STATISTICAL ANALYSIS PLAN

Study Title: Relugolix Versus Leuprolide in Patients with Prostate Cancer: A Randomized, Open-Label Study to Assess Major Adverse Cardiovascular Events (REPLACE-CV)

Protocol Version:

Original	26 Aug 2022
Amendment 1	16 May 2023
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Statistical Analysis Plan Version

Version 1.0	26 Aug 2022

VERSION: 2.0

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INDICATION: Prostate Cancer

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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LIST OF ABBREVIATIONS

Term	Description
ADT	androgen deprivation therapy
AE	adverse event
CEC	clinical event adjudication committee
CI	confidence interval
DMC	data monitoring committee
FDA	United States Food and Drug Administration
G-S	group sequential
HR	hazard ratio
ICH	International Council for Harmonisation
MACE	major adverse cardiovascular event
ITT	Intent-to-treat
PSA	prostate-specific antigen
PT	preferred term
SAP	statistical analysis plan
SD	standard deviation

1. INTRODUCTION

This document describes detailed statistical analysis to be conducted for study protocol amendment 2 MVT-601-056 (dated 29 Feb 2024), entitled, "Relugolix Versus Leuprolide in Patients with Prostate Cancer: A Randomized Open-Label Study to Assess Major Adverse Cardiovascular Events (REPLACE-CV)." This Statistical Analysis Plan (SAP) will provide details to further elaborate statistical methods as outlined in the protocol amendment 2 MVT-601-056 as well as analysis conventions to guide the statistical programming work.

This SAP is developed in accordance with the International Council on Harmonisation (ICH) guidelines:

- Food and Drug Administration (FDA) draft guidance (Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics, May 2019);
- International Conference on Harmonisation (ICH) guidelines E3 (Structure and Content of Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials);
- ICH E9(R1) (Addendum: Estimands and Sensitivity Analysis in Clinical Trials, May 2021).

All decisions regarding statistical analysis of the study, as defined in this SAP, will be made prior to database lock for interim analysis or unblinding of the study data for final analysis. The SAP is to be finalized and approved by the sponsor before unblinding of the study data or the lock of study database. Any changes to the final SAP (or SAP amendments, if applicable) after the study database lock will be clarified in the clinical study report (CSR) with "change from the planned analysis".

The study was terminated early by the Sponsor in Nov 2023. The FDA was notified on 01 Dec 2023, and investigative sites were notified on 04 Dec 2023 to stop enrollment.

Analyses will be performed using SAS® version 9.4 or higher (SAS Institute, Inc., Cary, NC 27513).

1.1. Study Objectives and Endpoints

The study objectives are summarized in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoint
Objective	
• To describe the safety of relugolix in the study population	• The safety of relugolix will continue to be assessed in the study population. Adverse events (AEs) as characterized by type, frequency, severity, seriousness, and relationship to study drugs

2. STUDY DESIGN

2.1. Summary of Study Design

The original study was a randomized open-label study to evaluate the risk of MACE in patients with prostate cancer with defined high-risk cardiovascular disease who are appropriate to be treated either with relugolix or leuprolide acetate for a planned duration of 12 months or more. This study was terminated by the Sponsor on 01 Dec 2023. In an effort to avoid treatment interruptions, patients who had been enrolled will be allowed to remain on study drug up to a period of 12 months ending Dec 2024 if they choose to remain in the discontinuation phase of the study. During this discontinuation phase, all active investigative sites will be expected to formulate a transition plan for their study patients from this clinical study to standard of care (SoC) as soon as practicable.

The study population includes men ages 18 and older with prostate cancer. Deviations from inclusion and exclusion criteria are not allowed. Eligibility criteria are described below.

Inclusion Criteria:

1. Was previously enrolled in the original version and amendment 1 of this study
2. Has voluntarily resigned and dated the informed consent form prior to transition to the discontinuation phase of this study

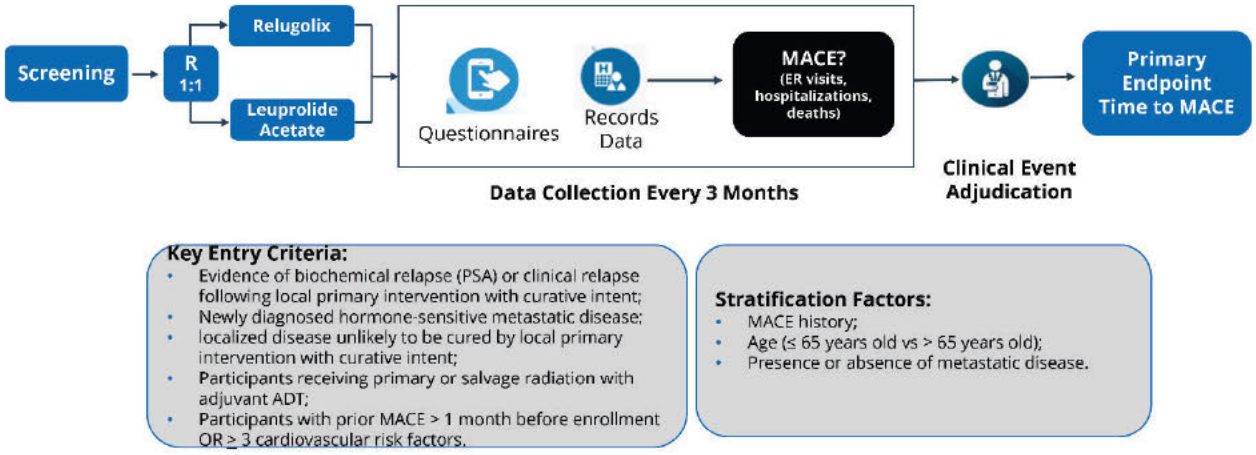
Exclusion Criteria:

Not applicable as patients were previously excluded under the original version and amendment 1.

Disclosure Statement:

This is a randomized study with collection of clinical data at baseline and at follow-up.

Figure 1: Study Schema



Abbreviations: ADT = androgen deprivation therapy; ER = emergency room; MACE = major adverse cardiovascular event; PSA = prostate-specific antigen; R = randomization.

2.2. Sample Size Considerations

The original study is an event-driven study. A two-stage group-sequential design is considered in the study. The type-I error is controlled by the α-spending methodology of Lan and DeMets (1983). The upfront estimated total sample size of the study is approximately 2250 patients (from whom a target total of 237 events [ie, 237 patients who have events] are to be observed) to achieve 90% power for the target hazard ratio of 0.65 at a two-sided significance level (alpha) of 0.05. The study is adequately powered to detect clinically meaningful treatment effect (target hazard ratio [HR] = 0.65) and will be monitored at 60% (information fraction, 142 events [ie, 142 patients who have events]) with the possibility of early termination if there is overwhelming evidence of efficacy or futility. The following assumptions are considered: percentage of patients remaining event-free at one-year in the leuprolide acetate group is 93.5% (ie, MACE rate at one-year is 6.5%), about 96% in the relugolix group (ie, MACE rate at one-year is about 4%) and dropout rate is 5% at one-year for either relugolix group or leuprolide acetate group. A constant hazard ratio is assumed throughout the study and a stratified log-rank test and Cox proportional hazards model are used to analyze the data

As of 04 Dec 2023, study was terminated and enrollment into the study was stopped.

3. PLANNED ANALYSES

For the original study of group-sequential (G-S) design study, there are two planned analyses (one formal interim analysis and a final analysis).

As of 04 Dec 2023, study was terminated and no formal efficacy statistical analyses will be performed but safety analyses will be performed.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING OF MISSING DATA

4.1. Data Presentation Conventions

All statistical analyses will be conducted using SAS® Version 9.4 or higher.

Statistical tests for the primary and secondary endpoints will be assessed at a two-sided $\alpha = 0.05$ significance level, and all confidence intervals will be reported as two-sided, unless otherwise stated.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated.

4.2. Analysis Populations

As of Dec 2023, only safety population will be analyzed.

4.2.1. Safety Population

Safety population is defined as all randomized patients who are treated with at least one dose of relugolix or one injection of leuprolide after the date of randomization to the study. Safety population will be used to analyze other safety data including treatment-emergent serious adverse events and clinical laboratory tests as obtained per standard of care.

4.3. Definitions, Computations, and Conventions

4.3.1. Definition of Date of First Dose and Date of Last Dose of Study Drug

The date of the first dose of study drug (relugolix or leuprolide) is defined as the date when a patient receives the first dose of study drug (the date of visit for injection of leuprolide acetate or the self-reported date of drug intake of relugolix by the patient). The date of the last dose of study drug is defined as the date a patient receives the last dose of study drug. If the date of last dose of study drug is unknown, the last date the study drug was known to have been taken will be used.

4.3.2. Study Day

Study day will be calculated with respect to the date of randomization (Study Day 1). For assessments conducted on or after the date of randomization, study day will be calculated as:

(Assessment date – date of randomization) + 1

For assessments conducted before the date of the randomization , study day will be calculated as:

(Assessment date – date of randomization)

4.3.3. Definition of Treatment Duration

Treatment duration is defined as the duration of time from the date of the first dose of study drug to the date of the last dose of study drug as follows:

(Date of last dose of study drug– Date of first dose of study drug) + 1

For patients with partial or completely missing last dose of study drug, the following algorithm will be used to impute:

- If the last date of study drug is completely missing, the last known study drug taken date will be used as the last date of study drug;
- If the last date of study drug is partially missing
    - If only year YYYY is recorded, then impute this date: 31DECYYYY, if year = year of last known drug taken date and last date of study drug = minimum of (last known drug taken date, date of death, imputed date);
    - If both year and month are available, impute the missing day as the last day of the month and last date of study drug = minimum of (date of death, imputed date)

4.3.4. Definition of Baseline Value and Post-Baseline Value

Unless otherwise specified, baseline values are defined as the last measurement before the first administration (date) of study drug. A postbaseline value is defined as a measurement taken after the first administration of study drug. Change from baseline is defined as (postbaseline value − baseline value).

4.4. Patient Disposition

The number and percentage of patients for each of the disposition (to be defined) categories will be summarized by treatment group for the ITT population. Reasons for discontinuation of study treatments and study will be collected and summarized in the study.

4.5. Screen Failure

Patients who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. Number and percent of screen failure patients will be summarized.

4.6. Protocol Deviation

Protocol deviations will be categorized as important or minor per the study protocol deviation plan which will be established prior to patient enrollment of the study. Number and percent of patients with important protocol deviation will be summarized for the ITT population.

4.7. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group for the ITT population. Categorical data will be summarized using frequencies and percentages, by treatment group and overall. Summaries of continuous data will display the mean, SD, median, minimum, and maximum. The numbers and percentages of missing values will also be summarized.

4.8. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities and will be summarized on ITT population by system organ class and preferred term (PT). A patient with multiple occurrences of medical history within a PT will be counted only once in that PT.

4.9. Prior Medications and Concomitant Medications

Prior medications and concomitant medications taken during the study treatment period will be summarized for all patients in the ITT population by treatment group. Medications are considered concomitant if exposure occurs during the treatment period (including use of enzalutamide, abiraterone, darolutamide, or apalutamide) while on study drug.

5. STUDY DRUG EXPOSURE AND COMPLIANCE

Following randomization, patients will follow SOC practices with their investigator, which for the leuprolide acetate group will include visits for injection of leuprolide acetate. The investigator must record all dates of leuprolide acetate administration in the electronic data capture system. For the relugolix group, patients will self-administer relugolix at home.

Each patient will have a follow-up visit (either in office or by telehealth; per the investigator's discretion) during this discontinuation phase until they transition to SOC.

6. SAFETY ANALYSES

Safety analyses will be performed on the safety population including summary of adverse event, serious adverse events, laboratory data, and vital signs.

6.1. Adverse Events and Serious Adverse Events

Per protocol, serious adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative) using questionnaires submitted electronically. Serious adverse events will also be reported by the investigators electronically through the electronic data capture.

The severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE v5.0) and will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities 25.1 or higher.

Treatment-emergent serious adverse event is defined as any serious adverse event that occur after administration of the first dose of study drug and prior to the end of the study.

Serious adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. Listing for all serious adverse events will be provided.

Tabular summaries with the number and percentage of patients with the following adverse events (but not limited to) will be provided:

- Overview of adverse events
- All adverse events
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
  - By decreasing frequency of preferred term and relatedness to study drug

- All serious adverse events
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- Serious adverse events leading to study drug withdrawn
  - By system organ class and preferred term
  - By decreasing frequency of preferred term
- Serious adverse events in fatal outcome
  - By system organ class and preferred term
  - By decreasing frequency of preferred term

6.2. Laboratory Data

Laboratory values from non-protocol specified laboratory assessments performed at a local laboratory will be listed in a by-patient listing.

6.3. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and oral temperature are measured at baseline. A by-patient listing will be provided.

7. REFERENCES

ICH guidelines E3
ICH E9
ICH E9(R1)