Statistical Analysis Plan

Horizon Therapeutics USA, Inc.

HZNP-TEP-001

A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics, and Explore Efficacy of TEPEZZA in Patients with Diffuse Cutaneous Systemic Sclerosis

Protocol Version: 02 February 2022(Version 5.0)

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History of Revisions

Effective Date	Version	Author	Description of Changes
25 JAN 2021	1.0	PPD	Original Version
07 DEC 2022	2.0	PPD	Main reasons for updating the SAP: • Protocol update • Update scope of work for abbreviated CSR due to study termination by sponsor

Prepared by: PPD Date: ___/___/___

Approved by: PPD Date: ___/___/___

Approved by PPD Date: ___/___/___

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LIST OF ABBREVIATIONS

Abbreviation	Full Notation
CCI [redacted]	[redacted]
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
CSR	clinical study report
dcSSc	diffuse cutaneous systemic sclerosis
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IGF-1	insulin-like growth factor-1
IGF-1R	insulin-like growth factor-1 receptor
CCI [redacted]	[redacted]
[redacted]	[redacted]
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CCI [redacted]	[redacted]
PK	pharmacokinetic(s)
CCI [redacted]	[redacted]
TEAE	treatment-emergent adverse event
QOL	quality of life
SAP	statistical analysis plan
CCI [redacted]	[redacted]

1. INTRODUCTION

HZNP-TEP-001 study is terminated by sponsor due to lack of enrollment. As a result, an abbreviated clinical study report (CSR) will be provided for this study. This statistical analysis plan (SAP) describes the listings that will be generated for the abbreviated CSR. The SAP is based on protocol: HZNP-TEP-001 V5.0 amendment 4, dated on 02 February, 2022 by Horizon Therapeutics U.S.A., Inc. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to evaluate the safety of TEPEZZA versus placebo on the proportion of subjects who experience a treatment-emergent adverse event (TEAE) through Week 24 in subjects with diffuse cutaneous systemic sclerosis (dcSSc).

2.2 Other Objectives

Other objectives include:

CCI

CCI [redacted]

2.3 Pharmacokinetic and Anti-drug Antibody Objectives

1. Evaluate the pharmacokinetics (PK) of TEPEZZA
2. Evaluate the immunogenicity of TEPEZZA

2.4 Safety and Tolerability Objectives

To assess safety and tolerability of TEPEZZA including AEs, AEs of special interest (AESI) (hyperglycemia, hearing impairment, infusion reaction, new onset or exacerbation of inflammatory bowel disease), vital signs, clinical safety laboratory evaluations and inflammatory laboratory evaluations.

3. STUDY ENDPOINTS

Study endpoints are defined to address study objectives. A total of 3 subjects enrolled at the time of trial termination decision was made. Due to a small number of subjects enrolled in the study, summary statistics will be not generated for these pre-defined endpoints. Instead, by-subject listings will be provided to support an abbreviated CSR preparation.

3.1 Primary Endpoint

The proportion of subjects who experience a TEAE (as defined by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) through Week 24 in subjects with dcSSc.

3.2 Other Endpoints

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- CCI
- CCI
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.3 PK and Anti-drug Antibody Endpoints

- PK of teprotumumab.
- The incidence of anti-drug antibody (ADA) and titer levels.

3.4 Safety and Tolerability Endpoints

Safety data such as adverse events, vital signs, and labaoratory test results will be presented in listings.

4. STUDY DESIGN AND PLAN

This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter study. Subjects will be screened for the study within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 25 subjects who meet the study eligibility criteria will be randomized on Day 1 in a 3:2 ratio to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo every 3 weeks. During the 24-week double-blind Treatment Period, study drug will be infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 with a comprehensive visit at Week 24 (end of treatment). All study drug dosing will be performed at the clinic or infusion center under the supervision of clinic staff or nurses. At any scheduled infusion, the infusion rate may be reduced, or the dose may be interrupted or held based on tolerability. On each dosing day, scheduled assessments (except for AE and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to study drug infusions. After each of the first 2 infusions, subjects will be contacted by phone/email the following day. Additional phone/email contacts and clinic visits may also be conducted for any subject experiencing an infusion-associated event.

At the end of the Treatment Period (Week 24), subjects will enter a 24-week Follow-up Period, during which study drug will not be administered and a clinic visit will be scheduled for Weeks 28, 36 and 48. A phone call or email at Weeks 32 and 42 will occur to inquire how the subject is doing and women of childbearing potential will be asked if they have missed a menstrual cycle and will have a serum pregnancy test, if required.

Subjects who prematurely discontinue prior to completing the Treatment Period will return to the clinic and undergo the scheduled Week 24 assessments; such subjects will also be encouraged to continue in the 24-week Follow-up Period. If a subject prematurely discontinues prior to completing the 24-week Follow-up Period, he/she will return to the clinic and undergo the Week 48 assessments.

5. DETERMINATION OF SAMPLE SIZE

Approximately 25 subjects will be randomized in a 3:2 ratio to receive TEPEZZA or placebo every 3 weeks.

For a TEAE that occurs in 20% of TEPEZZA-treated subjects in the dcSSc population, a sample size of 15 subjects provides approximately 95% probability that the TEAE will be observed at least once.

This study is not powered to detect a statistically significant difference in the proportion of ACR-CRISS responders unless the difference is very large. For example, if 10% of all placebo subjects were responders and 75% of all TEPEZZA subjects were responders, this study would have 87% power to find a difference (α=0.050, 2-tailed).

6. LISTINGS

For the abbreviated CSR, no statistical analysis will be performed. Instead, by-subject data listings will be provided to support the CSR. Data will be presented as reported. The following listings will be provided:

- Demographics
- Inclusion/exclusion criteria
- Medical/surgical history
- Systemic sclerosis history
- Substance use
- Subject disposition
- Protocol deviation
- Safety data
- Efficacy data

7. CHANGES IN THE PLANNED ANALYSIS

Due to the early termination of the trial by sponsor, only abbreviated CSR will be created for this study. No statistical analysis will be performed for this study. Instead, by-subject data listings will be provided to support the CSR preparation.