# STATISTICAL ANALYSIS PLAN

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SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS

**THN102-201**

EudraCT number: 2015-005035-41

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# I. LIST OF ABBREVIATIONS AND KEY TERMS

## List of Abbreviations

| Abbreviations | Description of abbreviations |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Transaminase |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ASCM | Analysis Set Classification Meeting |
| AST | Aspartate Transaminase |
| ATC | Anatomical Therapeutic Chemical |
| BDRM | Blinded Data Review Meeting |
| BMI | Body Mass Index |
| CI | Confidence Intervals |
| CRF | Case Report Form |
| CS | Classification Specifications |
| CSR | Clinical Study Report |
| DBP | Diastolic Blood Pressure |
| DMC | Data Monitoring Committee |
| ECG | Electrocardiogram |
| EDS | Excessive Daytime sleepiness |
| EOS | End of Study |
| ESS | Epworth Sleepiness Scale |
| FAS | Full Analysis Set |
| GD | Global Development |
| H | High |
| ICH | International Conference on Harmonization |
| ITT | Intent-to-Treat |
| L | Low |
| LLN | Lower Limit of Normal |
| LOCF | Last Observation Carried Forward |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified Intent-to-Treat Set) |
| N | Normal |
| PD | Pharmacodynamic |
| PD1-x | Protocol Deviation 1-x |
| PDAS | Pharmacodynamic Analysis Set |
| PK | Pharmacokinetic |
| PKAS | Pharmacokinetics Analysis Set |
| PPS | Per-Protocol Analysis Set |
| PT | Preferred Term |
| QTc | Corrected Q-T Interval |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis Software |
| SBP | Systolic Blood Pressure |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| TLF | Tables, Listings and Figures |
| ULN | Upper Limit of Normal |
| WHO-DD | World Health Organization Drug Dictionary |

## List of Key Terms

| Terms | Definition of terms |
|---|---|
| | |
| Endpoint | A variable that pertains to the trial objectives |
| Variable | Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values. |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data, to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial.

This statistical analysis is coordinated by the responsible biostatistician of the study. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database hard lock.

# 2 FLOW CHART AND VISIT SCHEDULE

This is a prospective, 5-sites, double-blind, randomised placebo-controlled study using a complete 3-way cross-over design in narcoleptic patients with or without cataplexy (type 1 and type 2, respectively) with excessive day sleepiness

Please refer to Study Flow Chart in the protocol and Section 3.2 of this document for more details on the study design and visit schedule.

# 3 STUDY OBJECTIVE(S) AND DESIGN

## 3.1 Study Objective(s)

### 3.1.1 Primary Objective

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

### 3.1.2 Secondary Objectives

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

## 3.2 Study Design

This Phase IIa study is a multi-site, double-blind (investigator and subject), randomised, placebo controlled, 3-way cross-over trial, involving 2 treatments with the combination drug THN102 (Modafinil/Flecainide 300 /3 mg, Modafinil/Flecainide 300 /27 mg) versus Modafinil 300mg/placebo, in narcoleptic patients with or without cataplexy (type 1 and type 2) with

excessive daytime sleepiness despite modafinil treatment. Type 1 patients should represent >70% of overall population. There are 5 periods during the study for each patient: stabilisation under modafinil 300mg/d, the 3-double blind cross-over Period I, II, and III, and washout.

**Table 3-1 Study design overview**

| Period | Design | Week | Modafinil 2 + 1 tablet | Flecainide 2 + 1 capsule |
|---|---|---|---|---|
| Stabilization | Open | 1 + 2 | 200 + 100mg | |
| **Period I** | Double-blind | 3 + 4 | 200 + 100mg | 0, 1 or 9 mg |
| **Period II** | Double-blind | 5 + 6 | 200 + 100mg | 0, 1 or 9 mg |
| **Period III** | Double-blind | 7 + 8 | 200 + 100mg | 0, 1 or 9 mg |
| Washout | Open | 9 | 200 + 100mg | |

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

The 3 double blind periods follow a two-week stabilisation period for modafinil at 300 mg/day (open) and are followed by a one-week washout period with the same modafinil dose.

This Phase IIa study involves a double-blind, randomised, 3-way cross-over design for Period I, II, and III, and consequently implies 6 possible sequences for the 3 treatments:

- A: THN102 300/0 or Modafinil/Flecainide 300/0 mg,
- B: THN102 300/3 or Modafinil/Flecainide 300/3 mg,
- C: THN102 300/27 or Modafinil/Flecainide 300/27 mg

as presented in the following table:

**Table 3-2 Treatment sequence per period**

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

## 3.3 Randomisation

Allocation of a randomized patient number will be done by principal investigator or delegate at each site on Visit 1, using chronological entry. The subject numbers will be distributed in blocks

of 6 for each site with reserve samples maintained at secondary clinical packaging CRO pending further distribution to achieve flexibility and coherence. A 3-digit number between #101 to #160 will be used.

# 4 SAMPLE SIZE

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

# 5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

Detailed criteria for analysis sets will be laid out in data review meeting and the allocation of subjects to analysis sets will be determined prior to database hard lock.

In case this is not specified otherwise, for subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (e.g. ANOVAs with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the randomised sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomised treatment will be excluded from the analysis.

## 5.1 All Randomized Set (RND)

The All Randomized Analysis Set (RND) consists of all randomised subjects.

## 5.2 Modified Intent-To-Treat Set (mITT)

The modified Intent-To-Treat Analysis Set (mITT) consists of all randomised subjects who received treatment for at least one study period and who present no major protocol deviations for relevant parameters measured.

Final criteria and judgments on inclusion of subjects in the mITT are to be documented as part of the Blind Data Review Meeting held prior to unblinding and database lock.

The mITT will be used for the analysis of primary and secondary efficacy endpoints, as well as selected demographic and baseline characteristics.

As per ITT principle subjects will be analysed based on the planned sequence of treatments.

## 5.3 Per Protocol Set (PP)

The Per-Protocol Set (PP) includes all patients who have completed the study without the following major protocol deviations.

- Not between 80% and 120% of doses received (for each of stabilization period, Period 1,2 and 3).
- ESS<14 at baseline (V2).
- Significant concomitant use of prohibited psychotropic medication.
- Stabilization period (V1 to V2) <12 days.

Final criteria and judgments on exclusion of subjects from the PPS are to be documented as part of the Blind Data Review Meeting held prior to unblinding and database lock.

The PPS will be used for the analysis of primary efficacy endpoint only. If PP deviates at least by more than 4 patients from the mITT set, the other key secondary endpoints might also be analyzed on the PP set. Also, selected demographic and baseline characteristics will be summarized for the PPS.

## 5.4 Safety Analysis Set (SAF)

The Safety analysis set (SAF) consists of all subjects who received at least one dose of study drug.

Final criteria and judgments on inclusion of subjects in the SAF are to be documented as part of the Blind Data Review Meeting held prior to unblinding and database lock.

The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

Subjects will be analysed based on the actual sequence of treatments.

## 5.5 Pharmacokinetics Analysis Set (PKAS)

The Pharmacokinetics analysis set (PK) consists of all subjects who have received treatment as per protocol (even if study not completed) and who present no major protocol deviations with an impact on PK.

Final criteria and judgments on inclusion of subjects in the PKAS are to be documented as part of the Blind Data Review Meeting held prior to unblinding and database lock.

The PK is used for all tables and graphical summaries of the PK data.

Subjects will be analysed based on the actual sequence of treatments.

# 6 ANALYSIS VARIABLES

### 6.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Epworth Sleepiness Scale (**ESS**) total score at the end of each post baseline treatment period.

The total score for each subject is the sum of scores on 8 individual fields assessed for these subjects. Both the individual fields score as well as the total score will be recorded on the CRF and therefore no calculation of the total score should be required to derive this endpoint.

Missing scores will not be imputed.

The score of each individual field can range from 0 to 3 and therefore the total score can range from 0 to 24. A higher score signifies a higher chance of dosing off or falling asleep.

An example of the form used to capture this information can be found in the Appendix B of the protocol.

### 6.1.2 Secondary Efficacy Endpoints

- The following secondary efficacy endpoints, as derived from the ESS total score, are:
  - Good response on ESS scale at the end of each post baseline treatment period, defined as a decrease in ESS total score ($ESS_{post\text{-}baseline}$) from baseline ($ESS_{baseline}$) greater than or equal to 3.

$$\Delta ESS = ESS_{baseline} - ESS_{post\text{-}baseline} \geq 3$$

    A baseline ESS total score corresponds to the ESS assessment performed on Visit V2. This endpoint will be derived as a binary variable.

  - Absence of residual somnolence defined as a ESS total score of less than 11:

$$ESS < 11$$

    This endpoint will be derived as a binary variable.
    However, if ESS at baseline (V2) is not 14 or above, the period for a given patient will not be included for this specific efficacy endpoint derivation.

- Daily sleepiness assessment based modified ESS (mESS) to better capture the EDS daily pattern.

  mESS is recorded on the CRF for 3 different subperiods (or time slots) during a normal day (07:00 am to 12:00 pm, 12:00 pm to 17:00 pm and 17:00pm to 22:00 pm). A total of 12 fields by time slot with 0 to 4 as score gives a maximum of 36 points per time slot (am, pm, eve) and a total of 108 for the total. This is in contrast to ESS (maximum is 24). All these fields are recorded on the CRF and therefore no calculation of the total score should be required to derive this endpoint.

$$mESS_{07:00\ to\ 22:00} = mESS_{07:00\ to\ 12:00} + mESS_{12:00\ to\ 17:00} + mESS_{17:00\ to\ 22:00}$$

  An example of the form used to capture this information can be found in the Appendix C of the protocol.

- 14-item fatigue scale overall score as well as the physical symptoms subscale score and a mental symptom subscale score will be recorded on the CRF and therefore no calculation should be required to derive this endpoint.

  An example of the form used to capture this information can be found in the Appendix D of the protocol.

- European Scale of Quality of Life (EQ-5D)

  The EQ-5D is the only efficacy related questionnaire assessing the status on the day of visit and not over the past week. It has two parts:

  - The first part is a descriptive system that classifies respondents into one of five distinct health states/dimensions. The descriptive system consists of the following five dimensions (Mobility (MO), Self-care (SC), Usual activities (UA), Pain/discomfort (PD), Anxiety/depression (AD). The possible score for each dimension ranges is recorded on the CRF.

In addition, the Total score is recorded in the CRF. A higher score signifies a higher number of symptoms present.

- The second part is a 100 mm visual analog scale (EQ-VAS) responses recorded in the CRF. An increase in VAS indicates an improvement in health state.

An example of the form used to capture this information can be found in the Appendix E of the protocol.

- PGI-S (Patient Global Impression for Severity)

  The global score is recorded in the CRF in every visit and in addition the change from baseline (PGS-C) is also recorded for post-baseline visits V3, V4, V5 and V6 (after V2) and at V6 vs. V5.

  In addition, the following endpoint, will be derived for each subject based on the initial PGI-C global score obtained, at each post baseline treatment period (visits V3, V4, V5):
  - A subject is considered a PGI-C responder if a PGI-C score of_1='Very much improved' or 2= 'Much improved', has been recorded and a non-responder if any other PGI-C score has been recorded.
    This endpoint will be derived as a binary variable.

- CGI-S (Clinical Global Impression for Severity) for sleepiness and cataplexy

  The sleepiness, cataplexy (for type 1 patients only) and global score is recorded in the CRF in every visit for severity and in addition the change from baseline is also recorded for post-baseline visits V3, V4, V5 and V6 (after V2) and at V6 vs. V5.

  In addition, the following endpoint, will be derived for each subject based on the initial CGI-C global score obtained, at each post baseline treatment period (visits V3, V4, V5):
  - A subject is considered a CGI-C responder if a CGI-C score of_1='Very much improved' or 2= 'Much improved', has been recorded and a non-responder if any other CGI-C score has been recorded.
    This endpoint will be derived as a binary variable.

- Information reported on patient diary – completed at home daily:
  - Number of diurnal involuntary episodes of sleepiness.
  - Number of diurnal involuntary sleep attacks.
  - Number and duration of voluntary naps and total duration during day time.
  - Number of cataplexy episodes: partial vs generalized (type 1 only).
  - Occurrence of hypnagogic hallucinations and sleep paralysis (type 1 only).
  - Nocturnal awakening.
  - Total duration of nocturnal sleep time.

  All this information is recorded on the CRF.

  The total number of occurrences recorded during only the last (second) week for each patient will be divided by the total number of days (7 days), with non-missing data to derive the mean daily number of occurrences recorded for the patient for each given visit interval. Records from the last 7 days of the 2-week period between 2 visits will be used for this derivation. Subjects with between visits period longer or shorter than 2 weeks will assessed on an individual case during the blinded review of the data. If the

number of occurrences is missing for part of the day (either day or night symptoms) then a half day will be used in the denominator.

For each of these quantities the mean daily occurrence will be calculated for each patient for each treatment from stabilization to washout.

### 6.1.3 Exploratory Efficacy Endpoints

Not applicable

### 6.1.4 Other Efficacy Variables

Not applicable

## 6.2 Safety Variables

Safety will be assessed by evaluation of the following variables:

- Adverse events (TEAEs; frequency, severity, seriousness, and relationship to study drug).
- Clinical laboratory variables (hematology, serology, biochemistry including liver enzymes and total bilirubin, and urinalysis).
- Vital signs (systolic and diastolic blood pressure and heart rate).
- 12-lead electrocardiogram (ECG) (HR, RR interval, PR interval, QRS complex, QT interval, QTc interval, QTcF interval, sinus rhythm evaluation).
    - The corrected QT interval by Fredericia (QTcF) (ms) will be derived based on the formula: $QTcF = \frac{QT}{\sqrt[3]{RR}}$ where QT expressed in (ms) and RR expressed in (s) are captured in the CRF.
- Physical examination.
- Beck Depression Inventory (BDI) evaluation for depressive symptoms total score and score for suicidal thoughts.

**Run-in Adverse Event**

Adverse events with onset before the start of the 'Stabilization' period, will be recorded separately.

**Stabilisation period Adverse Event**

Adverse events observed after starting administration of Modafinil drug at 'Stabilisation' period and before the start of the Treatment 'Period I', will be recorded separately

**Treatment Emergent Adverse Event (TEAE)**

**A TEAE** is defined as an adverse event observed after starting administration of the test drug/comparative drug at Period I up until the end of Period III and before the start of the Washout period. If the adverse event onset check box is marked as "Period I or Period II or period III", then the adverse event will be considered treatment emergent and will be assigned to the treatment corresponding that period of the treatment sequence.

**Washout period adverse event**

Adverse events observed at Washout period until end of study, will be recorded separately.

A drug-related AE is defined as any AE with at least possible relationship to study treatment as assessed by the investigator or with missing assessment of the causal relationship.

A condition-related AE is defined as any AE with at least possible relationship to study condition as assessed by the investigator or with missing assessment of the causal relationship.

## 6.3 Pharmacokinetic Variables

Plasma concentrations for modafinil and flecainide at each visit from V1 to V5.

In case of an additional visit for whatever reason during the study or within 80 hours after V5 or of a prolonged visit at site, another PK sample will be collected to measure plasma concentration.

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

## 6.4 Pharmacodynamic Variables

Not applicable

## 6.5 Other Variables

- The duration of exposure

  For each subject, the Length of Time on treatment will be calculated in days, for each of these periods:

  - Stabilisation
  - Period I
  - Period II
  - Period III
  - Washout

  using the following formula

  ('Date last dose of study drug' - 'Date first dose*) + 1

  for each of the periods of Stabilization, Period I, Period II, Period II and Washout, where first and last dose would be retrieved by the Patient Diary for each period.
  For Stabilisation, Period I, Period II and Period III the protocol calls for ±1 day deviation in each period, i.e. a range between 13 to 15 days. The following definitions will be used for variations in duration of exposure and thus to define the type of deviation and thus the impact on population and analysis:

  - As per protocol: ± 1 day (range between 13 and 15 days)
  - Minor deviation: ± 2 days (12 or 16 days)
  - Marked deviation: ± 3 days (11 or 17 days)
  - Major deviation: ± 4 days (10 or 18 days)

  Subjects with a minor deviation in Period I, II, or III may be included for the involved period in the mITT population. Subjects with a marked deviation will be discussed during the Blind Data Review Meeting and will be included in treatment providing no other confounding factor is detected for that period. Subjects with major deviations will be excluded from mITT population.

  It is acceptable to keep a subject with 10 days in Stabilisation if the modafinil dose before starting study was at 300 mg.

For Washout period the duration as per protocol is 7 ± 2 days (range 5 to 9 days) but no deviation will be considered for excluding patient from assessment,

- Percent compliance

  Compliance to the dosing schedule will be examined for subjects in the SAF population for each of the following periods:

  - Stabilization
  - Period I
  - Period II
  - Period III
  - Washout

  Compliance for each of period will be based on the 1st control level compliance recorded in the relevant CRF page for modafinil and for flecainide as:

$$\frac{\text{(number of units given – number of units returned)}}{\text{( number of days for the period according to visit days * 3)}} \times 100$$

- Prior, concomitant and post treatment medication

Prior medication is defined as medication with at least one dose taken before the date of the first dose of study drug. Therefore, prior medication will include medications with:

- a start date and end date before the date of first dose
- a start date before the date of first dose but end date is after date of first dose (inclusive) or if it is marked as ongoing.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug up until the end of Period III. Therefore, concomitant medication will include medications with:

- a start date between the date of first dose (inclusive) and the date of last dose (inclusive)

Post treatment medication is defined as medication with a start date after the date of last dose i.e. started after the end of Period III and during Washout to end of study period.

# 7 STATISTICAL METHODOLOGY

## 7.1 General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g.10%, 25%, 75% and 90%) will be mentioned in the relevant section. In addition, for continuous PK parameter $C_{ss}$ if available, the coefficient of variation will be calculated and for $C_{ss}$ the geometric mean and CV will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%.

Summaries based on mITT and PP (e.g. disposition, baseline and efficacy data) will be presented by planned treatment/sequence, unless specifically stated otherwise. Safety analysis and other summaries based on SAF will be presented by actual treatment/sequence received.

All statistical comparisons will be made using two sided tests at the $\alpha$=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference, all alternative hypotheses will be two-sided, unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using SAS® Version 9.4 or higher. Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.

For the definition of subgroups of interest please refer to section 7.8.

## 7.2 Study Population

### 7.2.1 Disposition of Subjects

- Number and percentage of subjects, randomized, exposed, completed and discontinued the study, by primary reason for study discontinuation, for randomized subjects by treatment sequence and overall;
- Number and percentage of subjects in each analysis set, for all subjects, by treatment sequence and overall;
- Number and percentage of subjects excluded from PP by reason for exclusion defined in section **Erreur ! Source du renvoi introuvable.**, by treatment sequence, and overall, for mITT.

### 7.2.2 Protocol Deviations

Protocol deviations data listing will be provided by site and subject for each period.

### 7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed by treatment sequence and subject and summarized by descriptive statistics by treatment sequence and overall.

Descriptive statistics for age, weight, body mass index (BMI) and height at study entry will be presented. Frequency tabulations for sex will be presented. This will be done for the, mITT and SAF by treatment sequence and overall and if needed for additional analysis sets.

Number and percentage of subjects randomized in each site will be presented by treatment sequence and overall for the SAF.

Medical history is coded in MedDRA. Medical and surgical history will be listed by treatment sequence and subject.

### 7.2.4 Prior and Concomitant Medications

Prior, concomitant medications are coded with WHO-DD, and will be listed by treatment sequence, subject and period by therapeutic subgroup (ATC 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name.

A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

## 7.3 Study Drugs

### 7.3.1 Exposure

The following information on drug exposure will be presented for each treatment group for the SAF:

Duration of exposure will be summarized in two ways for each period.

- Descriptive statistics.
  Frequency tabulation (counts and percentages of subjects) based on the following duration categories for Period I, II and III
    - As per protocol: ± 1 day (range between 13 to 15 days)
    - Shorter exposure:12 days or less
    - Longer exposure: 16 days or more
    - Minor deviation: ± 2 days (12 or 16 days)
    - Marked deviation: ± 3 days (11 or 17 days)
    - Major deviation: ± 4 days (10 or 18 days)

### 7.3.2 Treatment Compliance

Compliance with the dosing schedule will be examined for subjects in the SAF.

Percent overall compliance will be summarized in two ways:

- Descriptive statistics.
- Percent compliance will be categorized according to the following categories:
    - less than 60%
    - at least 60%, less or equal to 79%
    - at least 80%, less or equal to 100%
    - greater than 100% and less or equal to 120%
    - greater than 120%

## 7.4 Analysis of Efficacy

### 7.4.1 Analysis of Primary Endpoint(s)

The primary analysis will be performed on the ESS total score on the mITT.

The primary endpoint variable will be summarized by treatment group, overall.

In order to compare the mean changes across the THN102 treatment groups, two null hypotheses will be constructed:

- $H_{01}$: Effect of THN102 high dose (Modafinil 300mg/27mg) is equal to effect of placebo (Modafinil 300mg/0mg)
- $H_{02}$: Effect of THN102 low dose (Modafinil 300mg/3mg) is equal to effect of placebo (Modafinil 300mg/0mg)

The accompanying alternative hypotheses are respectively:

- $H_{11}$: Effect of THN102 high dose (Modafinil 300mg/27mg) is NOT equal to effect of placebo (Modafinil 300mg/0mg)
- $H_{12}$: Effect of THN102 low dose (Modafinil 300mg/3mg) is NOT equal to effect of placebo (Modafinil 300mg/0mg)

The ESS total scores will be subjected to Analysis of Variance (ANOVA) using a linear mixed effects model setting, with maximum likelihood estimates and Kenward-Rogers adjustment for degrees of freedom, suitable for this 3x3 crossover design. The model will include the treatment, period and sequence as fixed effects and the subject nested within sequence as a random effect and possibly baseline ESS score at V2 as covariate.

Treatment least square means and mean differences will be reported with their standard errors and 95% confidence intervals. The significance of the differences between the THN102 high dose (Modafinil 300mg/27mg) and modafinil alone (placebo) will be assessed at the two-sided 5% level. The THN102 low-dose treatment (Modafinil 300mg/3mg) will be analyzed in a similar fashion. In addition, the significance of the differences between the average THN102 low and high dose (i.e. both THN doses together) versus modafinil alone (placebo) will be assessed at the two-sided 5% level.

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

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

Results may also be presented graphically as well.

Supportive analysis:

To examine the robustness of the results, an analysis of the primary endpoint will be conducted on the per protocol set. The method used for this analysis will be identical to the primary analysis described in section 7.4.1.1.

### 7.4.2 Analysis of Secondary Endpoints

The continuous secondary efficacy parameters, such as the modified ESS for daily pattern at each day separately for each set (am:7:00 to 12:00; pm:12:00 to 17:00; eve: 17:00 to 22:00: Global: 7:00 to 22:0), the EQ-5D score and VAS, the 14-item fatigue score, and the derived endpoints from the patient diaries will be analysed in the mITT set using the same method as for the primary endpoint.

Categorical secondary efficacy parameters of Good Response on ESS and the ESS absence of residual somnolence as rates of responders will be compared in the mITT set between the each THN102 dose group and modafinil alone using a Mc-Nemar test. The following categorical secondary efficacy parameters, EQ-5D category responses, PGI-S and PGI-C score, the CGI-S and CGI-C scores for sleepiness and cataplexy, will be compared using the Wilcoxon signed-rank test for paired ordinal data.

Additional methods might be explored if needed.

### 7.4.3 Analysis of Exploratory Endpoints

Not applicable.

### 7.4.4 Analysis of Other Variables

Not applicable.

## 7.5 Analysis of Safety

All analysis of safety will be presented by treatment for SAF, unless specified otherwise.

### 7.5.1 Adverse Events

Adverse events for Period 1 Period 2 and Period e will be presented by treatment and total active treatment (THN102 300/3 and THN102 300/27).

The coding dictionary for this study will be MedDRA. It will be used to summarize AEs by SOC and PT.

All information obtained on adverse events will be listed by treatment sequence, subject and period. An adverse event will be assigned to the period according to its onset (or worsening, respectively). An adverse event starting in one period and continuing into the next period is counted only in the onset period.

An overview table will include the following details:

- Number of TEAEs,
- Number and percentage of subjects with TEAEs,
- Number of drug related TEAEs,
- Number and percentage of subjects with causally drug related TEAEs,
- Number of serious TEAEs,
- Number and percentage of subjects with serious TEAEs,
- Number of serious drug related TEAEs,
- Number and percentage of subjects with serious drug related TEAEs,
- Number of TEAEs leading to permanent discontinuation of study drug,
- Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug, and
- Number of deaths.

In addition, a similar overview table will be provided for each of Stabilization and Washout period AEs by treatment (Modafinil alone).

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized for each treatment. Summaries will be provided for:

- TEAEs
- drug related TEAEs,
- serious TEAEs,
- drug related serious TEAEs,
- TEAEs leading to permanent discontinuation of study drug,
- drug related TEAEs leading to permanent discontinuation of study drug,

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized for each treatment.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by severity and by relationship to study drug. In the

subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity or relationship, then the subject will be counted only once with the worst severity and highest degree of relationship, however, if any of the severity or relationship values are missing then the subject will be counted only once with missing severity or relationship. In the adverse event count, the adverse events will be presented in each category they were classified to. Drug related TEAEs will be presented in a similar way by severity only.

### 7.5.2 Clinical Laboratory Evaluation

All laboratory data will be listed by treatment sequence, subject, and period and if normal ranges are available abnormalities will be flagged.

Quantitative clinical laboratory variables, i.e. hematology and biochemistry will be summarized using mean, standard deviation, minimum, maximum and median for each treatment.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented for each treatment group.

#### 7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria for liver tests – defined as Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

**Table 7-3 Definition of Liver Safety Monitoring and Assessment rules**

| Parameter | Criteria |
|---|---|
| ALT | > 3xULN |
| | > 5xULN |
| AST | > 3xULN |
| | > 5xULN |
| Total Bilirubin | > 1xULN |
| | > 1.5xULN |
| ALP | > 1.5xULN |
| | > 2xULN |
| ALT or AST AND Total Bilirubin(*) | ALT or AST > 3x ULN & TBL > 2x ULN |

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzyme and total bilirubin tests during the investigational period will be presented by treatment group.

### 7.5.3 Vital Signs

All vital signs data will be listed by treatment sequence, subject, period. If ranges are available abnormalities (and relevant orthostatic changes) will be flagged.

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate sitting and when requested standing at 3 min) will be summarized using mean, standard deviation, minimum, maximum and median by treatment.

### 7.5.4 Electrocardiograms (ECGs)

ECG data from 12-lead assessments will be listed by treatment sequence, subject and period. Abnormalities will be flagged.

ECG variables (expect for QTc) will be summarized using mean, standard deviation, minimum, maximum and median for each treatment group.

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results as assessed by investigator for the 12 lead ECG will be tabulated by treatment group.

### 7.5.5 Pregnancies

A detailed listing of all pregnancies will be provided by treatment sequence, subject and period.

### 7.5.6 Other Safety-Related Observations

**BDI**

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

## 7.6 Analysis of PK

### 7.6.1 Estimation of Pharmacokinetic Parameters

The relevant PK parameters will be calculated using WinNonlin software (Pharsight Corp, Mountain View, California, US) by a PK expert if possible.

### 7.6.2 Statistical Analysis

All subjects of the PK analysis set will be included in the pharmacokinetic data analysis. Individual PK data for all randomised subjects will be listed

All concentrations below LLOQ, above ULOQ, or missing data will be labeled as such in the concentration data listings. Concentrations below LLOQ will be treated as zero in summary statistics for concentration data. Concentrations above ULOQ will be replaced by ULOQ. A geometric mean will not be reported if the dataset includes zero values. Not reported concentration (N.R.) will be excluded from the summary statistics, and for PK analysis.

Descriptive statistics will be provided for concentrations and PK parameter (if available). These will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), min and max. For concentration summaries in addition frequency (n, %) of concentrations below the lower limit of quantification (LLOQ) and above the upper limit of quantification (ULOQ) and not reported concentration (N.R.) will be provided.

Any additional PK analysis will be considered on a separate document and is out of scope for the reporting activity described in this SAP.

## 7.7 Analysis of PD

Not applicable.

## 7.8 Subgroups of Interest

Primary efficacy endpoint and selected secondary efficacy endpoints and or selected safety variables may be summarized by the treatment group for the subgroups defined based on the categorized variables listed below:

**Table 7-4 Subgroup analysis**

| Grouping variable | Subgroups |
|---|---|
| **Sex** | Female |
| | Male |
| **Narcolepsy type at V1** | Type 1 |
| | Type 2 |

## 7.9 Other Analyses

Not applicable.

## 7.10 Interim Analysis

No interim analysis is planned.

## 7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

### 7.11.1 Missing Data

As a general principle, no imputation of missing data for other variables will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment group, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

Subjects who change their planned treatments or doses or have missing outcome measurements will not be excluded from the primary analysis in the mITT set unless considered as major violations. Major and minor violations will be defined in the Section 5.3.1. Under the assumption that outcomes are missing at random, the mixed-model can propagate uncertainty due to missing data into estimates of treatment efficacy and other quantities of interest. So missing data will not be imputed or replaced prior to the analysis.

### 7.11.2 Outliers

All values will be included in the analyses.

### 7.11.3 Visit-Periods

The study protocol gives the overall study schedule and the permissible intervals for these visits expressed as the number of days relative to Visit 1 start of stabilazation. The total time each subject will be in the study will not exceed 15 weeks with a maximum of 4 weeks for the pre-investigational period and a maximum of 11 weeks for the investigational period.

Analyses will not exclude subject data due to the subject's failure to comply with the visit schedule in general unless specified otherwise.

If a subject repeats a specific period then, the later occasion will be considered for the intended analysis, but all occasions will be listed.

# 8 DOCUMENT REVISION HISTORY

| Version | Date | Changes | Comment/rationale for change |
|---|---|---|---|
| 1.00 | 26-MAR-2018 | NA | Document finalized |
| 2.00 | 24-JAN-2019 | Section 3.3 Randomization | Correction on the text referring to the 3-digit number between #101 to #160 to be used, as per updates present in Clinical Study Protocol V. 4.1. |
| | | Section 5.3 Per Protocol Set (PP) | Amended definition of PP based on team decision. |
| | | Section 6.2.1 Secondary Efficacy Variables PGI-C/CGI-C | Text added to describe derivation of PGI-C/CGI-C responders. |
| | | Section 6.2 Safety Variables ECG | Text added to describe the intention to derive the corrected QT interval using Fredericia QTcF formula. |
| | | Section 6.5 Percent compliance | Text amended to state the derivation of compliance based on the 1st control level compliance derivation only as more reliable. Text on second level compliance was removed as per team decision. |
| | | Section 7.2.1 Disposition of Subjects | Text on disposition of subjects during screening/run-in period removed, due to data not planned to be collected in the CRF . |
| | | Section 7.5.1 Adverse Events | Text added to state that Adverse events for Period 1 Period 2 and Period will be presented also for total active treatment (THN102 300/3 and THN102 300/27). |
| | | Section 7.3.2 Treatment Compliance | Percent compliance categories were amended to expand to 120% and beyond. |
| | | Section 7.5.4 Electrocardiograms | Text added to state that QTc collected in CRF will not be summarized in tables. Instead QTcF will be added. |
| | | Section 7.11.3 Visit-Periods | Added text stating the proposed intended approach of analysis in case of repeated periods. |
| | | Section 9 References | Added latest protocol version. |

# 9 REFERENCES


| | |
|---|---|
| [1] | ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics) |
| [2] | ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics) |

| | |
|---|---|
| [3] | 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 |
| [4] | WHO – Drug Dictionary. WHO Collaborating Centre for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden. |
| [5] | THN102-201: SAFETY AND EFFICACY OF THN102 ON SLEEPINESS IN NARCOLEPTIC PATIENTS, CLINICAL STUDY PROTOCOL version 4.1, Amendment 1, 28 April 2017. |

# 10 APPENDICES

## 10.1 Appendix 1: Key Contributors and Approvers

### List of Key Contributors and Approvers

**Key Contributors**

The following contributed to or reviewed this Statistical Analysis Plan as relevant to their indicated discipline or role.

| **Primary author (s)** | |
|---|---|
| | |

# Author and Approver Signatories

XXXXX Senior Biostatistician, was the study statistician for this study.

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