STATISTICAL ANALYSIS PLAN

Study: SP1006

Product: Rotigotine

A REMOTE, DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY OF ROTIGOTINE TRANSDERMAL SYSTEM IN ADOLESCENT SUBJECTS WITH IDIOPATHIC RESTLESS LEGS SYNDROME

SAP/Amendment Number	Date
SAP/1	27 Aug 2020
SAP/2	25 Apr 2023

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CGI	Clinical Global Impressions
DEM	Data Evaluation Meeting
eCRF	electronic Case Report form
ECG	12-lead electrocardiograms
EoM	end of the Maintenance Period
ES	Enrolled Set
FAS	Full Analysis Set
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
nR	ratio of hepatocellular to cholestatic values
PD	pharmacodynamic
PK	pharmacokinetic
PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PT	preferred term
RLS	Restless Legs Syndrome
RLS-6	Restless Legs Syndrome - 6 Syndrome Rating Scales
RLS-QoL	restless legs syndrome quality of life

RS	Randomized Set
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
SS	Safety Set
T3	triiodothyronine
T4FR	thyroxine free
TEAE	treatment-emergent adverse event
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This document contains details for the statistical analyses of study SP1006 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 Statistical Analysis Plan (SAP) describes the statistical principles that will be applied for the analyses as well as tables and listings that are foreseen for this study. Changes in the statistical methodology will result in an 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

2.1.1 Primary objective

To demonstrate the efficacy of rotigotine against placebo in adolescent subjects with idiopathic Restless Legs Syndrome (RLS) over a 12-week Maintenance Period.

2.1.2 Secondary objectives

To investigate the safety and tolerability of rotigotine in adolescent subjects with idiopathic RLS.

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

- Change from Baseline in International Restless Legs Rating Scale (IRLS) sum score at end of the Maintenance Period (EoM)
- Change from Baseline in Clinical Global Impressions (CGI) Item 1 at EoM

2.2.1.2 Secondary efficacy variables

- Change from Baseline in Restless Legs-6 Rating Scales (RLS-6) at EoM

2.2.1.3 Other efficacy variables

- Change from Baseline in CGI Item 1 by visit*
- Change from Baseline in RLS-6 Rating Scales by visit*
- Change from Baseline in IRLS sum score by visit*

* For the IRLS, CGI, and RLS-6 the EoM visit is already covered under primary and secondary variables.

2.2.2 Safety variables

- Occurrence of treatment emergent adverse events (TEAEs)

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

2.2.3 Other variables

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

2.3 Study design and conduct

This is a Phase 3, remote, double-blind, randomized, adaptive placebo-controlled study of fixed dose administration of the rotigotine transdermal system. The study will be conducted in adolescent subjects, 13 to17 years of age, with idiopathic RLS. Subjects will be randomized to 1 of 3 treatment groups: placebo, 2mg/24h rotigotine, or 3mg/24h rotigotine.

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. Mobile study personnel will visit subjects'/legal representatives' homes to complete certain study procedures (e.g., neurological exams, physical exams, ECGs, lab collections, and vital signs).

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists must discontinue therapy at least 14 days prior to Visit 2/Baseline. Subjects taking L-dopa must discontinue therapy at least 7 days prior to Visit 2/Baseline.

The Screening Period will be followed by the Titration Period. Subjects will receive their first dose of study medication at Visit 3/Day 1. Subjects will be initiated either on placebo or 1mg/24h rotigotine. The dose of rotigotine taken by subjects randomized to rotigotine will then be up-titrated on a weekly basis by 1mg/24h at a time to 2mg/24h or 3mg/24h, depending on the subject's assigned dose level.

Subjects will be allowed to back-titrate one dose level during the Titration Period. Subjects are to complete the Titration Period at the back-titrated dose level and remain at this dose level for the duration of the Maintenance Period. Subjects who do not tolerate the assigned dose in the first week (placebo or 1mg/24h) will be withdrawn from the study. If subjects withdraw due to lack of efficacy, they are eligible to roll-over to the open-label study, RL0007, after the 3 weeks of the Titration Period are completed.

The Titration Period will be followed by a 12-week Maintenance Period. Subjects will remain at the assigned (or back-titrated) dose level throughout the Maintenance Period. At the end of the Maintenance Period, subjects will enter a Taper Period lasting up to a maximum of 4 days (de-escalation of study medication), followed by a 30-day Safety Follow-Up Period.

Visits will be scheduled every week during the Titration Period. During the Maintenance Period, visits will be scheduled every 4 weeks. There is a 4-day interval until the end of the Taper period, followed by a 30-day interval (±5 days) until the Safety Follow-Up Visit.

2.4 Adaptations due to interim analysis decision

Due to early stopping of the study, this section is no longer applicable.

2.5 Determination of sample size

The sample size estimate is based on the efficacy results observed in the adult RLS Phase 3 confirmatory trial SP792, which was conducted in the USA. In this study, a range of rotigotine doses were compared to placebo.

The sample size computation assumes that adolescent and adult patients will show a similar effect of rotigotine with respect to IRLS score and CGI (Item 1) changes from Baseline in comparison to placebo, with a similar proportion of patients not included in the primary analysis.

In the adult study, the observed difference between the 3mg/24h rotigotine group and placebo in the Change from Baseline to end of 3-month Maintenance Period in IRLS sum score was 5.9. A difference between rotigotine and placebo of 4.0 can be considered as clinically relevant. The common standard deviation (SD) estimate in the adult study was 7.9. For the CGI Item 1, the difference between 3mg/24h rotigotine group and placebo was 0.8 with a SD of 1.2.

With these assumptions, a total sample size of 45 evaluable patients in each group will provide a power of 93% for the IRLS endpoint, and a power of 87% for the CGI (Item 1) endpoint in the analysis of the 3mg/24h dose. Assuming independence of the 2 endpoints will result in a power of 80% for the analysis of the co-primary variables. Since it is known that the 2 endpoints will have a relatively high correlation (approximately 0.7), the calculated 80% is a conservative estimator for the power.

Assuming similar effects for the 2mg/24h dose group, the conditional power for the 2mg/24h dose group is also 80% with an overall power for the study >60%. To obtain 135 evaluable patients (i.e., FAS), 138 patients must be randomized (assuming approximately 2% of the randomized patients cannot be utilized).

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 (e.g., changes from Baseline) will be generated.

Unless otherwise noted, all summaries will be displayed by randomized treatment group (placebo, rotigotine 2mg/24h and rotigotine 3mg/24h, respectively) regardless of the doses individual subjects received. A summary with all treatment groups combined (i.e., total column) will be presented for the demographic and Baseline characteristics, for the prior medications, as well as for the medical history.

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 randomized treatment, 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 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. This period includes Visit 2/Day 0 at which the subjects are randomized, and study medication is assigned and shipped.

- Titration Period:

  The Titration Period starts at the day of the first patch application (Day 1) and ends on the day prior to Visit 6. In case of a premature withdrawal before Visit 6, 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 (or last known 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 6 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, then no Taper Period is defined for this subject.

- Treatment Period:

  The Treatment Period comprises the Titration Period, the Maintenance Period, and 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 Safety Follow-Up Visit. However, AEs starting within 30 days following the date of last patch removal will be considered for analysis, even if the start date is after the

date of last study assessment. If the subject rolls over into the RL0007 study, then the Safety Follow-up Period dates will be missing.

3.2.3 Visit mapping

The visits are planned as shown in the Protocol Table 5-1 Schedule of assessments. These visit windows were revised for the purpose of identifying important protocol deviations at visits 2, 7 and 8:

Visit	Day	Visit Window
Visit 1 (Screening)	Day -28 to Day -1	
Visit 2 (Baseline)	Day 0	+5 Days
Visit 3	Day 1	+5 Days
Visit 4	Day 8	± 1 Day
Visit 5	Day 15	± 1 Day
Visit 6 (Start of Maintenance)	Day 22	± 2 Days
Visit 7	Day 50	± 5 Days
Visit 8	Day 78	± 5 Days
Visit 9 (EoM)	Day 106	± 2 Days
Visit 10	Day 110	Visit 9 + 4 days
Safety Follow-Up	30 Days after End of Taper 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 fall within the protocol defined visit windows (Protocol Table 5-1) 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 labeled as the unscheduled visit.

3.3 Definition of Baseline values

Unless otherwise noted, baseline is defined as the last available value on or before the day of the first patch application.

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 unblinding.

3.5 Analysis sets

Six analysis sets will be defined for this study.

3.5.1 Enrolled Set (ES)

The ES will consist of all subjects with a signed informed consent form and any demographic data.

3.5.2 Randomized Set (RS)

The RS will consist of all subjects from the ES who have been randomized.

3.5.3 Safety Set (SS)

The SS will consist of all subjects from the RS who have at least one patch (rotigotine or placebo) applied. This population will be used for safety analysis.

3.5.4 Full Analysis Set (FAS)

The FAS will consist of all subjects from the SS who have a valid IRLS score with a valid post-Baseline IRLS score or a valid CGI Item 1 score at Baseline paired with a valid post-Baseline CGI Item 1 score. This population is the primary population for efficacy analysis.

A valid IRLS or CGI Item 1 score at Baseline is defined as a completely answered questionnaire on or before the date of first study medication. A valid post-Baseline IRLS or CGI Item 1 score is defined as a completely answered questionnaire during the Treatment Period, i.e., measured after Baseline and on or before one day after the last patch removal.

3.5.5 Per Protocol Set (PPS)

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

3.5.6 Pharmacokinetic Set (PKS)

The 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

The treatment comparisons of primary interest will be each rotigotine group versus placebo. All summaries/analyses will generally be performed using the randomized treatment, i.e., placebo, rotigotine 2mg/24h and rotigotine 3mg/24h independent from the dose of administration.

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 not be calculated. Missing IRLS baseline items and therefore the total score 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. Medications with a stop date prior to first patch application will be considered as prior medication but not as concomitant medication. For these cases, impute the day and month to January 1st of the year of the first patch application.

- Completely missing stop date:

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

- 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.

4.3 Interim analyses and data monitoring

Due to early stopping of the study, the interim analyses will no longer be performed.

4.4 Multicenter studies

Not applicable.

4.5 Multiple comparisons/multiplicity

Not applicable.

4.6 Use of an efficacy subset of subjects

Not applicable.

4.7 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Subject disposition will be presented for the RS 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 6) and either completed or withdrew (including reasons) during the Maintenance Period
- started the Taper Period and completed (attended Visit 10) or withdrew (including reasons) during the Taper Period.

Subjects will be counted as completed study and maintenance period, if they don't withdraw before EoM, and as completed titration/taper period, if they don't withdraw before the end of the titration/taper period.

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

Reasons for screen failure will be listed for the ES.

5.2 Protocol deviations

The subject incidence (and percentage) of important protocol deviations will be summarized both overall and by treatment group for the RS. These summaries will also be provided by site.

All important protocol deviations will also be listed for the RS.

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 for the RS:

- 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).

The following Baseline characteristics will be summarized for the SS:

- Time since diagnosis of RLS (years)

Other Baseline characteristics (e.g., lifestyle items) will be listed.

6.3 Medical history and concomitant diseases

Previous and ongoing diseases will be derived from the medical history form of the eCRF.

Medical history (except RLS) will be presented for the SS, summarized by MedDRA System Organ Class (SOC) and preferred term (PT).

Procedure history and concomitant medical procedures will be listed. Family medical history will be collected only when PDILI is reported and will be provided in a listing.

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. 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 during the study. 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 Pharmacological 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

If not stated otherwise, all efficacy analyses will be performed for the FAS.

8.1 Statistical analysis of the primary efficacy variables

The co-primary efficacy variables are change from Baseline to EoM in IRLS sum score and change from Baseline in CGI Item 1 to EoM.

8.1.1 Derivations of primary efficacy variables

The IRLS consists of 10 questions, each using a 5-point scale ranging from 0=not present to 4=very 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.

8.1.2 Primary analysis of the primary efficacy variables

Observed results and changes from Baseline in IRLS sum score and CGI (Item 1) will be summarized by visit and by treatment group.

8.1.3 Secondary analyses of the primary efficacy variable

Not applicable.

8.1.4 Supportive and sensitivity analyses of the primary efficacy variable

Not applicable.

8.2 Statistical analysis of the secondary efficacy variables

All summaries and analyses of the secondary efficacy variables will be based on the FAS.

8.2.1 Restless Legs Syndrome-6 Rating Scales

The RLS-6 Rating Scales (Kohnen et al, 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/none /not at all) to 10 (completely dissatisfied/very severe).

The change from baseline will be derived for each of the 6 subscales. No sum score will be calculated.

Summary statistics for observed values as well as changes from Baseline by visit will be provided for each of the RLS-6 rating scales.

9 PHARMACOKINETICS

9.1 Plasma concentration

Plasma samples will be collected at Visit 6 and Visit 9. For subjects in the rotigotine groups, plasma concentrations will be listed.

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

If not stated otherwise, all safety analyses will be conducted for the SS.

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).

All derivations of rotigotine doses given below are nominal doses, i.e., include placebo patches in the rotigotine 2mg/24h or placebo arm.

The final dose level ('final dose') is defined as the dose administered at the start of the Maintenance Period (i.e., at Visit 6) 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 6, 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 + 1).

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. If the dose of longest duration is 0mg/24h, but the subject was exposed at least once to active drug, the minimum active dose will be utilized.

Summary statistics will be presented for the following variables:

- Duration of exposure (days)
- Final dose (mg/24h) at the start of Maintenance (0 mg/24h, 1 mg/24h, 2 mg/24h and 3 mg/24h)
- Dose of longest duration (0 mg/24h, 1 mg/24h, 2 mg/24h and 3 mg/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" or missing 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) in the total rotigotine group within HLTs. If there is more than one PT with the same frequency in the total rotigotine group 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, Hemoglobin, Platelets, Red Blood Cells, White Blood Cells, 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, Blood Urea Nitrogen, Calcium, Chloride Creatinine, Ferritin, Gamma-glutamyl transferase, Glucose, Iron Binding Capacity Total, Iron Binding Capacity Unsaturated, Lactate Dehydrogenase, 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), where ULN is the upper limit of normal

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 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.

Summary statistics of body weight, calculated BMI, temperature, and respiratory rate (including corresponding changes from Baseline) will be presented by visit. Summary statistics of height percentile (based on CDC growth charts at http://www.cdc.gov/growthcharts) and including corresponding changes from Baseline will be presented by visit.

A listing of results for vital signs, and body weight, BMI, temperature, respiratory rate, height and height percentile 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, and QTcB interval) will be presented by visit.

ECG results and findings (normal, abnormal not clinically significant, and abnormal clinically significant) 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.

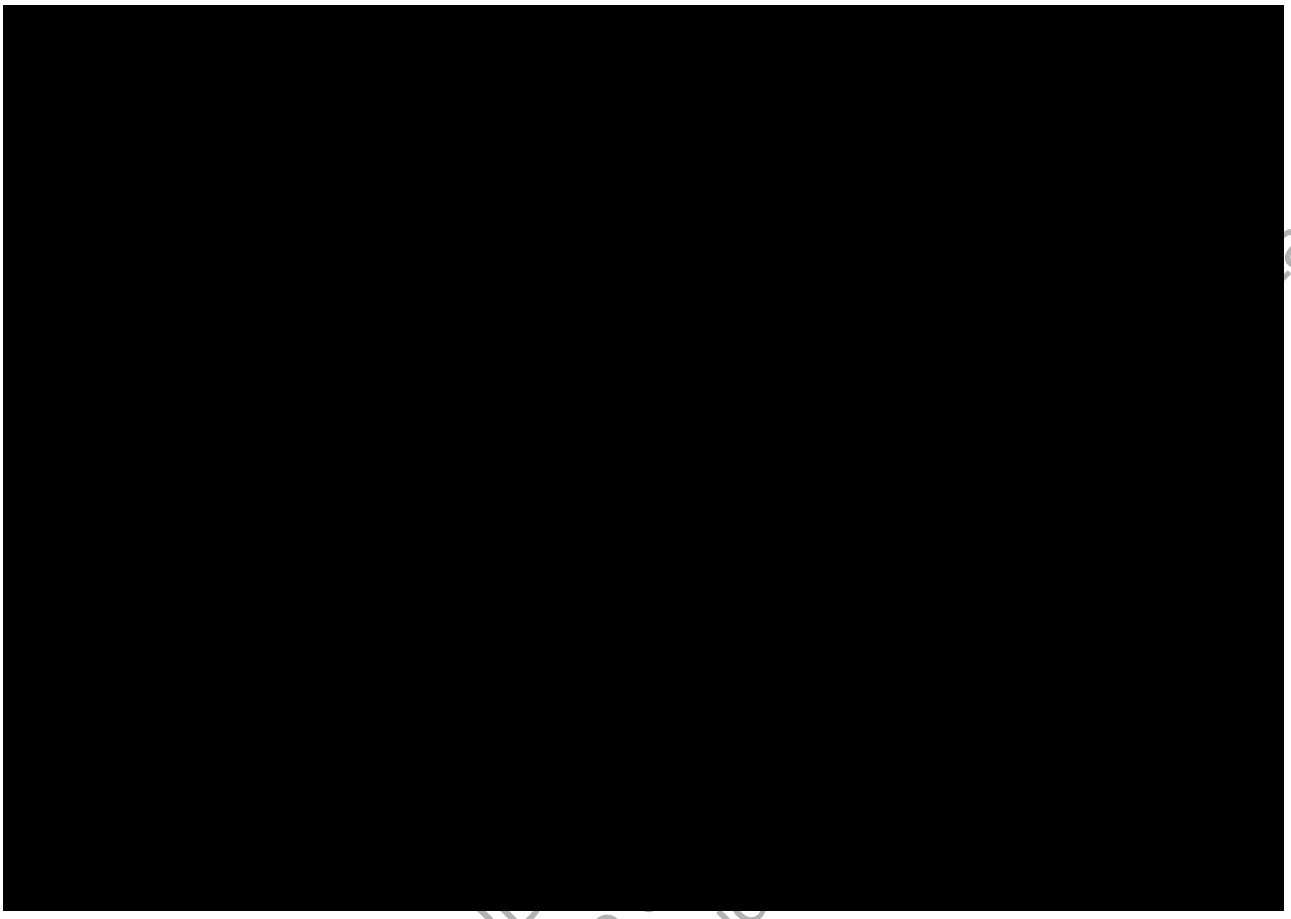
11 OTHER ANALYSES

11.1 Subject Quality of Life Questionnaire

The restless legs syndrome quality of life (RLS-QoL) questionnaire (Kohnen et al, 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 definition of important protocol deviations and other minor corrections.

- Section 2.4: Updated to describe actions resulting from the interim analysis decision
- Section 3.1: Removes Procedures from the list of summaries. These data will be listed only.
- Section 3.2.2: Clarifies study period definitions.
- Section 3.2.3:
    - Visit mapping table updated to reflect definition of important protocol deviations.
    - Clarification was added to indicate that any visit exclusions due to the IPD windows applies to the PPS only.
    - Clarification was added for the case where the efficacy endpoints were collected after a visit at an unscheduled visit.
- Section 3.5.5: Clarifies that only the visit that falls outside the IPD windows will be excluded from the PPS, not all subject efficacy data.
- Section 4.2.2: Added clarification for imputation of partial dates.
- Section 5.1: Removed reasons for screen failure.
- General: Grammatical and typographic corrections were made.
- Section 2 and Section 7: Updated wording to be in alignment with amended protocol. Clarification added for compliance calculation.
- Section 8.1.4: Added sensitivity analyses to assess impact of Covid-19 pandemic.
- Section 10.1: Replaced ‘Optimal dose’ with ‘Final back-titrated dose level’ to refer to the final dose level intended for the subject throughout the Maintenance Period.
- Section 10.4.2: Removed QTcF interval from list of ECG parameters.
- Section 10.4.4 : Added listing for changes in menstrual function.

13.2 Amendment 2

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 descriptive statistics for height percentiles including change from baseline; cited CDC growth chart reference.
- Section 12 "References": Added references for CDC growth charts, RLS-6 Rating Scales and ICH E9.
- 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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