STATISTICAL ANALYSIS PLAN

Study: RL0007

Product: Rotigotine

A REMOTE, OPEN-LABEL, LONG-TERM FOLLOW-UP STUDY TO DETERMINE THE SAFETY, TOLERABILITY, AND EFFICACY OF ROTIGOTINE TRANSDERMAL SYSTEM AS MONOTHERAPY IN ADOLESCENTS WITH RESTLESS LEGS SYNDROME

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LIST OF ABBREVIATIONS

AE	adverse event
ARDL	actual Rotigotine dose level
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CGI	Clinical Global Impressions
eCRF	electronic Case Report form
ECG	12-lead electrocardiograms
EoM	end of the Maintenance Period
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
HLT	High Level Term
ICH	International Council for Harmonization
IGF-1	insulin-like growth factor 1
IRLS	International Restless Legs Syndrome Study Group Rating Scale
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mMIDI	Modified Minnesota Impulsive Disorder Interview
PD	pharmacodynamic
PDILI	potential drug induced liver injury
PK	pharmacokinetic
PKS	Pharmacokinetic Set
PRD	planned Rotigotine dose
PRDL	planned Rotigotine dose level
PT	preferred term
RLS	Restless Legs Syndrome
RLS-6	Restless Legs Syndrome - 6 Rating Scales
RLS-QoL	restless legs syndrome quality of life
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SoM	Start of Maintenance Period
SS	Safety Set

T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document contains details for the statistical analyses of study RL0007 supporting the clinical study report which has been written in consideration of the International Council for Harmonization (ICH)/Food and Drug Administration (FDA) E9 Guidance documents (Phillips et al, 2003). The reader is referred to the study protocol and the electronic Case Report form (eCRF) for details of study conduct and data collection.

The SAP describes the statistical principles that are applied for the analyses as well as tables and listings that are foreseen for this study. Changes in the statistical methodology result in a SAP amendment. Amendments to this document will be finalized prior to database lock.

This study was terminated early, and therefore the analysis described in this analysis plan is much more limited than that described in the protocol.

2 PROTOCOL SUMMARY

2.1 Study objectives

The primary objective of this study is to assess the long-term safety and tolerability of rotigotine treatment in adolescents with idiopathic Restless Legs Syndrome (RLS).

The secondary objective of this study is to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.

2.1.1 Efficacy variables

2.1.1.1 Secondary efficacy variables

The key efficacy variables are change from Baseline at Visit 9 in International Restless Legs Rating Scale (IRLS) sum score, Clinical Global Impressions (CGI) Item 1 and Restless Legs-6 Rating Scales (RLS-6):

- Changes from Baseline in IRLS sum score at Visit 9
- Changes from Baseline in CGI Item 1 at Visit 9
- Changes from Baseline in RLS-6 at Visit 9

2.1.1.2 Other efficacy variables

Other efficacy variables are:

- Changes from Baseline in IRLS sum score at all visits except Visit 9
- Changes from Baseline in CGI Item 1 at all visits except Visit 9
- Changes from Baseline in RLS-6 at all visits except Visit 9

2.1.2 Safety variables

2.1.2.1 Primary safety variables

The primary safety variables are:

- Occurrence of treatment-emergent adverse events (TEAEs)
- TEAEs leading to permanent withdrawal of study medication

2.1.2.2 Other safety variables

Other safety variables are:

- Changes from Baseline in 12-lead electrocardiograms (ECGs)
- Changes from Baseline in vital signs (including orthostatic assessment)
- Changes from Baseline in hormone status
- Changes from Baseline in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes in menstrual function for all female subjects
- Changes from Baseline in Modified Minnesota Impulsive Disorder Interview (mMIDI)
- Changes from Baseline in body weight, height, and calculated body mass index (BMI)

2.1.3 Other variables

Other variables are:

- Plasma concentrations of unconjugated rotigotine
- Subject Quality of Life Questionnaire

2.2 Study design and conduct

This is a Phase 3, remote, open-label, LTFU study of monotherapy administration of the rotigotine transdermal system. Subjects entering this study from the previous rotigotine study in adolescents (SP1006) must have tolerated the first dose level of rotigotine in that study without meeting the withdrawal criteria.

The study will be conducted using the remote study model, which uses telemedicine technology (i.e., Science 37 PLATFORM) for interactions between the investigator/study staff and study subjects/legal representatives.

The study will begin with a Titration Period of up to 3 weeks (at maximum) with the aim of achieving the individually optimized dosage. During the Titration Period, investigators should determine at each visit whether the subject has reached his or her optimal dose prior to completing the scheduled assessments. Once subjects have reached their optimal dose, they should proceed to Maintenance Period (Visit 5) and complete those assessments.

Titration will be followed by a Maintenance Period of up to 1 year. Dose adjustment of rotigotine is allowed at any time during the Maintenance Period, based on clinical judgment up to a maximum dose of 3mg/24h. At the End of Maintenance (EoM), subjects will enter a 4-day Taper Period followed by a 30-day Safety Follow-Up.

Visits will be scheduled every week during the Titration Period, every 3 months for the Maintenance Period, and at the end of the Safety Follow-Up.

2.3 Determination of sample size

No statistical sample size calculation was performed for this study. Initially, a maximum of 138 subjects from a prior study (SP1006) are expected to participate in the current study, based on the assumption that all planned subjects from SP1006 will roll-over into the present study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3 or higher. All tables and listings will use Courier New font size 9.

A complete set of raw data listings containing both all documented data and all calculated data (eg, changes from Baseline) will be generated.

Unless otherwise noted, all summaries will be displayed by the final dose group (rotigotine 1mg/24h, rotigotine 2mg/24h and rotigotine 3mg/24h). The 'final dose' is the final titrated or back-titrated dose level administered at the start of the Maintenance Period. The 'final dose' for subjects who withdrew before the Maintenance Period is defined as the last dose taken. A summary with all dose groups combined (i.e., total column) will be presented for the demographic and Baseline characteristics, and for the prior and concomitant medications.

In general, summary statistics for quantitative variables will include n (number of available measurements), arithmetic mean, SD, median, minimum, and maximum. For categorical parameters, descriptive statistics will consist of the number and percentage of subjects in each category. Unless otherwise specified the denominator for calculating percentages will be the number of subjects in the respective population.

Unless otherwise noted, all percentages with the exception of 0 and 100 will be expressed to 1 decimal place. 100% will be presented as integer. If a category has the frequency 0 the percentage value will be omitted. Mean and median changes from baseline lower than the minimal displayable change will be displayed without sign (e.g., -0.00 will be displayed as 0.00).

For descriptive statistics, the following rules regarding decimal places will apply:

- n will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.
- Minimum and maximum will have the same number of decimal places as the original value.

Unless otherwise noted, listings will be sorted by optimal dose, site-subject number, parameter (if applicable) and time point (if applicable). All listings will include assessments on scheduled and unscheduled visits; data from unscheduled visits will appear in chronological order together with the scheduled time points – a repeated measurement will appear directly after the time point for which the repeat measurement was performed.

In individual subject data listings, values are presented as documented in eCRF using the same number of digits. Derived data are presented with 1 digit more than the original data used in the derivation. Dates are presented as documented without imputing incomplete dates.

3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

The relative day of a visit or an event with respect to the first application of study medication will be presented in subject data listings. Relative days will be calculated as follows:

- If the start (stop) date occurred prior to the first application of study medication, the relative day is calculated as start (stop) date minus date of first patch application. That means that in subject data listings, relative days based on this situation will be preceded by a '-'.
- If the start (stop) date occurred on or after the first application of study medication but prior to the last patch removal, the relative day is calculated as start (stop) date minus date of first patch application + 1.
- If the start (stop) date occurred after the date of last patch removal, the relative day is calculated as start (stop) date minus date of first patch application + 1. In subject data listings, relative days based on this situation will be preceded by a '+'.

Relative days will not be presented for partial or missing dates.

3.2.1.2 Date of last patch removal

The date of last patch application is documented on the Study Termination page of the eCRF. If the date of last patch application on this page is missing the last available kit start date on the Drug Accountability log form, with less patches returned than dispensed, will be used as the date of last patch application. Thus, the date of the last patch removal is defined as the date of the last patch application + 1.

3.2.2 Study periods

The following time periods are defined for this study.

- Screening Period:

  The Screening Period starts with Visit 1 and ends the day before the date of the first patch application.

- Titration Period:

  The Titration Period starts at the day of the first patch application and ends the day before the date of Visit 5. In case of a premature withdrawal before Visit 5, the Titration Period ends at the day of the Withdrawal Visit. If the Withdrawal Visit is missing or the date of the last patch removal is before the Withdrawal Visit, the Titration Period ends at the day of last patch removal.

- Maintenance Period:

  The Maintenance Period starts at Visit 5 and ends at Visit 9. If the subject withdraws prior to Visit 9, the Maintenance Period ends at the day of the Withdrawal Visit date or the last patch removal date (or last known patch removal date), whichever is earlier.

- Taper Period:

  The Taper Period starts at the date of last maintenance patch removal and ends at the day of last patch removal. If the day of last patch removal is on the date of last maintenance patch removal, i.e., no de-escalation was performed for any reason, no Taper Period is defined for this subject.

- Treatment Period:

The Treatment Period comprises the Titration Period, the Maintenance Period, the Taper Period, i.e., it starts with the day of first patch application and ends on the maximum end date of the Titration, Maintenance and Taper periods.

- Safety Follow-Up Period:

  The Safety Follow-Up Period starts the day after the end of the Treatment Period and ends at the date of the last study assessment. However, AEs starting within 30 days following the date of last patch removal will be included for analysis, even if the start date is after the date of last study assessment.

3.2.3 Visit mapping

The visits are planned for the follow days:

Visit	Day	Visit Window
Visit 1 (Screening)	Day -4 to Day -1	
Visit 2, Day 1	Day 1	
Visit 3, Day 8	Day 8	± 3 Days
Visit 4, Day 15	Day 15	± 3 Days
Visit 5 (SoM)	Day 22 (or after reaching optimal dose)	± 3 Days
Visit 6 (Month 3)	90 Day after SoM	± 14 Days
Visit 7(Month 6)	180 Day after SoM	± 14 Days
Visit 8 (Month 9)	270 Day after SoM	± 14 Days
Visit 9 (EoM)	360 Day after SoM	± 14 Days
Safety Follow-Up	30 Days after End of Taper Period	± 5 Days

During the Titration Period, the investigator should determine whether the subject has reached his/her final titrated dose level prior to completing the scheduled assessments for that visit. Subjects who have reached their final dose level should proceed to the Maintenance Period (Visit 5) and complete those assessments. Subjects who are back-titrated during the Titration Period will automatically enter the Maintenance Period.

Analysis by visit will be done as documented in the eCRF, i.e., no visit correction will be conducted due to deviations from scheduled time points.

Assessments at premature Withdrawal of the study are documented in the eCRF pages of Visit 9 (EoM/ Withdrawal). For data listings, assessments of Withdrawal Visit and of Visit 9 as scheduled will be presented separately as

- Premature Withdrawal for subjects who prematurely terminated the study
- Visit 9 (EoM) for subjects who completed the study.

Unscheduled assessments may be recorded during the study. Information collected in the log forms (e.g., AEs and concomitant medications) is included in the analysis. However, assessments at unscheduled visits will not be considered in the by visit analysis unless data captured at these visits falls within the SAP defined visit windows shown above and there was no corresponding endpoint data collected at the same scheduled visit. The information collected during unscheduled visits will be presented in the listings as an unscheduled visit.

3.3 Definition of Baseline values

Unless otherwise noted, baseline is defined as the last assessment before first dosing in the previous RLS study of rotigotine (SP1006).

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to database lock.

3.5 Analysis sets

3.5.1 Enrolled Set (ES)

The ES will consist of all subjects with a signed informed consent form.

3.5.2 Safety Set

The Safety Set (SS) will consist of all subjects who have at least one patch (rotigotine) applied. This analysis set will be used for all analyses except for the pharmacokinetic data.

3.5.3 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will consist of all subjects from the SS who provided at least 1 valid post-dose plasma concentration of unconjugated rotigotine.

Due to early stopping of the study, the analyses planned using the PKS will no longer be performed.

3.6 Treatment assignment and treatment groups

Generally, all summaries/analyses will be performed using the final dose group, i.e., the starting dose of the maintenance period. In addition, some summaries/analyses will be present for longest dose or actual dose.

3.7 Center pooling strategy

Not applicable.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA 25.1). Prior or concomitant medication will be coded using the most recent version of the World Health Organization Drug Dictionary (WHO DD MAR/2022).

3.9 Changes to protocol-defined analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical outputs will be performed using SAS Version 9.3 or higher. None of the planned analyses require SAS Version 9.4 and can all be performed on SAS Version 9.3.

Analyses will not be performed as defined in the study protocol due to early study termination. All data will be listed, and key summary tables will be produced.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

Subjects who prematurely discontinue the study will be evaluated based on the data collected at each visit attended. If the premature discontinuation occurs at a scheduled visit, data collected at that visit will be summarized at the scheduled visit time point. Otherwise, the data will be attributed to the next scheduled visit for the purpose of by-visit endpoint summaries.

With respect to AEs, events with missing intensity will be assumed to be severe. Events with missing relationship to study medication per the investigator will be assumed to be related. Events with a missing answer to the question "Serious Adverse Event?" will be considered serious.

4.2.1 Missing efficacy data

For subjects who prematurely withdraw for any reason before EoM, values for planned efficacy assessments scheduled at subsequent visits will not be imputed. Efficacy assessments must be performed no later than 1 day after the last patch removal to be utilized for analysis (valid measurements).

For IRLS analysis if any item is missing, the IRLS sum score will be not calculated. Missing IRLS baseline value will be regarded as an important protocol deviation.

4.2.2 Missing and Incomplete Dates for Adverse Events and Concomitant Medication

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment in the study or not. For the purposes of imputing missing date or missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and

stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

- Missing start day, but month and year present:

  If the first patch application occurred in the same month and year as the occurrence of the AE/medication, the start day of the event/medication will be assigned to the day of first patch application.

  Otherwise, the start day will be set to the 1st day of the month.

- Missing start day and month, but year present:

  If the first patch application occurred in the same year as the occurrence of the AE/medication, the start day and month will be assigned to the date of first patch application.

  Otherwise, the start day and month will be set to January 1st.

- Missing end day, but month and year present:

  The end day will be set to the last day of the month.

- Missing end day and month, but year present:

  The end day and month will be set to the date of study termination or the date equivalent to 30 days after last patch removal, whatever occurs later.

  However, if the study termination year and year for the date which is 30 days after the last patch removal are greater than the event/concomitant medication year, the day and month are to be set to December 31st.

- Completely missing start date:

  An AE will be considered as occurring during treatment.

  Medications with an unknown stop date or a stop date after the date of the first patch application will be considered as concomitant medication but not as prior medication.

- Completely missing stop date:

  Adverse events with a completely missing stop date will be considered ongoing.

  Medications with a start date before the first patch application will be considered as prior and concomitant medications. Medications with a start date during the Treatment Period will be considered as concomitant medication.

- Imputed stop date prior to imputed start date:

  If the year of start date is the same as the year of first patch application and the stop date is after the date of first patch application, then set the start date to the date of first patch application.

  Otherwise, set the start day and month to January 1st of the start year.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant, or an adverse event was treatment emergent, the medication will be considered as concomitant or the adverse event will be considered treatment emergent.

4.2.3 General Imputation Rule for Incomplete Dates

Where necessary for the calculation of derived variables (e.g., age), partial dates will be imputed using the earliest calendar date based on the partial date provided. This rule is valid for all partial dates with the exception of the following:

- Start and stop dates of AEs
- Start and stop dates of prior and concomitant medication
- Stop dates of past and concomitant diseases
- Patch application dates

Completely missing dates will not be replaced, and the corresponding derived variables will be set to missing.

5 STUDY POPULATION CHARACTERISTICS

Study population characteristics will be summarized for the SS and by final dose group and all subjects combined.

5.1 Subject disposition

Subject disposition will be presented in terms of the number of subjects who

- completed or withdrew (including reasons) during the study
- started the Titration Period (attended Visit 2 and was treated) and subsequently completed (attended Visit 5) or withdrew (including reasons) during the Titration Period
- started the Maintenance Period (attended Visit 5) and either completed or withdrew (including reasons) during the Maintenance Period
- started and completed the Taper Period, with reasons if applicable
- and completed the Safety Follow-up Period or withdrew (including reasons) prior to the Safety Follow-up visit

Subjects will be counted as completed study and maintenance period, if they don't withdraw before EoM, and as completed titration, taper, and safety follow-up periods, if they don't withdraw before the end of the respective period.

Summaries will also be provided for discontinuations due to AEs and disposition of analysis sets. Reasons for screen failure will be listed.

5.2 Protocol deviations

All important protocol deviations will be listed.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Age will be derived in years applying all rules for missing date imputation as described in Section 4.2.3 as integer ((Date of informed consent - date of birth) / 365.25).

Weight recorded in pounds (lb) will be converted to kilograms (kg) as weight(lb)*0.4536kg/lb.

Height recorded in inches (in) will be converted to height in centimeters (cm) as height(in)*2.54cm/in.

The BMI will be calculated as weight (kg) / (height (m))^2.

The following demographics will be summarized:

- Age (years)
- Age (EudraCT age categories)
- Age (clinicaltrials.gov age categories)
- Gender (Male; Female)
- Racial Group (American Indian/Alaskan Native; Asian; Black; Native Hawaiian or Other Pacific Islander; White; Other/Mixed)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI (<18.5, 18.5-<25, 25-<30, 30-<35, 35-<40, >=40, Missing)

6.2 Other Baseline characteristics

Time since diagnosis of RLS will be derived in years applying all rules for missing date imputation as described in Section 4.2.3 as integer ((date of informed consent - date of diagnosis) / 365.25).

Baseline characteristics will be listed only.

6.3 Family medical history

Family medical history will be listed for cases where a potential drug-induced liver injury (PDILI) is reported.

6.4 Prior and concomitant medications

Medications will be considered as prior if the start date of the medication is before the date of first patch administration (in RL0007). Medications will be considered as concomitant if it was taken at least once in the Treatment Period starting with the first patch administration and ending the day of last patch removal. Medications starting prior to first patch application and continuing into the Treatment Period will be considered both prior and concomitant medication.

For cases of partial or missing dates the rules described in Section 4.2.2 will be applied.

Prior and concomitant medications will be summarized for the SS. The number and percentage of subjects who used prior or concomitant medications, respectively, will be presented according to the Anatomical Therapeutic Chemical main group, the therapeutic subgroup, and the preferred drug name.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance will not be calculated for the early study termination scenario. Refer to Section 10.1 for information about study medication exposure.

8 EFFICACY ANALYSES

All efficacy analyses will be performed for the SS and summarized by final dose group and all subjects combined.

8.1 Statistical analysis of key efficacy variables

The key efficacy variables are the changes from Baseline at EoM (Visit 9) in IRLS sum score, CGI Item 1 and RLS-6, but will be presented and analyzed together with all other visits. No imputation will be applied.

8.1.1 Derivations of key efficacy variables

The IRLS consists of 10 questions, each using a 5-point scale ranging from 0=not present to 4=severe. The IRLS sum score will be calculated by summing up the single scores of all applicable questions, i.e., the sum score will range between 0 and 40. If any answer is missing, the IRLS sum score will also be missing.

The CGI item 1 (Severity of Illness) scale ranges from 0 to 7 as follows: : 0=not assessed, 1=normal, not ill at all, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill.

The RLS-6 Rating Scales (Kohnen, 2003) is designed to assess the severity of RLS and consists of 6 subscales. The subscales assess severity of symptoms at the following times of the day/evening: falling asleep, during the night, during the day at rest, and during the day when engaged in daytime activities. In addition, the subscales assess satisfaction with sleep and severity of daytime tiredness/sleepiness. Scores for each of the 6 subscales range from 0 (completely satisfied) to 10 (completely dissatisfied). No sum score will be calculated.

8.1.2 Analysis of the key efficacy variables

Summary statistics for observed values as well as changes from Baseline by visit will be provided for IRLS sum score, each subscale of the RLS-6 rating scales and CGI item 1.

9 PHARMACOKINETICS

9.1 Plasma concentration

Plasma samples will be collected at Visit 5 and Visit 9. The results of plasma concentrations of unconjugated rotigotine will be presented in a listing.

9.2 Population Pharmacokinetics

The plasma concentrations of unconjugated rotigotine may also be used for population PK-PD analyses. Details and methods of these analyses will be described in the Data Analysis Plan and the results will be reported in a separate modeling report.

10 SAFETY ANALYSES

All safety analyses will be conducted for the SS and results will be presented by final dose group and for all subjects combined.

10.1 Extent of exposure

The duration of exposure will be calculated as (date of last patch removal – date of first patch application + 1 day).

The final dose level ('final dose') is defined as the dose administered at the start of the Maintenance Period (i.e., at Visit 5) and intended to be used during the Maintenance Period. If the subject down titrates to the previous dose during the Titration Period and continues on that dose at Visit 5, then the back-titrated dose level is the 'final dose'.

The determination of the dose of longest duration is based on the entries given in the drug dosing log of the eCRF. The duration of a single dose will be calculated as the sum of the durations of each dosing interval with intake of the respective dose whereas the duration of each dosing interval will be calculated as (end date – start date).

Where more than one dose has the same longest duration, the highest dose will be selected. For subjects who dropped out during the Titration Period, the last applied dose during the Titration Period will be used as dose of longest duration.

A listing will be presented for the following variables:

- Duration of exposure (days)
- Final dose level (mg/24h) at the start of Maintenance (1mg/24h, 2mg/24h and 3mg/24h)
- Dose of longest duration (1mg/24h, 2mg/24h and 3mg/24h)

A listing of patch adhesiveness findings, including date and time of detachment, location and side of body, percent adherence and kit number will be provided.

10.2 Adverse events

Adverse events will be documented throughout the entire study on an ongoing basis. TEAEs are defined as events that started during the Treatment Period or within 30 days following the end of the Treatment Period (i.e., on or after the date of first patch application and within 30 days following the date of last patch removal) or any unresolved event already present before administration of treatment that worsens in intensity following exposure to the treatment. For AEs with a partial or missing start date, the imputation rules as described in Section 4.2.2 will be applied.

Adverse events with a missing start date are defined as treatment-emergent if the end date of the AE is not on or before the date of first patch application.

An AE with action taken regarding study medication reported on the AE page of the eCRF as "drug permanently withdrawn" will be regarded as an AE leading to discontinuation of study medication.

Adverse events which have the question "Serious Adverse Event?" answered "yes" are considered serious.

Treatment emergent AEs will be tabulated by MedDRA SOC, High Level Term (HLT) and PT. The number and percentage of subjects experiencing each event at least once will be summarized in addition to the number of events. In summaries of TEAEs by relationship and intensity, respectively, the number of events will not be presented.

All summaries will be sorted alphabetically by SOC and HLT and by frequency of events (PT) within HLTs. If there is more than one PT with the same frequency these events will be sorted alphabetically.

An overview of the incidence and frequency of all TEAEs, serious TEAEs, TEAEs leading to discontinuation of study medication, related TEAEs, severe TEAEs, all deaths, and TEAEs leading to death will also be provided.

The following tabular summaries will be presented also.

- TEAEs
- TEAEs by intensity
- TEAEs by maximum intensity
- TEAEs by relationship to study medication per the Investigator
- Serious TEAEs
- Serious TEAEs by Relationship to study medication per the Investigator
- non-serious TEAEs above reporting frequency threshold of 5%

Individual subject data listings will be presented for all AEs.

10.3 Clinical laboratory evaluations

The following laboratory parameters are measured within the study:

- Hematology parameters: Hematocrit (HCT), Hemoglobin (HGB), Platelets (PLAT), Red Blood Cells (RBC), White Blood Cells (WBC), and differential count and percentile (Lymphocytes, Basophils, Eosinophils, Monocytes, Neutrophils)
- Liver Function Tests and other Chemistry parameters: Alanine Aminotransferase (ALT), Aspartate Transaminase (AST), Albumin, Alkaline Phosphatase (ALP), Bicarbonate (Total CO2), Blood Urea Nitrogen (BUN), Calcium, Chloride (CL) Creatinine, Ferritin, Gamma-glutamyl transferase (GGT), Glucose, Iron Binding Capacity Total (IBCT), Iron Binding Capacity Unsaturated (IBCU), Lactate Dehydrogenase (LDH), Potassium, Phosphorus, Serum Iron, Sodium, Total cholesterol, Total bilirubin, Total protein, Transferrin, Uric acid
- Endocrine parameters: Estradiol (females only), Follicle-stimulating Hormone (FSH), Insulin-like Growth Factor 1 (IGF-1), Luteinizing Hormone (LH), Progesterone (females

only), Prolactin, Testosterone (males only), Thyroxine Free (T4FR), Triiodothyronine (T3), Thyroid Stimulating Hormone (TSH)

  - Endocrine normal ranges are provided by the central lab and included in the dataset specifications.

- Urinalysis: Color, Appearance, Glucose, Protein, Blood, Ketones, Urine Pregnancy Test

Summary statistics of the observed values and their change from Baseline and the frequency of abnormal values based on normal ranges will be presented by visit for laboratory parameters of hematology, chemistry and endocrinology.

Laboratory data outside the reference range will be highlighted with "L" for low and "H" for high in all laboratory subject data listings where applicable.

Individual subject data listings will be presented for laboratory parameters of hematology, chemistry and endocrinology. Urinalysis and pregnancy test results will only be listed.

10.3.1 Elevated liver function tests

A listing of subjects with elevated liver function results will be provided. This listing will include subjects who potentially meet Hy's Law at least 1 time during exposure. Potential Hy's Law is defined as a subject with AST or ALT >= 3x upper limit of normal and total bilirubin >= 2x upper limit of normal where ALP <2 at the same visit.

For all subjects potentially meeting Hy's Law, the ratio of hepatocellular to cholestatic values will be calculated using the following formula and included in the listing:

nR = max(ALT /ULN, AST /ULN) / (ALP /ULN)

Potential cholestatic injury is defined as a ratio of hepatocellular to cholestatic values <=2, potential mixed hepatocellular/cholestatic injury is defined as values >2 and <5, and potential hepatocellular injury is defined as values >=5.

10.4 Vital signs, physical findings, and other observations related to safety

10.4.1 Vital signs

Summary statistics of the observed values and changes from Baseline for vital sign parameters (systolic and diastolic blood pressure, and pulse rate) will be presented by visit and final dose group for supine measurements (after 1 and 5 minutes) as well as standing measurements (after 1 and 3 minutes). Observed values and change from Baseline values will also be presented for the orthostatic reaction after 1 and 3 minutes standing.

Orthostatic hypotension will be assessed using the difference between supine and standing systolic and diastolic blood pressure at each visit. For systolic BP, diastolic BP and pulse, the difference will be calculated using the 5-minute supine values with both the 1 and 3 minute standing values for each parameter, respectively. A drop in systolic BP of ≥20 mmHg or a drop in diastolic BP of ≥10 mmHg after 1 or 3 minutes in the standing position is indicative of orthostatic hypotension.

A listing of results for vital signs, and body weight, BMI, temperature, respiratory rate, height and height percentile (based on CDC growth charts at http://www.cdc.gov/growthcharts) will be provided. A separate listing for orthostatic hypotension will also be provided.

10.4.2 Electrocardiograms

Summary statistics of the observed values and changes from Baseline for ECG parameters (Heart rate, RR interval, PQ/PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval) will be presented by visit.

ECG results and findings will be listed.

10.4.3 Modified Minnesota Impulsive Disorders Interview

Assessments of mMIDI will only be listed.

10.4.4 Physical and neurological examinations

Physical and neurological examination abnormalities will be listed only. Changes in menstrual function will also be listed.

10.4.5 Suicide ideation and behavior

Suicide ideation and behavior will be measured using the Columbia-Suicide Severity Rating Scale (C-SSRS). Results of the C-SSRS will only be listed.

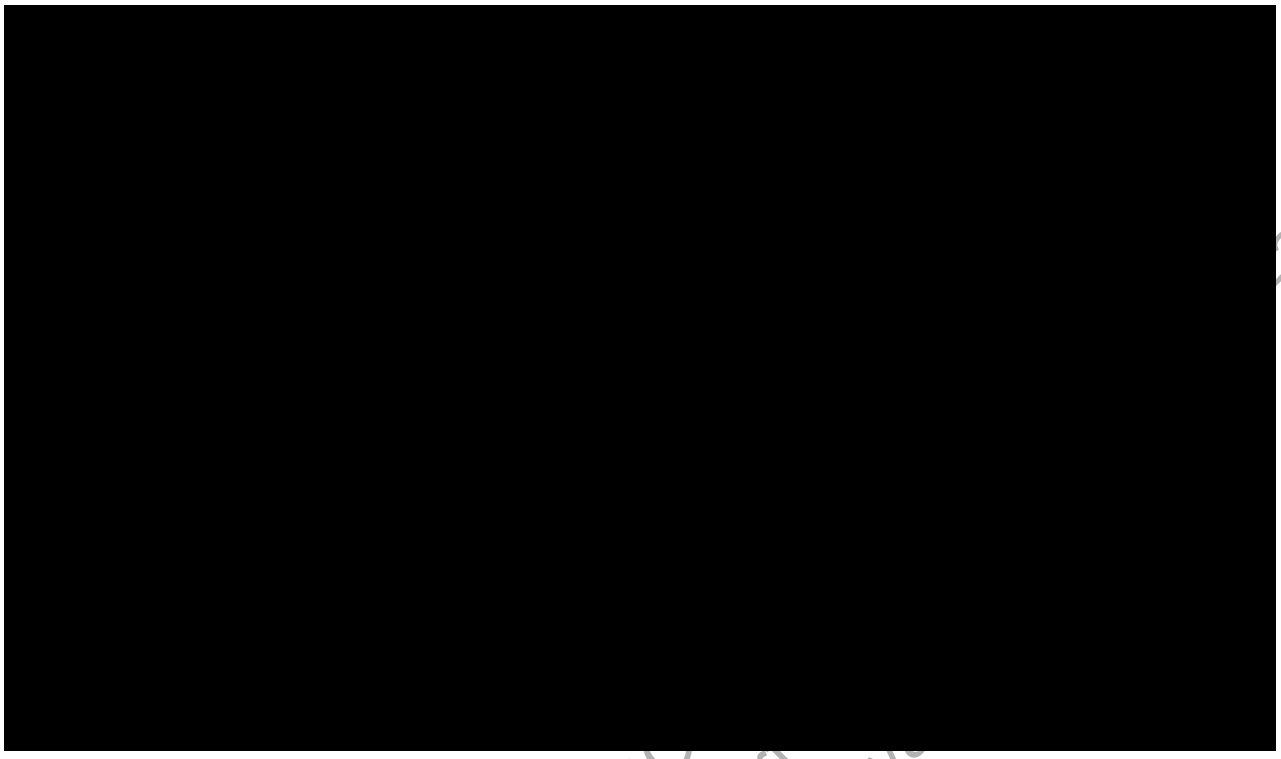
11 OTHER ANALYSES

11.1 Subject Quality of Life Questionnaire.

The restless legs syndrome quality of life (RLS-QoL) (Kohnen, 2002) will be used to evaluate quality of life. This disease-specific instrument consists of 12 questions with numeric outcome (0 – 5). The RLS-QoL total score will be calculated as the sum of all 12 items.

Subscales will be calculated as the sum of the items within each subscale. If an item within the subscale is missing, then the subtotal for that subscale will also be missing. The exception to this rule is for missing answers to question 7 [redacted]) at Baseline. The answer to this question might be not applicable, which will be substituted by a score of 0 (not at all).

[redacted]



A listing of individual items, subscales and total score will be provided.

12 REFERENCES

CDC growth charts: http://www.cdc.gov/growthcharts
Kohnen R, Benes H, Heinrich B, Kurella B. Development of the disease-specific restless legs syndrome quality of life (RLS-QoL) questionnaire [abstract]. Mov Disord. 2002;17 Suppl 5:232.

Kohnen R, Oertel WH, Stiasny-Kolster K, Benes H, Trenkwalder C. Severity rating of RLS: review of ten years experienced with the RLS-6 scales in clinical trials [abstract]. Sleep. 2003;26 Abstract suppl: A342.

Phillips A, Haudiquet V. ICH E9 guideline 'Statistical principles for clinical trials': a case study. Stat Med. 2003;22(1):1-11; discussion 13-7.

13 APPENDICES

13.1 Amendment 1

Rationale for the amendment:
This amendment reflects changes for consistency with the SSD SAP, clarification regarding treatment periods and other minor corrections. It also reflects a reduced list of displays due to early study termination.

- Section 3.2.1.2: Clarification of the definition of the date of last patch removal.
- Section 3.2.2: Clarifies study period definitions.
- Section 4.2.1: Clarification of missing data handling for IRLS efficacy endpoint.
- Section 4.2.2: Added instructions for AE and concomitant medication missing start dates.
- Section 10.1: Clarification of the definition of 'final dose'.
- Section 10.2: Clarification of the definition of TEAEs.
- Section 10.3: Administrative editing of list of lab parameters to include full spelling and abbreviations.
- Section 10.4.1 "Vital Signs": Updated to add height percentile; cited CDC growth chart reference.
- Section 12 "References": Added reference to CDC growth charts, RLS-6 and RLS-QoL; removed two statistical references.
- General: Grammatical and typographic corrections were made.
- General: Statistical analyses have been removed and the number of summary tables reduced.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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