or recent (within one year) history of substance abuse or dependence disorder as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM-V), e. g. alcohol. Tobacco use is accepted.	case by case
PD#16.	8. Other active clinically significant illness, including unstable cardiovascular or malignant pathology, significant abnormality in physical examination or clinical laboratory results at VS1, which could interfere with the trial conduct or counter-indicate the trial treatments or place the subject at risk during the trial or compromise the trial participation.	case by case
PD#17.	9. Subjects with hepatic impairment (serum total bilirubin ≥ 2 mg/dL, except in patients diagnosed with Gilbert's syndrome, or prothrombin time [PT] ≥ 13.7 s (except in patients on therapeutic anticoagulation), or serum albumin < 3.5 g/dL), or renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2, according to Kidney Disease Improving Global Outcomes (KDIGO)).	case by case
PD#18.	10. Known hypersensitivity to IMP (active ingredients or excipients of modafinil or flecainide capsules).	case by case
PD#19.	11. Subjects currently (or within 6 weeks before VS1) under one of the following medications (isolated intake up to 1 week can be accepted): a. Neuroleptics, anxiolytics, anticonvulsants. Benzodiazepines and benzodiazepine-like drugs are only authorised if used regularly at stable indicated doses with an evening intake as sleep promoting agents. b. Flecainide or other class I antiarrhythmic drugs. c. Psychostimulants (except caffeine if no abuse and stable consumption) such as, but not limited to, modafinil, methylphenidate, amphetamine. d. Antidepressants except if maintained at stable dose for at least 6 weeks before visit VS1 and anticipated to remain stable during the trial in subjects with mild or moderate unipolar depression. e. Antiemetic medications (except domperidone), myo-relaxing drugs and opioids. f. Dopaminergic medications, unless they have been used at stable doses for at least 4 weeks before screening and it is anticipated that the doses will not be changed throughout the trial. Efficacious medication for Parkinson's disease should not be discontinued for the sole purpose of the subject's enrolment into this clinical trial but must be maintained at stable dosage levels. g. Centrally acting anti-obesity drugs. h. TNF-alpha inhibitors.	case by case

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#20.	12. Pregnancy or lactation. Women of childbearing potential who intend to be pregnant during the next few months.	case by case
PD#21.	13. Subjects protected by the law (legal guardianship).	minor
PD#22.	14. Subjects participating in any other clinical trial within 60 days prior to visit VS1 in this trial or still in the protected period imposed by a previous trial.	case by case
PD#23.	15. Subjects working in an occupation requiring variable shift work or routine night shifts.	major
PD#24.	16. Subjects who plan to travel involving time zone changes.	case by case

Additional trial conduct deviations

No.	Deviation	Major/ Minor/ Case by case review
PD#25.	IMP treatment compliance according to eCRF or diary <80% or >120%, by treatment period and overall	case by case
PD#26.	IMP repeatedly taken not according to schedule (earlier than 7:00 or later than 9:00)	case by case
PD#27.	Duration of treatment and washout periods	case by case
PD#28.	IMP intake deviations related to PK analysis	case by case
PD#29.	Intake of prohibited medications	case by case
PD#30.	Adverse events that may significantly affect the key efficacy or PK trial endpoints	case by case
PD#31.	PDs from the global Protocol deviations log that may significantly affect the key efficacy or PK endpoints and are not covered by other listings	case by case

The specific content and format of listings to be reviewed during the BDR meeting (including any additional requirements that may be necessary to aid in review) will be determined outside the scope of this SAP.

Additional protocol deviation criteria were defined during the BDR meeting held on 10-FEB-2020. These deviations are described in full in the BDRM report (version Final 1.0, 20-FEB-2020). For a description of the rules and how they apply to efficacy and pharmacokinetic analysis, see Section 5.6 and Section 5.7 respectively.

The following tables and listing will be provided:

Table 15.1.6.1.S Major Protocol Deviations – Safety
Table 15.1.6.2.S Major Protocol Deviations – Full Analysis
Number and percentage of subjects with major protocol deviations will be summarised by affected trial period and overall. The categories of major protocol deviations will be included. Percentage will be based on the number of subjects in the respective analysis set.

Listing 16.2.2.1 Major Protocol Deviations – Safety
Major protocol deviations will be listed including the affected trial periods.

5.1.3 Inclusion/Exclusion

The trial specific inclusion/exclusion criteria are presented in Section 4.2 and 4.3 of the Clinical Trial Protocol. For each criterion, as appropriate, a response of "Yes/No" is to be obtained at VS1, VS2, and checked again prior to confirmation of eligibility at Visit VR.

The following listing will be provided:

Listing 16.2.2.2 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled
Listing of inclusion criteria which were not met and exclusion criteria which were met will be presented per subject.

5.2 Demographic and Other Baseline Characteristics

5.2.1 Demographics

The following demographic characteristics will be presented:

- Age (years)
- Gender
- Race
- Ethnicity
- Alcohol consumption (≤ 200 mL beer or 100 mL wine per day, > 200 mL beer or 100 mL wine per day)
- Education (12 years or less, more than 12 years)

The following baseline characteristics will be presented:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Subject alcohol consumption status at baseline will be presented in listings only.

The following tables will be presented:

Table 15.1.7.1.1.S Demographics – Safety
Table 15.1.7.1.2.S Demographics – Full Analysis
Table 15.1.7.1.3.S Demographics – Per Protocol
Demographic data will be summarised using standard summary statistics or frequency tabulations as appropriate. Percentage for categorical variables will be based on the number of subjects in the respective analysis set.

Table 15.1.7.2.1.S Baseline Characteristics – Safety
Table 15.1.7.2.2.S Baseline Characteristics – Full Analysis
Table 15.1.7.2.3.S Baseline Characteristics – Per Protocol
Weight, height and BMI data at baseline will be summarised using standard summary statistics.

Listing 16.2.4.1 Demographics and Baseline Characteristics – Enrolled
Demographic and baseline characteristics' data will be listed for the subjects in the enrolled set.

5.2.2 Baseline Disease Stage

At visit VS1, the onset date of Parkinson's disease and excessive daytime sleepiness as well as medication for these indications will be collected.

Additionally, the stage of Parkinson's disease at visit VS1 will be assessed using the modified Hoehn & Yahr scale. The scale contains 8 progression levels (0, 1, 1.5, 2, 2.5, 3, 4, 5).

The following table and listing will be presented:

Table 15.1.7.3.1.S Baseline Disease Stage – Safety
Table 15.1.7.3.2.S Baseline Disease Stage – Full Analysis
Table 15.1.7.3.3.S Baseline Disease Stage – Per Protocol

Hoehn & Yahr score will be summarised at baseline using standard frequency tabulations.

Listing 16.2.4.2 Baseline Disease Stage – Enrolled
Subjects' neurological history will be listed. The substance names of medications taken for Parkinson's disease and excessive daytime sleepiness at the date of visit VS1 will also be displayed.

5.2.3 Medical History

Medical history encompasses relevant prior or ongoing relevant diseases, conditions, hospitalisation, and surgical procedures. Medical history records are collected at Visit VS1.

Medical history of the subjects includes:

- Diagnosis
- Start date
- Stop date (or ongoing)
- Medication taken (yes, no)

Medical history is classified as:

- **Prior medical conditions** are the conditions which started and ended prior to Visit VS1.
- **Ongoing medical conditions** are the conditions which are ongoing at Visit VS1 and include conditions with a stop date after Visit VS1.

The following tables and listings will be provided:

Table 15.1.8.1.1.S Prior Medical Conditions – Safety
Table 15.1.8.1.2.S Prior Medical Conditions – Full Analysis
Table 15.1.8.2.1.S Ongoing Medical Conditions – Safety
Table 15.1.8.2.2.S Ongoing Medical Conditions – Full Analysis
Medical history will be summarised displaying counts and percentages of subjects having at least one medical condition and will be presented by MedDRA SOC and by PT within the SOC. SOCs and PTs within the SOC are to be sorted by descending order of overall incidence. Subjects with two or more occurrences of the same condition (as qualified by its PTs) will be counted only once for the respective PT. Percentage will be based on the number of subjects in the respective set.

Listing 16.2.4.3 Medical History – Enrolled
Medical history conditions will be listed for the subjects from the enrolled set.

5.3 Prior and Concomitant Medications

Prior and concomitant medications and therapies are documented in the eCRF.

The following information is collected:

- Medication / therapy name
- Indication (Parkinson's disease, excessive daytime sleepiness, medical history diagnosis – specified, adverse event – specified, other)
- Route
- Total daily dose (units)
- Frequency
- Start date
- Stop date (or ongoing)

Medications and therapies will be classified as 'prior', 'concomitant' or 'post-treatment' based on start/stop dates:

- **Prior medications/therapies** are defined as those medications/therapies starting and ending prior to the first IMP intake as recorded in the eCRF.
- **Concomitant medications/therapies** are defined as medications/therapies started at or after the first IMP intake as recorded in the eCRF and include medications/therapies started prior to the first IMP intake but continued during the trial.
- **Post-treatment medications/therapies** are defined as medications/therapies which started after the last IMP intake as recorded in the eCRF.

If the start date of medication/therapy is incomplete or missing, it will be assumed to be concomitant except if the incomplete start date or the stop date indicates that the medication/therapy started prior to the first IMP intake or after the last IMP intake.

Concomitant medications will be assigned to treatments based on the preceding IMP intake. Medications taken during a washout period will be assigned to the treatment of the IMP taken in the preceding treatment period. If the start or end date indicates that the medication was taken concurrently with multiple treatments, it will be assigned to every corresponding treatment. If the start or end date is incomplete such that it could belong to more than one treatment, the concomitant medication will be assigned to all such treatments.

The following tables and listings will be provided:

Table 15.1.9.1.1.S Prior Medications – Safety
Table 15.1.9.1.2.S Prior Medications – Full Analysis
Table 15.1.9.2.1.T Concomitant Medications – Safety
Table 15.1.9.2.2.T Concomitant Medications – Full Analysis
The number and percentage of subjects with at least one medication within each ATC 2nd level subgroup and substance name will be presented for the respective set. The ATC 2nd level subgroups and substance name within ATC 2nd level subgroup will be ordered by descending overall incidence.

Listing 16.2.4.4 Medications and Therapies – Enrolled
All medications, prior, concomitant and post-treatment, will be listed for the subjects from the enrolled set.

5.4 Exposure to IMP and Compliance

5.4.1 Exposure to IMP

Exposure data from eCRF includes:

- date of first IMP intake
- date of last IMP intake
- date of IMP dispensed
- number of capsules dispensed (modafinil and flecainide)
- date of IMP returned
- number of capsules returned (modafinil and flecainide)

Exposure data from the subject treatment diaries includes:

- date
- number of capsules taken (modafinil and flecainide)

The **date of first IMP intake** is the intake of the first morning dose as recorded in the eCRF. If the date of first intake as recorded in the eCRF is missing, the first IMP intake recorded in the subjects' diaries will be used.

The **date of last IMP intake** is the date of last IMP intake recorded at trial termination page. If the date of last intake of the last evaluated dose is missing, the last IMP intake recorded in the subject diaries will be used.

The treatment period duration will be calculated in days as follows:

$$treatment\ period\ duration\ (days) = end\text{-}of\text{-}treatment\ visit\ date - baseline\ visit\ date$$

For the purposes of treatment period duration calculation, visit VR as well as end-of-washout visits V1C and V2C are considered as baseline visits.

Treatment duration based on IMP exposure data will be calculated for each treatment period as:

$$treatment\ duration\ (days) = last\ IMP\ intake\ date\ - first\ IMP\ intake\ date\ + 1$$

within the respective treatment period. The overall treatment and treatment period durations will be calculated as the sum of corresponding individual durations.

The following will be provided:

Table 15.1.10.1.1.T Treatment Duration (days) – Safety
Table 15.1.10.1.2.T Treatment Duration (days) – Full Analysis
Table 15.1.10.1.3.T Treatment Duration (days) – Per Protocol
The default summary statistics of treatment period duration and treatment duration will be presented by period and overall.

5.4.2 Compliance

Compliance based on the eCRF and subject diaries will be calculated as follows:

$$eCRF\ compliance\ (\%) = \frac{100 * (N\ tablets\ dispensed - N\ tablets\ returned)}{treatment\ duration * N\ tablets\ prescribed\ per\ day}$$

$$diary\ compliance\ (\%) = \frac{100 * N\ tablets\ taken}{treatment\ duration * N\ tablets\ prescribed\ per\ day}$$

The default number of tablets prescribed per day is 2 tablets of modafinil and flecainide, for a total of 4 tablets per day. For subjects older than 65 years of age at visit VS1, on the first three days of each treatment period the dosage is halved, resulting in one tablet of modafinil and flecainide scheduled to be taken for a total of 2 tablets per day.

Compliance will be calculated for modafinil and flecainide tablets as well as overall. The overall compliance will be calculated via the sum of modafinil and flecainide tablets dispensed, returned or taken at the corresponding timepoint.

Compliance will be calculated for each treatment period and overall. The individual treatment duration or overall treatment duration (see Section 5.4.1) will be used respectively.

Compliance will be summarised as follows:

Table 15.1.10.2.1.T Treatment Compliance (eCRF) – Safety
Table 15.1.10.2.2.T Treatment Compliance (eCRF) – Full Analysis
Table 15.1.10.2.3.T Treatment Compliance (eCRF) – Per Protocol
The default summary statistics of compliance based on the eCRF within each treatment period and overall will be presented. Number and percentage of subjects will also be summarised by compliance categories (< 80%, ≥ 80% and ≤ 120%, >120%) for the respective analysis set. Compliance for modafinil and flecainide tablets will be displayed in addition to the overall compliance.

Table 15.1.11.2.1.T Treatment Compliance (Diary) – Safety
Table 15.1.11.2.2.T Treatment Compliance (Diary) – Full Analysis
Table 15.1.11.2.3.T Treatment Compliance (Diary) – Per Protocol
The default summary statistics of compliance based on the subject diaries within each treatment period and overall will be presented. Number and percentage of subjects will also be summarised by compliance categories (< 80%, ≥ 80% and ≤ 120%, >120%) for the respective analysis set. Compliance for modafinil and flecainide tablets will be displayed in addition to the overall compliance.

Listing 16.2.5.1 Exposure to IMP and Compliance – Safety

5.5 Safety Analysis

Safety will be assessed by evaluation of the following variables:

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

The safety set will be used for the analysis of the safety data.

5.5.1 Adverse Events

AEs will be coded according to MedDRA Version 21.0.

Adverse event data includes:

- adverse event name
- start date
- stop date or ongoing
- severity (mild, moderate, severe)
- relationship to the IMP (unrelated, unlikely, possible, probable, definite)
- action taken with IMP (no action, drug interrupted, drug withdrawn, unknown)
- other actions (none, medication required, tests required, hospitalisation required or prolonged, other)

- outcome (recovered/resolved, recovered/resolved with sequelae, recovering/resolving, not recovered/not resolved, fatal, unknown) and date of outcome
- serious (yes or no)

All AEs will be presented in listings.

Adverse event summaries will focus on **treatment-emergent adverse events (TEAEs)**, defined as AEs with an onset or worsening after the first IMP intake and not more than 7 days after the last IMP intake.

If the start date of an AE is incomplete or missing, it will be assumed to be treatment-emergent except if the stop date or the incomplete start date indicates that the event started prior to the first IMP intake or later than 7 days after the last IMP intake.

Treatment-emergent adverse events will be assigned to treatments based on the treatment period containing the AE onset date. If the onset date of an adverse event is during a washout period, it will be assigned to the preceding treatment period. If the AE onset date is incomplete such that it could belong to more than one treatment period, the AE will be assigned to all treatments corresponding to such treatment periods.

Based on collected data the following will be determined and will be used in addition to AEs overall for presentation in the applicable tables and listings:

- **Serious Adverse Events (SAEs):** defined as AEs considered by the investigator as serious.
- **Related TEAEs**: defined as AEs with relationships to the IMP assessed as being "possible", "probable" or "definite" and include AEs with missing IMP relationship assessments.
- **Unrelated TEAEs**: defined as AEs with relationships to the IMP assessed as being "unlikely" or "unrelated".
- **Severe TEAEs**: defined as AEs assessed as being "severe" in intensity and include the events with missing severity assessment.
- **TEAEs leading to discontinuation:** defined AEs whose action taken with IMP is "drug withdrawn" or other action taken is "withdrawal from trial".
- **TEAEs leading to death:** selected as those events where outcome of event is indicated as "fatal".

The **duration of the AE** will be calculated using the following formula:

$$AE\ Duration\ (days) = AE\ stop\ date - AE\ start\ date + 1$$

If the start or stop dates of the AE are incomplete or AE is still ongoing at the end of the trial, the duration will not be calculated.

The following tables and listings will be provided:

Table 15.2.1.1.1.S Overall Summary of TEAEs – Safety
Table 15.2.1.1.2.T Overall Summary of TEAEs – Safety
An overview of TEAEs:

- TEAE
- Non-Serious TEAE
- Serious TEAE
- Related TEAE
- Related Serious TEAE
- Severe TEAE
- TEAE leading to discontinuation
- Serious TEAE leading to discontinuation
- Related TEAE leading to discontinuation
- TEAE leading to death

will be displayed for the subjects in the safety set.

Table 15.2.1.2.T Incidence of TEAEs – Safety
Table 15.2.1.3.T Incidence of Non-Serious TEAEs – Safety
Table 15.2.1.4.T Incidence of Serious TEAEs – Safety
Table 15.2.1.5.T Incidence of Related TEAEs – Safety
Table 15.2.1.6.T Incidence of Related Serious TEAEs – Safety
Table 15.2.1.7.T Incidence of TEAEs Leading to Discontinuation – Safety
Table 15.2.1.8.T Incidence of TEAEs Leading to Death – Safety
TEAEs will be summarised by displaying the numbers of adverse events, as well as counts and percentages of subjects having experienced adverse events. Percentages will be based on the number of subjects in the safety set. SOCs and PTs within each SOC will be ordered by descending overall incidence.

Table 15.2.1.9.T Incidence of TEAEs by Severity – Safety
TEAEs will be summarised similarly as above within each adverse event severity level.

All adverse event data will be listed as follows:

Listing 16.2.6.1 Adverse Events: MedDRA Coding
Listing 16.2.6.2 Adverse Events: General – Enrolled
Listing 16.2.6.3 Serious Adverse Events – Safety
Listing 16.2.6.4 AEs Leading to Discontinuation – Safety
Listing 16.2.6.5 AEs Leading to Death – Safety
All AEs will be displayed by subject including the PT of an AE, start and stop dates, duration and other characteristics of AEs.

5.5.2 Clinical Laboratory Evaluation

Clinical laboratory values (haematology, biochemistry, and urinalysis) are collected at visit VS1, VR, V1B, V2B, and V3B/EDV for each laboratory parameter.

The following parameters are collected:

Haematology: Leukocytes, erythrocytes, haemoglobin, haematocrit, MCV, MCH, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils (%), lymphocytes (%), monocytes (%), eosinophils (%), basophils (%).

Biochemistry: sodium, potassium, urea, creatinine, total protein, albumin, total bilirubin, direct bilirubin, AST (GOT), ALT (GPT), alkaline phosphatase, uric acid, glucose (fasting and non-fasting), cholesterol, triglycerides.

Urinalysis: Leukocytes, nitrites, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, haemoglobin.

Haematology and biochemistry test results are assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter as provided by the corresponding laboratory.

Clinical significance of laboratory values is evaluated by the investigator.

Range values of laboratory results will be set to ½ of the specified threshold for analysis (e.g. a result of "<0.03" will be considered as 0.015 in summaries).

The following tables and listings will be provided:

Table 15.2.4.1.1.T Summary of Clinical Laboratory Tests: Haematology – Safety
Table 15.2.4.1.2.T Summary of Clinical Laboratory Tests: Biochemistry – Safety
Table 15.2.4.1.3.T Summary of Clinical Laboratory Tests: Urinalysis – Safety
The default summary statistics of clinical laboratory test results will be presented at each visit. The absolute change from baseline will be presented for haematology and biochemistry findings.

Table 15.2.4.2.1.T Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety
Table 15.2.4.2.2.T Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety
Number and percentage of subjects for each laboratory parameter will be displayed in CS Low, Low, Normal, High, and CS High categories. Percentage will be based on the number of subjects at specified visit.

Table 15.2.4.2.3.T Clinical Laboratory Tests: Incidence of Urinalysis Abnormalities – Safety
Number and percentage of subjects with abnormal values of urinalysis parameters will be displayed in normal/abnormal/CS abnormal categories. Percentage will be based on the number of subjects at specified visit.

Table 15.2.4.3.1.T Clinical Laboratory Tests: Shift Table of Haematology Results – Safety
Table 15.2.4.3.2.T Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety
Table 15.2.4.3.3.T Clinical Laboratory Tests: Shift Table of Urinalysis Results – Safety
Shift tables showing changes in the number and frequency of subjects with respect to the normal range between baseline and endpoint will be provided. Subjects with missing data will be presented as part of a "missing" category.

Listing 16.2.7.1 Laboratory Data – Haematology – Enrolled
Listing 16.2.7.2 Laboratory Data – Biochemistry – Enrolled
Values of laboratory tests will be listed.

Listing 16.2.7.3 Laboratory Data – Urinalysis – Enrolled
All urinalysis data will be listed.

5.5.3 Vital Signs

Vital signs (systolic and diastolic blood pressure as well as heart rate) will be measured twice: after 5 minutes supine rest and after 2 minutes in standing position (one set of supine and standing vital signs) at visits VS1, VR, V1B, V1C, V2B, V2C, and V3B/EDV.

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

Vital signs' parameters will be summarised using the mean value at each visit. The mean will be calculated if there is at least one non-missing value for a given parameter.

Results for systolic blood pressure, diastolic blood pressure, and heart rate will be classified according to whether the value was lower than (L), within (N) or higher than (H) the reference range for that parameter. The normal ranges are provided in Table .

Table 6: Normal Ranges for Vital Signs

Parameter	Lower Reference Range	Upper Reference Range
Systolic blood pressure – Supine [mmHg]	90	140
Diastolic blood pressure – Supine [mmHg]	60	90
Systolic blood pressure – Standing [mmHg]	80	140
Diastolic blood pressure – Standing [mmHg]	60	90
Heart rate [bpm]	50	100

The following tables and listings will be provided:

Table 15.2.5.1.T Summary of Vital Signs – Safety
Vital signs' parameters will be summarised including change from baseline at each visit.

Table 15.2.5.2.T Incidence of Vital Signs Abnormalities – Safety
Number and percentage of subjects will be displayed in Low, Normal and High categories for every vital signs' parameter. Percentage will be based on the number of subjects at specified visit.

Table 15.2.5.3.T Shift Table of Vital Signs Abnormalities – Safety
Shift tables showing changes in the number and frequency of subjects with respect to the normal range between baseline and endpoint will be provided. Subjects with missing data will be presented as part of a "missing" category.

Listing 16.2.8.1 Vital Signs – Enrolled

5.5.4 12-Lead Electrocardiogram (ECG) Data

A 12-lead electrocardiogram (ECG) will be recorded after 10 minutes in supine position at visits VS1, VR, V1B, V1C, V2B, V2C, and V3B/EDV. The following ECG parameters will be collected:

- Heart rate (bpm)
- R-R interval (ms)
- PR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QT interval – Bazett correction (ms)
- QT interval – Fridericia correction (ms)
- Mean electrical axis (degrees)
- ECG diagnosis
- ECG abnormality assessment
- Comparison to baseline

ECG abnormality assessments of "Incomplete Analysis" and "Uninterpretable" will be considered as part of the "Not Applicable" category in summaries.

The central ECG reading provider will also assess the ECG results against baseline, using the following categories:

- Improved
- Unchanged
- Worsened
- Not Applicable
- Not compared

The clinical significance of ECG abnormalities will be additionally assessed by the investigator. If the assessment of clinical significance differs between the investigator and the ECG reading provider, the investigator's assessment will be used in the analysis.

The following tables and listing will be presented:

Table 15.2.6.1.T Summary of ECG Parameters – Safety
ECG parameters will be summarised using default summary statistics including change from baseline at each visit.

Table 15.2.6.2.T Summary of ECG Diagnoses – Safety
The number and percentage of subjects with each ECG diagnosis will be displayed at each visit. Percentage will be based on the number of subjects at specified visit.

Table 15.2.6.3.T Summary of ECG Abnormality Assessments – Safety
Number and percentage of subjects with normal, abnormal, and CS abnormal ECG assessments will be displayed. Percentage will be based on the number of subjects at specified visit.

Table 15.2.6.4.T Shift Table of ECG Abnormality Assessments – Safety
Number and percentage of subjects with normal, abnormal, and CS abnormal ECG assessments will be displayed. Percentage will be based on the number of subjects at specified visit.

Listing 16.2.8.2 Electrocardiogram – Enrolled

5.5.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

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

The C-SSRS Screening version will be used at VS1 to obtain baseline data, and the C-SSRS Since Last Visit version will be used to capture changes in the subject's status at visits VR, V1B, V1C, V2B, V2C, and V3B/EDV.

The following table and listing will be presented:

Table 15.2.7.T Summary of Columbia-Suicide Severity Rating Scale – Safety
Number and percentage of subjects with suicidal ideation and suicidal behaviour will be summarised using standard frequency tabulations at every visit. Percentage will be based on the number of subjects at specified visit.

Listing 16.2.8.3 Columbia-Suicide Severity Rating Scale – Enrolled

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

An MDS-UPDRS questionnaire is administered on visits VR, V1B, V2B, and V3B/EDV. The MDS-UPDRS consists of four parts:

1. Non-motor aspects of experiences of daily living (13 items)
2. Motor aspects of experiences of daily living (13 items)
3. Motor examination (33 scores based on 18 items)
4. Motor complications (6 items)

with each item being scored using an integer rating of 0 to 4.

A score will be calculated for each part of the MDS-UPDRS as the sum of all items in that part of the questionnaire. According to Goetz et al. [5], a valid score for the MDS-UPDRS parts can be calculated if the respective part contains a number of missing values less than or equal to the following:

- Non-motor aspects of experiences of daily living – 1
- Motor aspects of experiences of daily living – 1
- Motor examination – 3
- Motor complications – 0

For subjects with partially missing data, a prorated score will be calculated by taking the sum of all non-missing items, dividing it by the number of non-missing items, and multiplying it by the total number of items in each part. The prorated score will be rounded to the nearest whole number.

The total MDS-UPDRS score will be calculated as the sum of the scores of each part. The total score will not be calculated if the score for any part of the MDS-UPDRS is missing.

The following table and listing will be presented:

Table 15.2.8.T Summary of MDS-UPDRS – Safety
Each part of the MDS-UPDRS as well as the total score will be summarised at baseline, and at the end of each treatment period using default summary statistics.

Listing 16.2.8.4 MDS-UPDRS Questionnaire – Enrolled

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

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale (QUIP-RS) is a tool designed to measure the severity of symptoms of impulse control disorders (ICDs) and related disorders. Subjects will complete the QUIP-RS at baseline (visit VR) and at the end of each treatment period (V1B, V2B, V3B/EDV).

The QUIP-RS consists of four primary questions, each applied to four ICDs (compulsive gambling, buying, eating and sexual behaviour) and three related disorders (medication use, punding and hobbyism). The QUIP-RS uses a 5-point scale (score 0-4 for each question) to rate the severity of each symptom based on its weekly frequency. The total ICD score ranges from 0 to 64, and the total QUIP-RS score for all ICDs and related disorders ranges from 0 to 112.

The following tables and listing will be presented:

Table 15.2.9.1.T Summary of QUIP-RS Items – Safety
Each part of the QUIP-RS will be summarised at baseline and at the end of each treatment period using default frequency tabulations.

Table 15.2.9.2.T Summary of QUIP-RS Scores – Safety
The total ICD score and total QUIP-RS score will be summarised at baseline and at the end of each treatment period using default summary statistics.

Listing 16.2.8.5 QUIP-RS Questionnaire – Enrolled

5.5.8 Physical Examination Findings

Physical examinations will be performed at visits VS1, VR, V1B, V2B, and V3B/EDV on the following body systems:

- Head
- Neck
- Eyes
- Ear-nose-throat
- Heart
- Respiratory
- Gastrointestinal
- Hepatic
- Urogenital
- Musculoskeletal
- Vascular
- Lymphatic
- Dermatologic
- Central-nervous system (CNS)
- Psychiatric

Clinical significance (yes/no) of any abnormal physical examination findings will be assessed by the investigator.

Physical measurements (height, weight, and BMI) of subjects will be performed at VS1. In addition, weight and BMI will be repeatedly assessed at visits VR, V1B, V2B, and V3B/EDV.

The following tables and listings will be presented:

Table 15.2.10.1.T Summary of Physical Measurements – Safety
Physical measurement parameters will be summarised using standard summary statistics including change from baseline at each visit.

Table 15.2.10.2.T Summary of Physical Examination Findings – Safety
Number and percentage of subjects with normal, abnormal, and CS abnormal physical examinations findings will be displayed at each visit. Percentage will be based on the number of subjects at specified visit.

Listing 16.2.8.6 Physical Measurements – Enrolled
Listing 16.2.8.7 Physical Examinations – Enrolled

5.5.9 Other Safety-Related Observations

5.5.9.1 Pregnancy Testing

On visits VS1, VR, V1B, V2B, and V3B/EDV, female subjects of childbearing potential will undergo urine pregnancy testing. Pregnancy test results will be assessed as "positive" or "negative" by the investigator.

The following listing will be provided:

Listing 16.2.8.8 Pregnancy Testing – Enrolled
Childbearing potential and pregnancy test data will be listed for each female in the enrolled analysis set.

5.5.9.2 Safety Laboratory Screening

During VS1, certain safety laboratory parameters will be assessed for the purposes of subject eligibility screening. The following serology parameters will be collected:

- HAV-AB (IgM) (Hepatitis A)
- HBsAg (Hepatitis B)
- HCV-AB (Hepatitis C)
- HIV-Ag/Ab (HIV)

Each serology parameter will be assessed as positive or negative.

Additionally, blood coagulation will be assessed using prothrombin time (PT), and renal impairment will be assessed using glomerular filtration rate (GFR).

The following listing will be provided:

Listing 16.2.8.9 Safety Laboratory Screening – Enrolled
Safety laboratory data collected for screening purposes will be listed for subjects in the enrolled analysis set.

5.6 Efficacy Analysis

Efficacy will be assessed by evaluation of the following variables:

- Epworth Sleepiness Scale (ESS) score change from baseline at the end of each treatment period
- ESS score responder rate at the end of each treatment period
- Absence of residual somnolence at the end of each treatment period
- Psychomotor Vigilance Test (PVT) variable change from baseline at the end of each treatment period
- Montreal Cognitive Assessment (MoCA) score change from baseline at the end of each treatment period
- Actimetry change from baseline at the end of each treatment period
- Number and duration of diurnal involuntary sleep attacks (subject diaries) change from baseline at the end of each treatment period
- Episodes of somnolence (subject diaries) change from baseline at the end of each treatment period

The Full Analysis set as well as the Per Protocol set will be used for the analysis of efficacy data.

Treatment periods will be considered as evaluable for efficacy analysis only if the following rules are satisfied:

- IMP is taken for at least 7 days during the treatment period
- Last IMP intake is at most 3 days before the corresponding end-of-treatment visit, i.e. a maximum of 3 IMP intakes can be missed leading up to the end-of-treatment visit.

Washout periods will be considered as evaluable for efficacy analysis only if the preceding treatment period is evaluable and the last IMP intake is 6 or more days before the corresponding end-of-washout visit.

For the purposes of these rules, EDVs are considered as end-of-treatment (if the preceding scheduled visit was VR/V1C/V2C) or end-of-washout (if the preceding scheduled visit was V1B/V2B) visits.

A trial period not being evaluable for efficacy analysis according to these rules is considered a major protocol deviation.

Efficacy analyses for the FAS will be performed using data available from all scheduled visits, as well as EDV visits satisfying the above criteria. Efficacy analyses for the PP will be performed using only data from trial periods unaffected by major protocol deviations.

5.6.1 Key Efficacy Analysis

On visits VS1, VR, V1B, V1C, V2B, V2C, and V3B/EDV subjects will fill out the Epworth Sleepiness Scale (ESS) questionnaire. The ESS consists of 8 questions with the answers on the scale of 0-3. The ESS score is the sum of the 8 items and has a range of 0-24. The **key efficacy variable** in this trial is the change from baseline of the ESS score at the end of each treatment period (visits V1B, V2B, and V3B/EDV).

The ESS score change from baseline will be analysed using a mixed linear regression model with the fixed effects of treatment, period, treatment by period interaction, sequence, and baseline score, and subject nested within sequence as a random effect. The model will be estimated using the restricted maximum likelihood method (REML). Degrees of freedom for the fixed effects will be estimated using the Kenward-Roger approximation.

The following SAS code will be used in mixed linear regression modelling:

```
PROC MIXED DATA=<Dataset> METHOD=REML;
      CLASS <Subject> <Treatment> <Period> <Sequence>;
      MODEL <Change from Baseline> = <Treatment> | <Period>
                                      <Sequence> <Baseline>
                                    / DDFM = KENROG;
      RANDOM int / SUBJECT=<Subject>(<Sequence>);
      LSMEANS <Treatment> / PDIFF CL;
RUN;
```

A statistically significant (p-value < 0.05) treatment by period interaction may indicate the presence of residual treatment (carryover) effects, which may bias the estimates of treatment effects. For this reason, if a statistically significant treatment by period interaction is found in the analysis of the key efficacy endpoint, the key efficacy analyses will be performed using data from the first period only. In such an event, the key efficacy endpoint will be modelled using an analysis of covariance (ANCOVA) model with the fixed effect of treatment and baseline score as a covariate.

The following SAS code will be used in the analysis of first-period data:

```
PROC MIXED DATA=<Dataset> METHOD=REML;
      CLASS <Treatment>;
      MODEL <Change from Baseline> = <Treatment> <Baseline>
                                    / DDFM = KENROG;
      LSMEANS <Treatment> / PDIFF CL;
RUN;
```

Additional exploratory analysis of the carryover effect is defined in section 5.6.2.

The following tables, listings and figures will be provided:

Table 15.3.1.1.1.S Summary of Epworth Sleepiness Scale Score – Full Analysis
Table 15.3.1.1.2.S Summary of Epworth Sleepiness Scale Score – Per Protocol
Table 15.3.1.2.1.T Summary of Epworth Sleepiness Scale Score – Full Analysis
Table 15.3.1.2.2.T Summary of Epworth Sleepiness Scale Score – Per Protocol
The Epworth sleepiness scale score will be summarised using default summary statistics at each visit. The ESS change from baseline will be summarised at each post-baseline visit.

Table 15.3.2.1.1 Analysis of Epworth Sleepiness Scale Score – Full Analysis
Table 15.3.2.1.2 Analysis of Epworth Sleepiness Scale Score – Per Protocol
Table 15.3.2.2.1 Analysis of Epworth Sleepiness Scale Score (First Period) – Full Analysis
Table 15.3.2.2.2 Analysis of Epworth Sleepiness Scale Score (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-values. Contrast estimates will be displayed for the difference between each pair of treatments.

Figure 15.3.1.1.S Subject-Level ESS Score Change from Baseline – Full Analysis
Figure 15.3.1.2.S Subject-Level ESS Score Change from Baseline – Per Protocol
ESS score change from baseline at the end of every treatment period will be displayed for each subject stratified by treatment sequence.

Figure 15.3.2.1.T Mean ESS Score Change from Baseline by Period – Full Analysis
Figure 15.3.2.2.T Mean ESS Score Change from Baseline by Period – Per Protocol
The mean and standard deviation of ESS score change from baseline pooled by treatment at the end of every treatment period will be displayed using a scatter plot with error bars.

Listing 16.2.9.1 Epworth Sleepiness Scale – Enrolled
Epworth sleepiness scale results will be listed for each subject in the enrolled analysis set.

5.6.2 Key Efficacy Endpoint Carryover Effect Estimation

If the key efficacy endpoint analysis shows a statistically significant treatment by period interaction (p-value < 0.05), modified key efficacy analyses will be performed to adjust for potential first-order carryover effects on the ESS score. For these analyses, the treatment of the previous treatment period will be assigned to each observation. The treatment by period interaction in the original efficacy model will not be included.

The treatment effects at end-of-treatment visits V1B, V2B and V3B will be estimated using a mixed linear regression model with the fixed effects of treatment, period, sequence, and residual treatment, baseline score as a covariate, and the random effect of subject nested within sequence. The carryover effect estimation will be performed using the following SAS code:

```
PROC MIXED DATA=<Dataset> METHOD=REML;
      CLASS <Subject> <Treatment> <Period> <Sequence> <LagTreatment>;
      MODEL <Change from Baseline> = <Treatment> <Period> <Sequence>
                                      <Baseline> <LagTreatment>
                                    / DDFM = KENROG;
      RANDOM int / SUBJECT=<Subject>(<Sequence>);
      LSMEANS <Treatment> / PDIFF CL;
RUN;
```

The following tables will be presented:

Table 15.3.2.3.1 Analysis of Epworth Sleepiness Scale Score Adjusted for Carryover – Full Analysis
Table 15.3.2.3.2 Analysis of Epworth Sleepiness Scale Score Adjusted for Carryover – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-values. Contrast estimates will be displayed for the difference between each pair of direct treatment effects.

5.6.3 ESS Responder Rate

The Epworth Sleepiness Scale (ESS) responder rate is defined as the proportion of subjects with a relative ESS score change from baseline of at least -25% after each treatment period.

The treatment differences in the ESS responder rate will be assessed using a generalised linear mixed regression model (GLMM) with the fixed effects of treatment, period, treatment by period interaction, sequence, and baseline score, and subject nested within sequence as a random effect. The logit link function will be used to model the binary response data. The model will be estimated using the default RSPL method. Degrees of freedom for the fixed effects will be estimated using the Kenward-Roger approximation.

The following SAS code will be used in GLMM estimation:

```
PROC GLIMMIX DATA=<Dataset> METHOD=RSPL;
      CLASS <Subject> <Treatment> <Period> <Sequence>;
      MODEL <Responder Status> = <Treatment> | <Period>
                                      <Sequence> <Baseline>
                                    / DIST=BINARY LINK=LOGIT DDFM = KENROG;
      RANDOM int / SUBJECT=<Subject>(<Sequence>);
      LSMEANS <Treatment> / PDIFF ODDSRATIO ILINK CL;
RUN;
```

The treatment least-squares means of the log-odds will be reported as well as their standard errors and 95% confidence intervals. Also, the odds ratios between each treatment will be displayed with 95% confidence intervals.

In case of model non-convergence, the treatment by period interaction will be removed from the model. If the simplified model fails to converge, the difference in response rate between treatments will be evaluated using an exact McNemar's test. Response at endpoint will be compared between each treatment at the two-sided 5% level.

McNemar's test will be performed using the following SAS code:

```
PROC FREQ DATA=<Dataset>;
      TABLES <Treatment 1 Response>*<Treatment 2 Response>;
      EXACT MCNEM;
RUN;
```

If a statistically significant (p-value < 0.05) treatment by period interaction is found in the analysis of the ESS responder rate, an additional analysis will be performed using only data collected during the first treatment period. If the full GLMM specification was not used due to model non-convergence, this additional analysis will be performed in case of a statistically significant treatment by period interaction in the key efficacy model (Section 5.6.1).

Model-based analysis of first-period data will be based on a generalised linear model (GLM) with the fixed effect of treatment and baseline as a covariate. The following SAS code will be used:

```
PROC GLIMMIX DATA=<Dataset>;
      CLASS <Treatment>;
      MODEL <Responder Status> = <Treatment> <Baseline>
                                    / DIST=BINARY LINK=LOGIT;
      LSMEANS <Treatment> / PDIFF CL;
RUN;
```

The following table and listing will be presented:

Table 15.3.3.1.1.S Summary of Epworth Sleepiness Scale Responder Rate – Full Analysis
Table 15.3.3.1.2.S Summary of Epworth Sleepiness Scale Responder Rate – Per Protocol
Table 15.3.3.2.1.T Summary of Epworth Sleepiness Scale Responder Rate – Full Analysis
Table 15.3.3.2.2.T Summary of Epworth Sleepiness Scale Responder Rate – Per Protocol
Epworth sleepiness scale responder rate at each post-baseline visit will be summarised using default frequency tabulations. Percentage will be based on number of subjects with data available at each timepoint.

Table 15.3.4.1.1 Analysis of Epworth Sleepiness Scale Responder Rate – Full Analysis
Table 15.3.4.1.2 Analysis of Epworth Sleepiness Scale Responder Rate – Per Protocol
Table 15.3.4.2.1 Analysis of Epworth Sleepiness Scale Responder Rate (First Period) – Full Analysis
Table 15.3.4.2.2 Analysis of Epworth Sleepiness Scale Responder Rate (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-value. Log-odds contrast estimates will be displayed for the difference between each pair of treatments.

5.6.4 Absence of Residual Somnolence

Residual somnolence is defined as an ESS score of 11 or more at the end of a treatment period. The rate of subjects with an absence of residual somnolence (i.e. ESS score < 11) at the end of each treatment period will be analysed using statistical methods described in Section 5.6.3.

In the case that a statistically significant (p-value < 0.05) treatment by period interaction is found in the model-based analysis of residual somnolence, an additional analysis will be performed using only data collected during the first treatment period. The statistical methods will be adjusted as described in Section 5.6.3.

The following tables will be presented:

Table 15.3.5.1.1.S Summary of Absence of Residual Somnolence – Full Analysis
Table 15.3.5.1.2.S Summary of Absence of Residual Somnolence – Per Protocol
Table 15.3.5.2.1.T Summary of Absence of Residual Somnolence – Full Analysis
Table 15.3.5.2.2.T Summary of Absence of Residual Somnolence – Per Protocol
Absence of residual somnolence at each post-baseline visit will be summarised using default frequency tabulations. Percentage will be based on number of subjects with data available at each timepoint.

Table 15.3.6.1.1 Analysis of Absence of Residual Somnolence – Full Analysis
Table 15.3.6.1.2 Analysis of Absence of Residual Somnolence – Per Protocol
Table 15.3.6.2.1 Analysis of Absence of Residual Somnolence (First Period) – Full Analysis
Table 15.3.6.2.2 Analysis of Absence of Residual Somnolence (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-value. Log-odds contrast estimates will be displayed for the difference between each pair of treatments.

5.6.5 Psychomotor Vigilance Test (PVT)

On visits VR, V1B, V1C, V2B, V2C, and V3B/EDV subjects will undergo 3-minute Psychomotor Vigilance Task evaluations. PVT will be performed up to four times during each visit: at 10:00 h, 12:00 h, 14:00 h, and 16:00 h (±15 minutes each) by default. If the default PVT schedule is too burdensome for a particular subject, it may be individually adapted to at least 3 assessments with a time window of at least 1 hour between each PVT assessment. The actual time of each PVT assessment will be collected in the eCRF.

The following PVT variables will be collected at every visit and timepoint:

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

A failure to react or any reaction exceeding 500 ms is considered a lapse. A reaction without stimulus or under 100 ms is considered a false start. Lapses and false starts are counted towards total errors.

For each PVT variable, the mean value during a visit will be used for analysis.

The PVT mean response time will be analysed using a mixed linear regression model as described in Section 5.6.1.

In the case that a statistically significant (p-value < 0.05) treatment by period interaction is found in the analysis of the PVT mean response time, an additional analysis will be performed using only data collected during the first treatment period. The statistical model will be adjusted as described in Section 5.6.1.

The following tables, listing, and figures will be presented:

Table 15.3.7.1.1.S Summary of PVT Mean Response Time – Full Analysis
Table 15.3.7.1.2.S Summary of PVT Mean Response Time – Per Protocol
Table 15.3.7.2.1.T Summary of PVT Mean Response Time – Full Analysis
Table 15.3.7.2.2.T Summary of PVT Mean Response Time – Per Protocol
PVT mean response time will be summarised using default summary statistics at each visit. The change from baseline will be summarised at each post-baseline visit.

Table 15.3.8.1.1.S Summary of PVT Errors – Full Analysis
Table 15.3.8.1.2.S Summary of PVT Errors – Per Protocol
Table 15.3.8.2.1.T Summary of PVT Errors – Full Analysis
Table 15.3.8.2.2.T Summary of PVT Errors – Per Protocol
The number of lapses and number of total errors during PVT evaluation will be summarised using default summary statistics at each visit. The change from baseline will be summarised at each post-baseline visit.

Table 15.3.9.1.1 Analysis of PVT Mean Response Time – Full Analysis
Table 15.3.9.1.2 Analysis of PVT Mean Response Time – Per Protocol
Table 15.3.9.2.1 Analysis of PVT Mean Response Time (First Period) – Full Analysis
Table 15.3.9.2.2 Analysis of PVT Mean Response Time (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-values. Contrast estimates will be displayed for the difference between each pair of treatments.

Figure 15.3.3.1.S Subject-Level PVT Performance Change from Baseline – Full Analysis
Figure 15.3.3.2.S Subject-Level PVT Performance Change from Baseline – Per Protocol
PVT mean response time change from baseline at the end of every treatment period will be displayed for each subject stratified by treatment sequence.

Figure 15.3.4.1.T Mean PVT Performance Change from Baseline by Period – Full Analysis
Figure 15.3.4.2.T Mean PVT Performance Change from Baseline by Period – Per Protocol
The mean and standard deviation of PVT mean response time change from baseline pooled by treatment at the end of every treatment period will be displayed using a scatter plot with error bars.

Listing 16.2.9.2 Psychomotor Vigilance Test – Enrolled
PVT variable data will be listed for each subject in the enrolled analysis set.

5.6.6 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment (MoCA) is a brief screening instrument to detect mild cognitive impairment. The MoCA assesses multiple cognitive domains including attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation and orientation. Subjects will complete the MoCA during the screening and washout visits VS1, VR, V1C, and V2C, and on end-of-treatment visits V1B, V2B, and V3B/EDV.

To decrease possible learning effects, the three (equivalent) versions 7.1, 7.2, and 7.3 will be used in alternation. MoCA scores range between 0 and 30. A score of 26 or over is considered to be normal.

For subjects with an education of 12 years or fewer, the MoCA score will be increased by 1. MoCA scores of 30 will not be increased.

MoCA scores will be analysed using a mixed linear regression model as described in Section 5.6.1.

In the case that a statistically significant (p-value < 0.05) treatment by period interaction is found in the analysis of the MoCA score, an additional analysis will be performed using only data collected during the first treatment period. The statistical model will be adjusted as described in Section 5.6.1.

The following tables and listing will be presented:

Table 15.3.10.1.1.S Summary of Montreal Cognitive Assessment Scores – Full Analysis
Table 15.3.10.1.2.S Summary of Montreal Cognitive Assessment Scores – Per Protocol
Table 15.3.10.2.1.T Summary of Montreal Cognitive Assessment Scores – Full Analysis
Table 15.3.10.2.2.T Summary of Montreal Cognitive Assessment Scores – Per Protocol
The Montreal Cognitive Assessment score will be summarised using default summary statistics at each visit. The change from baseline will be summarised at each post-baseline visit.

Table 15.3.11.1.1 Analysis of Montreal Cognitive Assessment Scores – Full Analysis
Table 15.3.11.1.2 Analysis of Montreal Cognitive Assessment Scores – Per Protocol
Table 15.3.11.2.1 Analysis of Montreal Cognitive Assessment Scores (First Period) – Full Analysis
Table 15.3.11.2.2 Analysis of Montreal Cognitive Assessment Scores (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-values. Contrast estimates will be displayed for the difference between each pair of treatments.

Listing 16.2.9.3 Montreal Cognitive Assessment– Enrolled

5.6.7 Actigraphy (Inactivity) Evaluation

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

Actigraphy measurements will be collected for 3 days prior to visit VR and for 3 days at the end of each treatment period. Charged actigraphy devices will be handed out to subjects at visits VS1, VR, V1C, and V2C, and actigraphy data will be collected during visits VR, V1B, V2B, and V3B/EDV.

Objective activity measures will be estimated from the raw activity data by a research team from [redacted] and provided to [redacted] for efficacy analysis. A description of this process and each evaluated objective activity measure is provided in the AX3 Analysis Plan, attached as an appendix to this SAP (see Section 9).

The following objective activity measures will be estimated for each day prior to the collection visit:

- Night Time Immobility Duration (minutes) **(NTID)**
- Night Time Mobility Periods **(NTMP)**
- Night Time Mobility Duration (minutes) **(NTMD)**
- Diurnal Immobility Periods **(DIP)**
- Diurnal Immobility Duration (minutes) **(DID)**
- Daily Physical Activity (g) **(DPA)**
- Nightly Physical Activity (g) **(NPA)**
- Daily Jerk (g/s) **(DJ)**

The following activity ratios will be estimated once per collection visit:

- Intradaily Variability **(IV)**
- Interdaily Stability **(IS)**
- Relative Amplitude **(RA)**

The results of each activity measure will be summarised at each visit. The mean value of assessments corresponding to the collection visit will be used for analysis. All values will be listed.

Activity ratios (**IV**, **IS**, **RA**) and physical activity variables (**DPA**, **DJ**) will additionally be analysed using a mixed linear regression model as described in Section 5.6.1.

In the case that a statistically significant (p-value < 0.05) treatment by period interaction is found in the analysis of an objective actigraphy measure, an additional analysis will be performed for that activity measure using only data collected during the first treatment period. The statistical model will be adjusted as described in Section 5.6.1.

Further statistical analyses of actigraphy data are defined outside the scope of this SAP.

The following tables and listing will be presented:

Table 15.3.12.1.1.S Summary of Objective Activity Measures – Full Analysis
Table 15.3.12.1.2.S Summary of Objective Activity Measures – Per Protocol
Table 15.3.12.2.1.T Summary of Objective Activity Measures – Full Analysis
Table 15.3.12.2.2.T Summary of Objective Activity Measures – Per Protocol
Objective activity measures will be summarised using default summary statistics at each visit. The absolute and relative change from baseline will be summarised at each post-baseline visit.

Table 15.3.13.1.1 Analysis of Objective Activity Measures – Full Analysis
Table 15.3.13.1.2 Analysis of Objective Activity Measures – Per Protocol
Table 15.3.13.2.1 Analysis of Objective Activity Measures (First Period) – Full Analysis
Table 15.3.13.2.2 Analysis of Objective Activity Measures (First Period) – Per Protocol
Estimates of each modelled effect will be displayed with standard errors, t-values and p-values. Contrast estimates will be displayed for the difference between each pair of treatments.

Listing 16.2.9.4 Objective Activity Measures– Enrolled

5.6.8 Subject Diary Data

Over the course of the trial, subjects will fill out paper-based diaries concerning their daily sleep and IMP intake patterns. One screening diary and three treatment diaries will be issued at visit VS1, and visits VR, V1C, and V2C respectively, and collected at visits VR, V1C, V2C, and V3B/EDV. The diaries will be filled in continuously from visit VS1 to V3B/EDV, including the washout periods after treatment periods I and II.

Analysis of drug exposure data collected from subject diaries is discussed in section 5.4.1.

Efficacy-related data collected from patient diaries will be summarized over the respective trial period (baseline, washout 1, washout 2, and treatment 1, 2, or 3) for the purpose of displaying them in summaries. Numeric variables will be standardized to amount per day, and for categorical variables subjects will be included in every category that occurred to them in the given period.

If there are less than 3 non-missing values over the course of a treatment or washout period for a given variable, it will be set to missing for the respective period in summaries. For treatment periods, only the last 3 non-missing values per parameter will be aggregated in summaries order to capture the full effect of the IMP.

All diary data will be listed.

Listing 16.2.9.5 Diary Sleep Data – Enrolled
Listing 16.2.9.6 Diary Exposure Data – Enrolled

5.6.8.1 Diurnal Involuntary Sleep Attacks

The number and total duration of diurnal involuntary sleep attacks will be recorded in the subject diaries. These data will be summarised as numeric variables as described in section 5.6.8.

The following tables will be presented:

Table 15.3.14.1.S Summary of Diurnal Involuntary Sleep Attacks – Full Analysis
Table 15.3.14.2.T Summary of Diurnal Involuntary Sleep Attacks – Full Analysis
The number and duration of diurnal involuntary sleep attacks will be summarised using default summary statistics for each trial period. The change from baseline will be displayed for each post-baseline period.

5.6.8.2 Somnolence Episodes

The number of somnolence episodes each day will be collected in the subject diaries. It will be summarised as a numeric variable as described in section 5.6.8.

The following tables will be presented:

Table 15.3.15.1.S Summary of Somnolence Episodes – Full Analysis
Table 15.3.15.2.T Summary of Somnolence Episodes – Full Analysis
The number of somnolence episodes will be summarised using default summary statistics for each trial period. The change from baseline will be displayed for each post-baseline period.

5.6.8.3 Other Efficacy-Related Variables

Other efficacy-related variables collected in the subject diaries include:

- Get-up time
- Total time (hours) slept last night
- Wake-up periods during night sleep:
  - Number (<5, between 5 and 10, >10)
  - Total duration (minutes)
- Voluntary naps:
  - Number
  - Total duration (minutes)
- Number of caffeinated drinks
- Going-to-bed time

Time in bed will be calculated as the difference in hours between the get-up time and the going-to-bed time of the preceding day. Time in bed will not be calculated if either of the datetime values are completely or partially missing.

Adjusted total time slept in hours will be calculated as follows:

$$Adj.\ total\ time\ slept = min(total\ time\ slept,\ \ time\ in\ bed - wake - up\ period\ duration)$$

With the exception of the number of wake-up periods during night sleep, these data will be summarised as numeric variables as described in section 5.6.8.

The following tables will be presented:

Table 15.3.16.1.S Summary of Other Efficacy-Related Diary Data – Full Analysis
Table 15.3.16.2.T Summary of Other Efficacy-Related Diary Data – Full Analysis
The secondary diary data will be summarised for each trial period using default summary statistics or frequency tabulations, as appropriate.

5.7 Pharmacokinetic Analysis

To assess the steady state pharmacokinetics of the IMP, blood samples will be collected upon subject arrival at study sites during visits VR, V1B, V1C, V2B, V2C, and V3B/EDV. Concentrations of flecainide and modafinil at each visit will be summarised. For summaries, concentrations below the lower limit of quantification (LLOQ) will be set to zero. Concentrations will be reported as collected in listings.

To summarise pharmacokinetic data the geometric mean (GeoMean), geometric standard deviation (GSD), and geometric coefficient of variation (GCV) will be displayed. These statistics will be calculated using the following formulae:

$$GeoMean = \sqrt[n]{y_1 \times y_2 \times \ldots \times y_n}$$

$$GSD = e^{\left(SD\left(ln(y_1), ln(y_1), \ldots, ln(y_n)\right)\right)}$$

$$GCV = \sqrt{e^{GSD^2} - 1} \times 100\%,$$

where *n* – number of observations, *SD* – standard deviation, *ln* – natural logarithm. Values of '0' will be removed from the calculation of the geometric mean, GSD, and GCV. The ratios GeoMean ÷× GSD will be displayed in addition to these statistics.

Evaluability of pharmacokinetic data

PK samples performed at the end of **treatment periods** will be analysed if an IMP intake was performed in the morning before the PK sample.

PK samples performed at the end of **washout periods** will be analysed if the last IMP intake is 6 or more days before the PK sample, and if the preceding end-of-treatment PK sample is evaluable according to the above rule.

Deviations from these rules will be considered as major protocol deviations in relation to PK analysis.

The following tables and listing will be presented:

Table 15.4.1.S Summary of Pharmacokinetics Concentrations – PK Analysis Set
Table 15.4.2.T Summary of Pharmacokinetics Concentrations – PK Analysis Set
The concentrations of modafinil and flecainide at each visit will be summarised using the geometric mean, geometric standard deviation, and geometric coefficient of variation in addition to the default summary statistics.

Listing 16.2.5.2 Pharmacokinetics Concentrations – Enrolled

6. INTERIM ANALYSIS

No interim analysis is planned.

7. CHANGES TO THE ANALYSIS AS LAID DOWN IN THE PROTOCOL AND AMENDMENTS

The definition of the Per Protocol set was changed to include subjects with major protocol deviations, if they have at least one treatment period unaffected by a major protocol deviation. Per Protocol analysis will be performed on all trial periods unaffected by a major protocol deviation.

8. REFERENCES

1. SAS® Institute Inc., Cary, North Carolina, United States of America, Version 9.4.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, version 21.0, March 2018.
3. WHO – Drug Dictionary. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden, March 2018 version
4. C.H. Adler, J.N. Caviness, J.G. Hentz, M. Lind, J. Tiede, Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease, Movement disorders: official journal of the Movement Disorder Society, 18 (2003) 287-293.
5. Christopher G. Goetz, Sheng Luo, Lu Wang, Barbara C. Tilley, Nancy R. LaPelle, Glenn T. Stebbins, Handling Missing Values in the MDS-UPDRS, Movement Disorders, 30 (2015) 1632-1638

9. APPENDICES

The following documents are attached as appendices to the SAP:

1. THN102_202_AX3_Analysis_Plan_Draft_1.3_20200115
2. THN102-202_Table_Shells_Final1.0_2020_02_21.docx
3. THN102-202_Listing_Shells_Final1.0_2020_02_21.docx
4. THN102-202_Figure_Shells_Final1.0_2020_02_21.docx

9.1 Tables

Appendix tables defined below will be provided in separate .rtf files for each output.

No	Table Identifier, Title	Output file
Baseline Characteristics		
1	Table 15.1.1.1.S Analysis Sets – Enrolled	THN102-202-T-1501010100S-sets-en.rtf
2	Table 15.1.1.2.T Analysis Sets – Enrolled	THN102-202-T-1501010200T-sets-en.rtf
3	Table 15.1.1.3 Reasons for Exclusions from Analysis Sets – Enrolled	THN102-202-T-1501010300-sets-excl-en.rtf
4	Table 15.1.2 Screening Failures – Enrolled	THN102-202-T-1501020000-scrfail-en.rtf
5	Table 15.1.3.1.S Subject Disposition – Randomised	THN102-202-T-1501030100S-disp-rs.rtf
6	Table 15.1.3.2.S Subject Disposition – Safety	THN102-202-T-1501030200S-disp-ss.rtf
7	Table 15.1.4.1 Number of Subjects by Country and Site – Enrolled	THN102-202-T-1501040100-countrysite-en.rtf
8	Table 15.1.4.2 Number of Subjects by Country and Site – Randomised	THN102-202-T-1501040200-countrysite-rs.rtf
9	Table 15.1.4.3 Number of Subjects by Country and Site – Safety	THN102-202-T-1501040300-ocuntrysite-ss.rtf
10	Table 15.1.5.S Number of Subjects by Visit – Safety	THN102-202-T-1501050000S-visits-ss.rtf
11	Table 15.1.6.1.S Major Protocol Deviations – Safety	THN102-202-T-1501060100S-mpd-ss.rtf
12	Table 15.1.6.2.S Major Protocol Deviations – Full Analysis	THN102-202-T-1501060200S-mpd-fas.rtf
13	Table 15.1.7.1.1.S Demographics – Safety	THN102-202-T-1501070101S-demo-ss.rtf
14	Table 15.1.7.1.2.S Demographics – Full Analysis	THN102-202-T-1501070102S-demo-fas.rtf
15	Table 15.1.7.1.3.S Demographics – Per Protocol	THN102-202-T-1501070103S-demo-pp.rtf
16	Table 15.1.7.2.1.S Baseline Characteristics – Safety	THN102-202-T-1501070201S-basechar-ss.rtf
17	Table 15.1.7.2.2.S Baseline Characteristics – Full Analysis	THN102-202-T-1501070202S-basechar-fas.rtf
18	Table 15.1.7.2.3.S Baseline Characteristics – Per Protocol	THN102-202-T-1501070203S-basechar-pp.rtf
19	Table 15.1.7.3.1.S Baseline Disease Stage – Safety	THN102-202-T-1501070301S-hoehn-ss.rtf
20	Table 15.1.7.3.2.S Baseline Disease Stage – Full Analysis	THN102-202-T-1501070302S-hoehn-fas.rtf
21	Table 15.1.7.3.3.S Baseline Disease Stage – Per Protocol	THN102-202-T-1501070303S-hoehn-pp.rtf
22	Table 15.1.8.1.1.S Prior Medical Conditions – Safety	THN102-202-T-1501080101S-mh-prior-ss.rtf
23	Table 15.1.8.1.2.S Prior Medical Conditions – Full Analysis	THN102-202-T-1501080102S-mh-prior-fas.rtf
24	Table 15.1.8.2.1.S Ongoing Medical Conditions – Safety	THN102-202-T-1501080201S-mh-ongoing-ss.rtf
25	Table 15.1.8.2.2.S Ongoing Medical Conditions – Full Analysis	THN102-202-T-1501080202S-mh-ongoing-fas.rtf
26	Table 15.1.9.1.1.S Prior Medications – Safety	THN102-202-T-1501090101S-priormed-ss.rtf
27	Table 15.1.9.1.2.S Prior Medications – Full Analysis	THN102-202-T-1501090102S-priormed-fas.rtf
28	Table 15.1.9.2.1.T Concomitant Medications – Safety	THN102-202-T-1501090201T-conmed-ss.rtf
29	Table 15.1.9.2.2.T Concomitant Medications – Full Analysis	THN102-202-T-1501090202T-conmed-fas.rtf

30	Table 15.1.10.1.1.T Treatment Duration (days) – Safety	THN102-202-T-1501100101T-trtdur-ss.rtf
31	Table 15.1.10.1.2.T Treatment Duration (days) – Full Analysis	THN102-202-T-1501100102T-trtdur-fas.rtf
32	Table 15.1.10.1.3.T Treatment Duration (days) – Per Protocol	THN102-202-T-1501100103T-trtdur-pp.rtf
33	Table 15.1.10.2.1.T Treatment Compliance (eCRF) – Safety	THN102-202-T-1501100201T-compl-ecrf-ss.rtf
34	Table 15.1.10.2.2.T Treatment Compliance (eCRF) – Full Analysis	THN102-202-T-1501100202T-compl-ecrf-fas.rtf
35	Table 15.1.10.2.3.T Treatment Compliance (eCRF) – Per Protocol	THN102-202-T-1501100203T-compl-ecrf-pp.rtf
36	Table 15.1.11.2.1.T Treatment Compliance (Diary) – Safety	THN102-202-T-1501110201T-compl-diary-ss.rtf
37	Table 15.1.11.2.2.T Treatment Compliance (Diary) – Full Analysis	THN102-202-T-1501110202T-compl-diary-fas.rtf
38	Table 15.1.11.2.3.T Treatment Compliance (Diary) – Per Protocol	THN102-202-T-1501110203T-compl-diary-pp.rtf
Safety Data		
39	Table 15.2.1.1.1.S Overall Summary of TEAEs – Safety	THN102-202-T-1502010101S-teae-sum-ss.rtf
40	Table 15.2.1.1.2.T Overall Summary of TEAEs – Safety	THN102-202-T-1502010102T-teae-sum-ss.rtf
41	Table 15.2.1.2.T Incidence of TEAEs – Safety	THN102-202-T-1502010200T-teae-ss.rtf
42	Table 15.2.1.3.T Incidence of Non-Serious TEAEs – Safety	THN102-202-T-1502010300T-teae-nonserious-ss.rtf
43	Table 15.2.1.4.T Incidence of Serious TEAEs – Safety	THN102-202-T-1502010400T-tesae-ss.rtf
44	Table 15.2.1.5.T Incidence of Related TEAEs – Safety	THN102-202-T-1502010500T-teae-rel-ss.rtf
45	Table 15.2.1.6.T Incidence of Related Serious TEAEs – Safety	THN102-202-T-1502010600T-tesae-rel-ss.rtf
46	Table 15.2.1.7.T Incidence of TEAEs Leading to Discontinuation – Safety	THN102-202-T-1502010700T-teae-disc-ss.rtf
47	Table 15.2.1.8.T Incidence of TEAEs Leading to Death – Safety	THN102-202-T-1502010800T-teae-death-ss.rtf
48	Table 15.2.1.9.T Incidence of TEAEs by Severity – Safety	THN102-202-T-1502010900T-teae-sev-ss.rtf
49	Table 15.2.4.1.1.T Summary of Clinical Laboratory Tests: Haematology – Safety	THN102-202-T-1502040101T-lbh-ss.rtf
50	Table 15.2.4.1.2.T Summary of Clinical Laboratory Tests: Biochemistry – Safety	THN102-202-T-1502040102T-lbb-ss.rtf
51	Table 15.2.4.1.3.T Summary of Clinical Laboratory Tests: Urinalysis – Safety	THN102-202-T-1502040103T-lbu-ss.rtf
52	Table 15.2.4.2.1.T Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety	THN102-202-T-1502040201T-lbh-abnorm-ss.rtf
53	Table 15.2.4.2.2.T Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety	THN102-202-T-1502040202T-lbb-abnorm-ss.rtf
54	Table 15.2.4.2.3.T Clinical Laboratory Tests: Incidence of Urinalysis Abnormalities – Safety	THN102-202-T-1502040203T-lbu-abnorm-ss.rtf
55	Table 15.2.4.3.1.T Clinical Laboratory Tests: Shift Table of Haematology Results – Safety	THN102-202-T-1502040301T-lbh-shift-ss.rtf
56	Table 15.2.4.3.2.T Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety	THN102-202-T-1502040302T-lbb-shift-ss.rtf
57	Table 15.2.4.3.3.T Clinical Laboratory Tests: Shift Table of Urinalysis Results – Safety	THN102-202-T-1502040303T-lbu-shift-ss.rtf
58	Table 15.2.5.1.T Summary of Vital Signs – Safety	THN102-202-T-1502050100T-vs-ss.rtf
59	Table 15.2.5.2.T Incidence of Vital Signs Abnormalities – Safety	THN102-202-T-1502050200T-vs-abnorm-ss.rtf
60	Table 15.2.5.3.T Shift Table of Vital Signs Abnormalities – Safety	THN102-202-T-1502050300T-vs-shift-ss.rtf
61	Table 15.2.6.1.T Summary of ECG Parameters – Safety	THN102-202-T-1502060100T-ecg-ss.rtf
62	Table 15.2.6.2.T Summary of ECG Diagnoses – Safety	THN102-202-T-1502060200T-ecg-diag-ss.rtf
63	Table 15.2.6.3.T Summary of ECG Abnormality Assessments – Safety	THN102-202-T-1502060300T-ecg-abnorm-ss.rtf
64	Table 15.2.6.4.T Shift Table of ECG Abnormality Assessments – Safety	THN102-202-T-1502060400T-ecg-shift-ss.rtf

65	Table 15.2.7.T Summary of Columbia-Suicide Severity Rating Scale – Safety	THN102-202-T-1502070000T-cssrs-ss.rtf
66	Table 15.2.8.T Summary of MDS-UPDRS – Safety	THN102-202-T-1502080000T-updrs-ss.rtf
67	Table 15.2.9.1.T Summary of QUIP-RS Items – Safety	THN102-202-T-1502090100T-quiprs-item-ss.rtf
68	Table 15.2.9.2.T Summary of QUIP-RS Scores – Safety	THN102-202-T-1502090200T-quiprs-score-ss.rtf
69	Table 15.2.10.1.T Summary of Physical Measurements – Safety	THN102-202-T-1502100100T-phys-meas-ss.rtf
70	Table 15.2.10.2.T Summary of Physical Examination Findings – Safety	THN102-202-T-1502100200T-phys-exam-ss.rtf
Efficacy Data		
71	Table 15.3.1.1.1.S Summary of Epworth Sleepiness Scale Score – Full Analysis	THN102-202-T-1503010101S-ess-fas.rtf
72	Table 15.3.1.1.2.S Summary of Epworth Sleepiness Scale Score – Per Protocol	THN102-202-T-1503010102S-ess-pp.rtf
73	Table 15.3.1.2.1.T Summary of Epworth Sleepiness Scale Score – Full Analysis	THN102-202-T-1503010201T-ess-fas.rtf
74	Table 15.3.1.2.2.T Summary of Epworth Sleepiness Scale Score – Per Protocol	THN102-202-T-1503010202T-ess-pp.rtf
75	Table 15.3.2.1.1 Analysis of Epworth Sleepiness Scale Score – Full Analysis	THN102-202-T-1503020101-ess-a-fas.rtf
76	Table 15.3.2.1.2 Analysis of Epworth Sleepiness Scale Score – Per Protocol	THN102-202-T-1503020102-ess-a-pp.rtf
77	Table 15.3.2.2.1 Analysis of Epworth Sleepiness Scale Score (First Period) – Full Analysis	THN102-202-T-1503020201-ess-a-first-fas.rtf
78	Table 15.3.2.2.2 Analysis of Epworth Sleepiness Scale Score (First Period) – Per Protocol	THN102-202-T-1503020202-ess-a-first-pp.rtf
79	Table 15.3.2.3.1 Analysis of Epworth Sleepiness Scale Score Adjusted for Carryover – Full Analysis	THN102-202-T-1503020301-ess-a-carryadj-trt-fas.rtf
80	Table 15.3.2.3.2 Analysis of Epworth Sleepiness Scale Score Adjusted for Carryover – Per Protocol	THN102-202-T-1503020302-ess-a-carryadj-trt-pp.rtf
81	Table 15.3.3.1.1.S Summary of Epworth Sleepiness Scale Responder Rate – Full Analysis	THN102-202-T-1503030101S-ess-resp-fas.rtf
82	Table 15.3.3.1.2.S Summary of Epworth Sleepiness Scale Responder Rate – Per Protocol	THN102-202-T-1503030102S-ess-resp-pp.rtf
83	Table 15.3.3.2.1.T Summary of Epworth Sleepiness Scale Responder Rate – Full Analysis	THN102-202-T-1503030201T-ess-resp-fas.rtf
84	Table 15.3.3.2.2.T Summary of Epworth Sleepiness Scale Responder Rate – Per Protocol	THN102-202-T-1503030202T-ess-resp-pp.rtf
85	Table 15.3.4.1.1 Analysis of Epworth Sleepiness Scale Responder Rate – Full Analysis	THN102-202-T-1503040101-ess-resp-a-fas.rtf
86	Table 15.3.4.1.2 Analysis of Epworth Sleepiness Scale Responder Rate – Per Protocol	THN102-202-T-1503040102-ess-resp-a-pp.rtf
87	Table 15.3.4.2.1 Analysis of Epworth Sleepiness Scale Responder Rate (First Period) – Full Analysis	THN102-202-T-1503040201-ess-resp-a-first-fas.rtf
88	Table 15.3.4.2.2 Analysis of Epworth Sleepiness Scale Responder Rate (First Period) – Per Protocol	THN102-202-T-1503040202-ess-resp-a-first-pp.rtf
89	Table 15.3.5.1.1.S Summary of Absence of Residual Somnolence – Full Analysis	THN102-202-T-1503050101S-ess-resid-fas.rtf
90	Table 15.3.5.1.2.S Summary of Absence of Residual Somnolence – Per Protocol	THN102-202-T-1503050102S-ess-resid-pp.rtf
91	Table 15.3.5.2.1.T Summary of Absence of Residual Somnolence – Full Analysis	THN102-202-T-1503050201T-ess-resid-fas.rtf
92	Table 15.3.5.2.2.T Summary of Absence of Residual Somnolence – Per Protocol	THN102-202-T-1503050202T-ess-resid-pp.rtf
93	Table 15.3.6.1.1 Analysis of Absence of Residual Somnolence – Full Analysis	THN102-202-T-1503060101-ess-resid-a-fas.rtf
94	Table 15.3.6.1.2 Analysis of Absence of Residual Somnolence – Per Protocol	THN102-202-T-1503060102-ess-resid-a-pp.rtf
95	Table 15.3.6.2.1 Analysis of Absence of Residual Somnolence (First Period) – Full Analysis	THN102-202-T-1503060201-ess-resid-a-first-fas.rtf
96	Table 15.3.6.2.2 Analysis of Absence of Residual Somnolence (First Period) – Per Protocol	THN102-202-T-1503060202-ess-resid-a-first-pp.rtf

97	Table 15.3.7.1.1.S Summary of PVT Mean Response Time – Full Analysis	THN102-202-T-1503070101S-pvt-fas.rtf
98	Table 15.3.7.1.2.S Summary of PVT Mean Response Time – Per Protocol	THN102-202-T-1503070102S-pvt-pp.rtf
99	Table 15.3.7.2.1.T Summary of PVT Mean Response Time – Full Analysis	THN102-202-T-1503070201T-pvt-fas.rtf
100	Table 15.3.7.2.2.T Summary of PVT Mean Response Time – Per Protocol	THN102-202-T-1503070202T-pvt-pp.rtf
101	Table 15.3.8.1.1.S Summary of PVT Errors – Full Analysis	THN102-202-T-1503080101S-pvt-err-fas.rtf
102	Table 15.3.8.1.2.S Summary of PVT Errors – Per Protocol	THN102-202-T-1503080102S-pvt-err-pp.rtf
103	Table 15.3.8.2.1.T Summary of PVT Errors – Full Analysis	THN102-202-T-1503080201T-pvt-err-fas.rtf
104	Table 15.3.8.2.2.T Summary of PVT Errors – Per Protocol	THN102-202-T-1503080202T-pvt-err-pp.rtf
105	Table 15.3.9.1.1 Analysis of PVT Mean Response Time – Full Analysis	THN102-202-T-1503090101-pvt-a-fas.rtf
106	Table 15.3.9.1.2 Analysis of PVT Mean Response Time – Per Protocol	THN102-202-T-1503090102-pvt-a-pp.rtf
107	Table 15.3.9.2.1 Analysis of PVT Mean Response Time (First Period) – Full Analysis	THN102-202-T-1503090201-pvt-a-first-fas.rtf
108	Table 15.3.9.2.2 Analysis of PVT Mean Response Time (First Period) – Per Protocol	THN102-202-T-1503090202-pvt-a-first-pp.rtf
109	Table 15.3.10.1.1.S Summary of Montreal Cognitive Assessment Scores – Full Analysis	THN102-202-T-1503100101S-moca-fas.rtf
110	Table 15.3.10.1.2.S Summary of Montreal Cognitive Assessment Scores – Per Protocol	THN102-202-T-1503100102S-moca-pp.rtf
111	Table 15.3.10.2.1.T Summary of Montreal Cognitive Assessment Scores – Full Analysis	THN102-202-T-1503100201T-moca-fas.rtf
112	Table 15.3.10.2.2.T Summary of Montreal Cognitive Assessment Scores – Per Protocol	THN102-202-T-1503100202T-moca-pp.rtf
113	Table 15.3.11.1.1 Analysis of Montreal Cognitive Assessment Scores – Full Analysis	THN102-202-T-1503110101-moca-a-fas.rtf
114	Table 15.3.11.1.2 Analysis of Montreal Cognitive Assessment Scores – Per Protocol	THN102-202-T-1503110102-moca-a-pp.rtf
115	Table 15.3.11.2.1 Analysis of Montreal Cognitive Assessment Scores (First Period) – Full Analysis	THN102-202-T-1503110201-moca-a-first-fas.rtf
116	Table 15.3.11.2.2 Analysis of Montreal Cognitive Assessment Scores (First Period) – Per Protocol	THN102-202-T-1503110202-moca-a-first-pp.rtf
117	Table 15.3.12.1.1.S Summary of Objective Activity Measures – Full Analysis	THN102-202-T-1503120101S-ax3-fas.rtf
118	Table 15.3.12.1.2.S Summary of Objective Activity Measures – Per Protocol	THN102-202-T-1503120102S-ax3-pp.rtf
119	Table 15.3.12.2.1.T Summary of Objective Activity Measures – Full Analysis	THN102-202-T-1503120201T-ax3-fas.rtf
120	Table 15.3.12.2.2.T Summary of Objective Activity Measures – Per Protocol	THN102-202-T-1503120202T-ax3-pp.rtf
121	Table 15.3.13.1.1 Analysis of Objective Activity Measures – Full Analysis	THN102-202-T-1503130101-ax3-a-fas.rtf
122	Table 15.3.13.1.2 Analysis of Objective Activity Measures – Per Protocol	THN102-202-T-1503130102-ax3-a-pp.rtf
123	Table 15.3.13.2.1 Analysis of Objective Activity Measures (First Period) – Full Analysis	THN102-202-T-1503130201-ax3-a-first-fas.rtf
124	Table 15.3.13.2.2 Analysis of Objective Activity Measures (First Period) – Per Protocol	THN102-202-T-1503130202-ax3-a-first-pp.rtf
125	Table 15.3.14.1.S Summary of Diurnal Involuntary Sleep Attacks – Full Analysis	THN102-202-T-1503140100S-sleepattack-fas.rtf
126	Table 15.3.14.2.T Summary of Diurnal Involuntary Sleep Attacks – Full Analysis	THN102-202-T-1503140200T-sleepattack-fas.rtf
127	Table 15.3.15.1.S Summary of Somnolence Episodes – Full Analysis	THN102-202-T-1503150100S-somnolence-fas.rtf
128	Table 15.3.15.2.T Summary of Somnolence Episodes – Full Analysis	THN102-202-T-1503150200T-somnolence-fas.rtf
129	Table 15.3.16.1.S Summary of Other Efficacy-Related Diary Data – Full Analysis	THN102-202-T-1503160100S-diary-other-fas.rtf

130	Table 15.3.16.2.T Summary of Other Efficacy-Related Diary Data – Full Analysis	THN102-202-T-1503160200T-diary-other-fas.rtf
Pharmacokinetic Data		
131	Table 15.4.1.S Summary of Pharmacokinetics Concentrations – PK Analysis Set	THN102-202-T-1504010000S-pc-pk.rtf
132	Table 15.4.2.T Summary of Pharmacokinetics Concentrations – PK Analysis Set	THN102-202-T-1504020000T-pc-pk.rtf

9.2 Listings

Appendix listings defined below will be provided to the sponsor in separate .rtf files for each output.

No	Listing Identifier, Title	Output file
Demographic and Study Population Data		
1	Listing 16.2.1.1 Screening Failures – Enrolled	THN102-202-L-16020101-scrfail-en.rtf
2	Listing 16.2.1.2 Subject Disposition – Randomised	THN102-202-L-16020102-disp-rs.rtf
3	Listing 16.2.1.3 Subject Disposition – Safety	THN102-202-L-16020103-disp-ss.rtf
4	Listing 16.2.1.4 Subject Visits – Enrolled	THN102-202-L-16020104-visits-en.rtf
5	Listing 16.2.3 Exclusions from Analysis Sets – Enrolled	THN102-202-L-16020300-sets-excl-en.rtf
6	Listing 16.2.2.1 Major Protocol Deviations – Safety	THN102-202-L-16020201-mpd-ss.rtf
7	Listing 16.2.2.2 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled	THN102-202-L-16020202-ie-en.rtf
8	Listing 16.2.4.1 Demographics and Baseline Characteristics – Enrolled	THN102-202-L-16020401-demo-en.rtf
9	Listing 16.2.4.2 Baseline Disease Stage – Enrolled	THN102-202-L-16020402-hoehn-en.rtf
10	Listing 16.2.4.3 Medical History – Enrolled	THN102-202-L-16020403-mh-en.rtf
11	Listing 16.2.4.4 Medications and Therapies – Enrolled	THN102-202-L-16020404-cm-en.rtf
12	Listing 16.2.5.1 Exposure to IMP and Compliance – Safety	THN102-202-L-16020501-imp-compl-ss.rtf
Safety Data		
13	Listing 16.2.6.1 Adverse Events: MedDRA Coding	THN102-202-L-16020601-ae-cod.rtf
14	Listing 16.2.6.2 Adverse Events: General – Enrolled	THN102-202-L-16020602-ae-en.rtf
15	Listing 16.2.6.3 Serious Adverse Events – Safety	THN102-202-L-16020603-sae-en.rtf
16	Listing 16.2.6.4 AEs Leading to Discontinuation – Safety	THN102-202-L-16020604-ae-disc-ss.rtf
17	Listing 16.2.6.5 AEs Leading to Death – Safety	THN102-202-L-16020605-ae-death-ss.rtf
18	Listing 16.2.7.1 Laboratory Data – Haematology – Enrolled	THN102-202-L-16020701-lbb-en.rtf
19	Listing 16.2.7.2 Laboratory Data – Biochemistry – Enrolled	THN102-202-L-16020702-lbh-en.rtf
20	Listing 16.2.7.3 Laboratory Data – Urinalysis – Enrolled	THN102-202-L-16020703-lbu-en.rtf
21	Listing 16.2.8.1 Vital Signs – Enrolled	THN102-202-L-16020801-vs-en.rtf
22	Listing 16.2.8.2 Electrocardiogram – Enrolled	THN102-202-L-16020802-ecg-en.rtf
23	Listing 16.2.8.3 Columbia-Suicide Severity Rating Scale – Enrolled	THN102-202-L-16020803-cssrs-en.rtf
24	Listing 16.2.8.4 MDS-UPDRS Questionnaire – Enrolled	THN102-202-L-16020804-updrs-en.rtf
25	Listing 16.2.8.5 QUIP-RS Questionnaire – Enrolled	THN102-202-L-16020805-quiprs-en.rtf
26	Listing 16.2.8.6 Physical Measurements – Enrolled	THN102-202-L-16020806-phys-meas-en.rtf
27	Listing 16.2.8.7 Physical Examinations – Enrolled	THN102-202-L-16020807-phys-exam-en.rtf
28	Listing 16.2.8.8 Pregnancy Testing – Enrolled	THN102-202-L-16020808-preg-en.rtf
29	Listing 16.2.8.9 Safety Laboratory Screening – Enrolled	THN102-202-L-16020809-lab-scrn-en.rtf
Efficacy Data		
30	Listing 16.2.9.1 Epworth Sleepiness Scale – Enrolled	THN102-202-L-16020901-ess-en.rtf
31	Listing 16.2.9.2 Psychomotor Vigilance Test – Enrolled	THN102-202-L-16020902-pvt-en.rtf
32	Listing 16.2.9.3 Montreal Cognitive Assessment – Enrolled	THN102-202-L-16020903-moca-en.rtf
33	Listing 16.2.9.4 Objective Activity Measures – Enrolled	THN102-202-L-16020904-ax3-en.rtf
34	Listing 16.2.9.5 Diary Sleep Data – Enrolled	THN102-202-L-16020905-diary-sleep-en.rtf
35	Listing 16.2.9.6 Diary Exposure Data – Enrolled	THN102-202-L-16020906-diary-imp-en.rtf

Pharmacokinetic Data		
36	Listing 16.2.5.2 Pharmacokinetics Concentrations – Enrolled	THN102-202-L-16020502-pc-en.rtf

9.3 Figures

Appendix figures defined below will be provided to the sponsor in separate .rtf files for each output.

No	Figure Identifier, Title	Output file
Demographic and Study Population Data		
1	Figure 15.1.1.S Flow Chart of Subject Disposition – Enrolled	THN102-202-F-15010100S-disp-en.rtf
2	Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled	THN102-202-F-15010200-anlset-en.rtf
Efficacy Data		
3	Figure 15.3.1.1.S Subject-Level ESS Score Change from Baseline – Full Analysis	THN102-202-F-15030101S-ess-subj-fas.rtf
4	Figure 15.3.1.2.S Subject-Level ESS Score Change from Baseline – Per Protocol	THN102-202-F-15030102S-ess-subj-pp.rtf
5	Figure 15.3.2.1.T Mean ESS Score Change from Baseline by Period – Full Analysis	THN102-202-F-15030201T-ess-mean-fas.rtf
6	Figure 15.3.2.2.T Mean ESS Score Change from Baseline by Period – Per Protocol	THN102-202-F-15030202T-ess-mean-pp.rtf
7	Figure 15.3.3.1.S Subject-Level PVT Performance Change from Baseline – Full Analysis	THN102-202-F-15030301S-pvt-subj-fas.rtf
8	Figure 15.3.3.2.S Subject-Level PVT Performance Change from Baseline – Per Protocol	THN102-202-F-15030302S-pvt-subj-pp.rtf
9	Figure 15.3.4.1.T Mean PVT Performance Change from Baseline by Period – Full Analysis	THN102-202-F-15030401T-pvt-subj-fas.rtf
10	Figure 15.3.4.2.T Mean PVT Performance Change from Baseline by Period – Per Protocol	THN102-202-F-15030402T-pvt-subj-pp.rtf