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Study ID: RAP-MD-99

Title: An Open-label, Long-Term Extended Access Protocol for Rapastinel as Adjunctive or Monotherapy Treatment in Patients with Major Depressive Disorder

Statistical Analysis Plan Date: 21 Aug 2019

1.0 TITLE PAGE

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RAP-MD-99

An Open-label, Long-Term Extended Access Protocol for Rapastinel as Adjunctive or Monotherapy Treatment in Patients with Major Depressive Disorder

STATISTICAL ANALYSIS PLAN

SAP Date: **August 21, 2019**

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3.0 LIST OF ABBREVIATIONS

ADT	antidepressant therapy
AE	adverse event
eCRF	electronic case report form
ET	early termination
ICF	informed consent form
IP	investigational product
IV	intravenous(ly)
MDD	major depressive disorder
OLTP	open-label treatment period
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety data as outlined and/or specified in the final study protocol, dated 03 Jul 2018. Specifications of tables, figures, and data listings are contained in a separate document.

RAP-MD-99 is a multicenter, open-label extended access treatment protocol in adult participants with MDD who completed lead-in studies RAP-MD-04, RAP-MD-05, or RAP-MD-33 study within approximately 1 month of Visit 1, or RAP-MD-06 at any time prior to Visit 1. The final visit from the lead-in study may serve as the first visit of protocol RAP-MD-99 where practical to maintain continuity of treatment. In other cases, the first visit of RAP-MD-99 may be conducted independent of the final visit of the lead-in study.

Following consent at the initial visit, participants will be screened and those who meet entry criteria may enter the OLTP and receive the first dose of open-label treatment (rapastinel). Consent, screening and dosing may all be conducted in a single visit at the discretion of the investigator to facilitate continuity of treatment. Participants may also enter RAP-MD-99 at a visit independent of the lead-in study occurring no more than 21 days after completion of the lead-in study.

During the OLTP participants will return to the study center for visits at which administration of rapastinel and wellness check are conducted. Visits should typically be spaced weekly or biweekly but may be up to 4 weeks apart (based on investigator discretion).

Each participant will be treated until the investigator discontinues them at their discretion, the participant discontinues for other reasons, or until the treatment protocol or study center is terminated by the Sponsor.

Appropriate safety follow-up upon discontinuation of participants from treatment will be at the discretion of the investigator.

This treatment protocol will be conducted as an Open-label Treatment Period (OLTP) of indeterminate duration.

There is no predetermined limit specified for the number of participants that may be enrolled in the OLTP.

The treatment protocol will be ended upon drug availability following marketing approval, termination of rapastinel development, or if sponsor determines that treatment protocol termination is appropriate for other reasons.

5.0 OBJECTIVES

The objective of this treatment protocol is to provide continued access to rapastinel for participants with MDD who have completed specified prior rapastinel studies.

6.0 PARTICIPANT POPULATIONS

Two analysis populations are defined for this study, as specified in the following subsections. All participants will be combined into one treatment group: Rapastinel 450 mg, for statistical analyses purposes.

6.1 ENROLLED PARTICIPANTS POPULATION

The Enrolled Participants Population will consist of all participants who signed the RAP-MD-99 informed consent form (ICF).

6.2 OPEN-LABEL SAFETY POPULATION

The Open-label Safety Population will consist of all participants who signed the RAP-MD-99 ICF and who received at least 1 dose of open-label rapastinel during the OLTP of the protocol.

7.0 STUDY PARTICIPANTS

7.1 PARTICIPANT DISPOSITION

The number and percentage of participants in each enrollment category (RAP-MD-04 Completer, RAP-MD-05 Completer, RAP-MD-06 Completer, RAP-MD-33 Completer), participants who completed the RAP-MD-99 study, and who prematurely discontinued from the OLTP will be summarized overall and by reasons for premature discontinuation for the Enrolled Participants Population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (eg, age, race, ethnicity, sex) and baseline characteristics (eg, weight, height, body mass index) will be summarized for the Open-label Safety Population.

Prior medication is defined as any medication taken within 12 months prior to the date of the first dose of open-label rapastinel in RAP-MD-99. *Concomitant medication* during the OLTP is defined as any medication taken on or after the date of the first dose of open-label rapastinel during the OLTP through the early termination or a follow-up visit that occurs up to 30 days after the last known dose of open-label rapastinel. The *WHO Drug Dictionary Enhanced*, will be used to classify prior and concomitant medications by therapeutic class and drug name. A data listing for the prior and concomitant medications will be provided.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to open-label rapastinel for the Open-label Safety Population during the OLTP will be summarized for treatment duration by weekly intervals, calculated from the number of days from the date of the first dose of open-label rapastinel taken to the date of the last dose taken during the OLTP, inclusive. Summary statistics will also be presented.

Participant-years, defined as the sum of the treatment duration of all participants divided by 365.25, will also be summarized.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Not applicable.

10.0 EFFICACY ANALYSES

Not applicable.

11.0 SAFETY ANALYSES

The safety analyses for the OLTP will be performed using the Open-label Safety Population. The summarization will be overall for the OLTP without consideration for dosing frequency.

Safety parameters will be limited to AEs.

11.1 ADVERSE EVENTS

AEs will be coded using the *Medical Dictionary for Regulatory Activities (MedDRA)*.

An AE (classified by preferred term) that occurs during the OLTP will be considered a treatment-emergent adverse event (TEAE) if it was not present before the date of the first dose of IP in the OLTP or was present before the first dose of IP of the first lead-in study and increased in severity during the OLTP. If more than 1 AE is reported before the date of the first dose of IP in the OLTP and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the OLTP that were also coded to that preferred term. An AE that occurred more than 30 days after the date of the last dose of open-label IP will not be counted as a TEAE. An AE that becomes serious during the OLTP will also be considered as TEAE.

The incidence of common (in ≥ 2% of participants) TEAEs during the OLTP will be summarized by preferred term and will be sorted by decreasing frequency.

An SAE that occurred between the date of the first dose of the open-label IP and 30 days after the date of the last dose of IP, inclusive, will be considered a treatment-emergent SAE (TESAE).

The incidence of death, TEAE, treatment-related TEAE, TESAE, TEAEs leading to premature discontinuation of IP during the OLTP will be summarized.

Listings will be presented for all participants with SAEs, participants with AEs leading to discontinuation, and participants who died (if any).

12.0 HEALTH ECONOMICS AND OUTCOMES ANALYSES

Not applicable.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this treatment protocol.

14.0 DETERMINATION OF SAMPLE SIZE

Not applicable.

15.0 COMPUTER METHODS

Statistical analyses will be performed using [redacted]

16.0 STATISTICAL AND DATA HANDLING CONVENTIONS

16.1 SUMMARY STATISTICS

The following statistical summaries will be presented for each type of data:

- Continuous variables will be summarized by descriptive statistics (number of participants, mean, standard deviation [SD], median, minimum, and maximum values).

- Categorical variables will be summarized by frequency distributions (counts and percentages).

16.2 VISIT TIME WINDOWS

Not applicable.

16.3 DERIVED EFFICACY AND SAFETY VARIABLES

Not applicable.

16.4 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

Not applicable.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If the severity is missing for an AE that started on or after the date of the first dose of the open-label IP, then a severity of *severe* will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

16.6 MISSING RELATIONSHIP TO INVESTIGATIONAL PRODUCT FOR ADVERSE EVENTS

If the relationship to the IP is missing for an AE that started on or after the date of the first dose of the open-label IP, a causality of *yes* will be assigned. The imputed values for relationship to the open-label treatment will be used for incidence summary; the values will be shown as missing in the data listings.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for an AE is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of open-label IP, the month and day of the first dose of open-label IP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of open-label IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label IP, the day of the first dose of open-label IP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of open-label IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of open-label IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of open-label IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of open-label IP, the first day of the month will be assigned to the missing day.

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of open-label IP, the date of the first dose of open-label IP will be assigned to the missing start date.

- If the stop date is before the date of the first dose of open-label IP, the stop date will be assigned to the missing start date.

16.8 MISSING DATE INFORMATION FOR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including background ADT, incomplete (ie, partially missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a participant, the start date will be imputed first. If the stop date is complete and the imputed start date is after the stop date, the start date will be imputed using the stop date. If the imputed stop date is before the start date (imputed or nonimputed start date), the start date will be the imputed stop date.

16.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of open-label IP, the month and day of the first dose of open-label IP will be assigned to the missing fields.

- If the year of the incomplete start date is before the year of the first dose of open-label IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the first dose of open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of open-label IP, the day of the first dose of open-label IP will be assigned to the missing day.

- If either the year of the incomplete start date is before the year of the date of the first dose of open-label IP or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of open-label IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of open-label IP or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of open-label IP, the first day of the month will be assigned to the missing day.

16.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of open-label IP, the month and day of the last dose of open-label IP will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of the last dose of open-label IP, *31 Dec* will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the last dose of open-label IP, *01 Jan* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of open-label IP, the day of the last dose of open-label IP will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the date of the last dose of open-label IP or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of open-label IP, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete stop date is after the year of the date of the last dose of open-label IP or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of open-label IP, the first day of the month will be assigned to the missing day.

16.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

Not applicable.

16.10 ACTUAL TREATMENT FOR ANALYSIS

Not applicable.

16.11 STRATIFICATION HANDLING CONVENTION

Stratifications not being implemented in this study.

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

- In addition to the open-label safety population defined in the protocol, the enrolled participants population is defined in this analysis plan for the analysis of disposition data.
- The number and percentage of participants in each enrollment category (RAP-MD-04 Completer, RAP-MD-05 Completer, RAP-MD-06 Completer, RAP-MD-33 Completer) will be summarized.
- The analysis of important protocol deviations will not be performed due to a reduced scope of statistical analysis for this study.
- There are no 'other baseline characteristics' to summarize besides the demographic parameters.
- Prior and concomitant medications will be presented only in data listings.
- Extent of exposure will be summarized by weekly intervals.
- TEAEs will only be summarized by the incidence of common (in ≥ 2% of participants). Summarizes of TEAEs during the OLTP by preferred term and sorted by decreasing frequency will not be performed due to a reduced scope of statistical analysis for this study.
- The summarization of TESAEs (number and percentage of participants) by preferred term and sorted decreasing frequency will not be performed due to a reduced scope of statistical analysis for this study.