Horizon Pharma Rheumatology LLC
(Formerly Crealta Pharmaceuticals LLC)

M0401 REPORT ANALYSIS PLAN
Protocol Number M0401

Observational Study of the Use of KRYSTEXXA® (pegloticase) in Adult Hyperuricemic Patients with Gout Refractory to Conventional Therapy

SPONSOR
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The RAP was updated to remove the data cut-off date for the month 36 analysis (Feb 2016 CSR), the final analysis was preformed using all data.
Final
March 25, 2018

Confidential

Approvals

[redacted]

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Date

Senior Director, Clinical Development and Operations

[redacted]

[redacted]: I approve this document

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Date

Associate Director, Biostatistics

M0401 Report Analysis Plan

Study Objectives

Primary

The primary objective of the study is to evaluate the frequency and severity of infusion reactions (IRs), anaphylaxis, and immune complex-related events.

Secondary

Secondary objectives are to identify Serious Adverse Events (SAEs) associated with pegloticase therapy and to further evaluate the efficacy of pegloticase in the patient population of adult hyperuricemic patients.

Patient Populations (Analysis Sets)

Intention-to-Treat Population

The Intention-to-Treat (ITT) population will consist of all patients completing the Baseline visit regardless of whether or not any study treatment was received. Patients must have met all inclusion/exclusion criteria and agreed to participate in the study.

Modified Intention-to-Treat Population

The Modified Intention-to-Treat (mITT) population will consist of all patients who received at least one infusion of study treatment. Patients must also have at least one post-baseline SUA measurement.

Per-Protocol Population

The Per-Protocol (PP) population will consist of all patients who complete the study including the treatment and follow-up phases.

Safety Population

The Safety population will consist of all patients who receive at least one (full or partial) infusion of pegloticase. All enrolled patients will be assumed to have taken pegloticase unless otherwise confirmed. If it is confirmed that a patient never took an infusion of pegloticase, then the patient will be excluded from all safety analysis. The safety population will be used for all safety analyses.

Primary Analysis Populations

The ITT population will be considered the population of primary interest for the efficacy analysis.

The assessment of safety will be based on the Safety population.

Report Format/Structure

- Enrollment
    - What has been done to address enrollment over the years?
    - Number of patients enrolled per calendar year?
    - Number of sites recruited for study since study initiation
        - Number of actively enrolling sites
            - Number of actively enrolling sites per calendar year
        - Number of sites dropping out per year
        - Reason for site drop outs
- Safety Endpoints
    - Number of IRs by dose (1st v. 2nd v. 3rd etc.)
    - IRs by severity or not by dose
    - Number of anaphylaxis by dose (1st v. 2nd v. 3rd etc.)
    - Anaphylaxis severity or not by dose
- Efficacy endpoints
    - Number of patients meeting the primary efficacy effect at 24 and 52 weeks
    - Number of protocol treated patients meeting the primary efficacy effect

1. Patient disposition flow chart:
    a. Total Number of patients screened
    b. Number of patients dosed
        i. Number of patients currently receiving drug
    c. Number of completers at 24 weeks
        i. How many were responders versus non responders (based on primary efficacy criteria)
    d. Number of completers at 52 weeks
        i. How many were responders versus non responders (based on primary efficacy criteria)
    e. Number of non-completers at 24 and 52 weeks
        i. Reason for non-completing (AE, IR, etc.)
    f. Number of patients treated per protocol through 24 and 52 weeks
        i. Chart out responders versus non-responders in this cohort
2. Dosing:
    a. Total number of infusions by study cut-off

b. Total number of infusions per patient
c. Number of IRs per total number of infusions

3. Protocol violations related to time SUA measured before pegloticase infusion
    a. Number of times SUA was over 6
    b. Number of patients who continued to receive infusion after SUA > 6 on 2 consecutive occasions in 24 and 52 week cohorts
    c. Number of patients with premature (> 48 hours before infusion) SUA measures with AE, SAE (IRs, anaphylaxis).
4. Protocol violations related to dosing (schedule other than Q2 week dosing)
    a. Number of patients with dosing violations with AE, SAE (IRs, anaphylaxis).
5. Number of patients in follow up
    a. Reasons for loss to follow-up? (AEs, SAEs, death, etc.)
6. How would protocol be amended to encourage enrollment, study compliance, and significantly less number of completers (200) versus the original protocol (500)?
7. What is the statistical implications of having 200 patients completing 24 weeks of treatment? .

Tables

Tables, where applicable, to include 24 week completers data (including demographics, SUA, IR, anaphylaxis data)

a. 24 week patient descriptions and outcomes relative to primary and secondary objectives