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Biostatistics & Statistical Programming /
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Brolucizumab

CRTH258A2309

A Single-Arm, Open-Label, Multicenter, Phase IIIb Study to Collect Safety and Electrocardiogram Data on Brolucizumab 6 mg Intravitreal Treatment in Patients with Neovascular Age-Related Macular Degeneration

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CRTH258A2309".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Study protocol (v00) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1 Primary Objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
• To collect information on ECG after IVT injection of brolucizumab 6 mg in patients with nAMD	• Incidence between 20 and 24h post-injection of clinically relevant treatment emergent changes in HR, PR, QRS, and QTc (heart rate corrected QT using Fridericia's formula, QTcF) interval (ms)

1.3.2 Secondary Objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
• To collect safety data after IVT injection of brolucizumab 6 mg in patients with nAMD	• Any ocular and non-ocular AEs (including clinically relevant ECG abnormalities) until the end of the study

1.4 Study design and treatment

This is a single-arm, open-label, multicenter phase IIIb study to collect Electrocardiogram (ECG) data after a single intravitreal (IVT) injection of brolucizumab 6 mg in patients with Neovascular Age-Related Macular Degeneration (nAMD).

Approximately 10-15 (male and female) patients ≥ 50 years old with nAMD are expected to be enrolled in the US and Puerto Rico. Patients will receive one single intravitreal injection (IVT) of brolucizumab 6 mg during the treatment phase of the study.

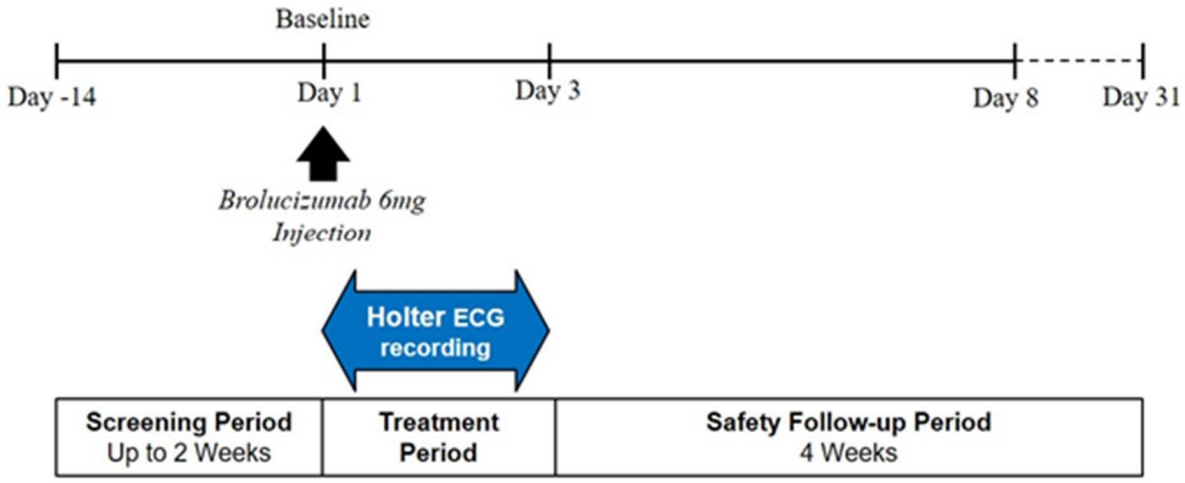
Figure 1-1 depicts the design of the study, starting from a screening epoch (2 weeks), a treatment period from Day 1 (Baseline visit) to Day 3 and the End of Study (EoS) on Day 8, with additional safety follow-up phone call will be performed on Day 31. Total study duration for each patient is up to 8 days.

Triplicate 12-lead ECG recording will be performed at screening to determine eligibility. A second triplicate 12-lead ECG recording will be collected approximately 2h prior to the brolucizumab IVT injection on Day 1. Holter ECG recording will start approximately 1 h prior

to the brolucizumab IVT injection and will end approximately 48h after the IVT injection. A third triplicate 12-lead ECG recording will be performed after the conclusion of Holter monitoring on Day 3.

There are no formal hypothesis in the study and all analysis will only be descriptive.

Figure 1-1: Study design



2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The study FIR template (mock slides) can be found in CREDI in the study RAP Cabinets/CREDI Projects/R/RTH258/CREDI Studies/RTH258A2309/Administrative Files (study level)/RAP or RAMP Meeting/.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

FIR will focus on the following analyses:

- Subject Disposition
- Demographics and baseline characteristics. Baseline characteristics include, but not limited to:
    - Age, blood pressure (systolic and diastolic), pulse rate
- Safety results:
    - Number and percentage of subjects with adverse events by body system and ocular/non-ocular events.
    - Number and percentage of subjects with adverse events by preferred term and ocular/non-ocular events.

- Overall incidence of AEs
- Summary statistics of 12-lead ECG parameters (HR, PR, QRS and QTcF) by timepoints (screening, baseline and 48h post injection)
- Summary statistics of the 12-lead Holter ECG parameters (HR, PR, QRS and QTcF) by timepoints (baseline, 20h, 22h and 24h post injection).
- Summary statistics of the frequency and proportion of patients in QTcF change ≥ 30 ms and ≥ 60 ms by visit/time (20h, 22h and 24h post injection) compared to baseline on the 12-lead Holter ECG.
- Summary statistics of the frequency and proportion of patients with QTcF > 450, 480, and 500 ms (baseline, 20h, 22h and 24h post injection) on the 12-lead Holter ECG.
- Individual plots of change from baseline for 12-lead Holter ECG parameters (HR, PR, QRS, QTcF and QTcB) with arithmetic mean overlaid over time.
- Listing of arrhythmic events on the 12-lead Holter ECG by timepoint (1h before injection to time of injection, 22 to 23 h after injection and 47 to 48 h after injection)

3 Interim analyses

Not applicable.

4 Statistical methods: Analysis sets

The safety analysis set will include all patients that received one (1) IVT injection of brolucizumab 6 mg. All analyses will be performed on the Safety Set unless otherwise specified.

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from safety analysis in case of these Protocol Deviations (PDs):		Exclude subject from safety analysis set
xxxxx	*xxxxxx*	*xxxxx*

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

6 Statistical methods for safety and tolerability data

All subjects within the safety analysis set will be included in the safety data analysis.

6.1 Variables

Company Confidential Information

6.2 Descriptive analyses

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