Statistical Analysis Plan

Protocol Title:	Long-Term Safety Extension of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia
Protocol Number:	HZNP-ACT-303 Version 1.0 (05-Apr-2016) Administrative Change 1 (21-Apr-2016)
Compound:	ACTIMMUNE
Phase:	III
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SIGNATURE PAGE AND APPROVALS

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2 Jun 2017
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ABBREVIATIONS

ABBREVIATION	DEFINITION OR DESCRIPTION
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
EMA	European Medicines Agency
FA	Friedreich's Ataxia
FARS	Friedreich's Ataxia Rating Scale
FARS-mNeuro	Friedreich's Ataxia Rating Scale excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score
FARStot	Total FARS Score
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
LLOQ	Lower Limit of Quantitation
LOD	Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TIW	Three times a week
TEAE	Treatment-emergent Adverse Event
ULOQ	Upper Limit of Quantitation
WHO-DD	World Health Organization Drug Dictionary

1. OVERVIEW

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Horizon Pharma Ireland, Ltd. protocol HZNP-ACT-303 (Long-Term Safety Extension of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia), Final Version 1.0 and Administrative Change 1, dated 21-Apr-2016.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3], for statistical practice.

The planned analysis identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analysis not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc, or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

In addition to the study protocol, the following documents were reviewed in preparation of this SAP:

- The electronic case report forms (eCRFs) for this Protocol
- ICH Guidance on Statistical Principles for Clinical Trials (E9).

The reader of this SAP is encouraged to also read the clinical protocol, and other identified documents, for details on the planned conduct of this study. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of this study are:

- To evaluate the long-term safety of ACTIMMUNE in subjects with Friedreich's Ataxia (FA).

2.2 Study Endpoints

The analysis for this study is for an abbreviated safety Clinical Study Report (CSR). All efficacy endpoints mentioned in the protocol have been removed and noted as changes to the planned analyses.

2.2.1 Safety Endpoints

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, and ECG interval data will be summarized with descriptive statistics for

Baseline of HZNP-ACT-303, post-dose, and change from Baseline of HZNP-ACT-303 to post-dose values. Shift tables will be presented for clinical laboratory values and ECG categorical results from Baseline of HZNP-ACT-303 to each post-dose visit. Physical examination findings will be listed by subject.

3. OVERALL STUDY DESIGN AND PLAN

This is a multi-center, open-label, long-term safety extension study of ACTIMMUNE in the treatment of FA in children and young adults. Subjects who complete 26 weeks of treatment in HZNP-ACT-302 will be eligible for enrollment in this study. The sample size is not based on statistical considerations.

The overall maximum treatment duration for an individual subject is open-ended and treatment will continue until ACTIMMUNE is commercially available for the treatment of FA in the US or until the Sponsor decides to discontinue development for this indication. The initial dose of ACTIMMUNE will be individualized for each subject and will be determined by the investigator, provided that the initial dose does not exceed the maximum tolerated dose in HZNP-ACT-302. The investigator may subsequently adjust the dose for any subject if deemed clinically appropriate, provided that the dose does not exceed 100 µg/m2. All doses of ACTIMMUNE will be administered by subcutaneous injection three times a week (TIW) at home.

Table 1.Schedule of Events

Study Phase	Treatment Period			End-of-Study or Premature Withdrawal[10]
	Baseline[6]	3-Month Visits[8]	6-Month Visits	
Study Days (± visit window)	Day 1 (Week 28 of Study HZNP-ACT-302)	90 (± 7) Days after Last Visit	Every 180 (± 14) Days	
Informed consent/assent	X			
Medical history[1]	X			
Review of inclusion/exclusion criteria	X			
Dispense study drug[2]	X	X[9]	X	
Drug compliance[3]		X[9]	X	X
TEAE, SAE assessment[4]	X[7]	X	X	X
Brief physical examination	X[7]		X	X
Vital Signs: blood pressure, pulse, temperature	X		X	X
Clinical laboratory evaluation (hematology, chemistry, urinalysis)	X		X	X
Electrocardiograms				X[11]
Urine pregnancy test[5]	X		X	X
FARS				X[11]
Prior/concomitant medications	X[7]	X	X	X

SAE=serious adverse event, TEAE=treatment-emergent adverse event.

[1] Changes in medical history from the Baseline of HZNP-ACT-301 will be recorded on the electronic case report forms. The medical history from the HZNP-ACT-301 study will be available for reference.

[2] Subjects will be given a 3-month supply of study drug at each clinic visit and an additional 3-month supply will be directly shipped to the subjects' home in between the required 6-month clinic visits. If direct shipments are not feasible, subjects will return to the clinic every three months to obtain study drug; however, assessments (other than adverse event queries) will only be performed every six months.

[3] Subjects will be instructed to return all used and unused study drug vials at each clinic visit.

[4] Adverse events occurring or worsening on or after the date of administration of the first dose of study drug through the end of the study will be considered treatment-emergent adverse events (TEAEs). All serious adverse events (SAEs) that occur on or after the date of administration of the first dose of study drug through two weeks after study discontinuation will be considered treatment-emergent SAEs (TESAEs) and will be recorded and reported to Horizon drug safety.

[5] Only for female subjects of childbearing potential.

[6] The Day 1 Visit of this study (HZNP-ACT-303) occurs on the same day as the EOS Visit (Week 28 Follow-Up Visit) for HZNP-ACT-302.

[7] Findings will be recorded for both the Day 1 (Baseline) Visit of this study and the Week 28 Follow-up Visit for HZNP-ACT-302.

[8] Subjects who are not able to receive direct-to-home study drug shipments will return to the clinic for interim clinic visits three months after the Baseline and 6-month assessment visits; those who are able to receive direct-to-home shipments will be contacted by telephone.

[9] Perform at clinic visits only; those with telephone visits will receive/return study drug supplies at next clinic visit.

[10] Subjects who complete the study will undergo final assessments while still on study drug and will then be transitioned to commercial product. Subjects who prematurely withdraw from the study will have the EOS assessments completed within two weeks of study drug discontinuation. In the event the Sponsor decides to discontinue development for the treatment of FA, all subjects will be contacted and instructed to return to the clinic for final assessments while still on active drug.

[11] For statistical purposes, the last on-treatment visit from HZNP-ACT-302 (Visit 26) will be used to assess changes to the EOS assessment in this study.

4. ANALYSIS AND REPORTING

4.1 Interim Analysis

No formal interim analysis is planned for this study.

4.2 Final Analysis

All final, planned analysis identified in the protocol and in this SAP will be performed after the last subject has completed the End of Study Visit and all relevant study data have been processed and integrated into the analysis data base.

Any post-hoc, exploratory analysis completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

5. ANALYSIS POPULATIONS

The following analysis populations are planned for this study:

- **Safety Population (SAFETY):** The Safety Population includes all subjects who receive at least one dose of open-label study drug after the Baseline Visit for HZNP-ACT-303. All analyses will be based on the Safety Population unless otherwise noted.

5.1 Sample Size

Subjects who complete 26 weeks of treatment in Study HZNP-ACT-302 will be eligible for enrollment. The sample size is not based on statistical considerations; therefore no inference will be drawn from any statistical tests conducted.

6. GENERAL ISSUES FOR STATISTICAL ANALYSIS

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed using SAS® Software (release 9.3 or higher) for Windows, unless otherwise specified.

Continuous (quantitative) variables will be summarized using descriptive statistics including number of non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variables will be summarized using the number and proportion of each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the raw data. Measures of location (mean and median) will be reported to 1 degree of precision more than the raw data and measures of spread (standard deviation) will be reported to two degrees of precision more than the raw data.

Assessments done on unscheduled visits will not be summarized but will be listed. All analyses will be completed on the Safety Population unless otherwise specified. Additionally, all summaries will be presented by overall treatment.

All final, planned analyses identified in the protocol and in this SAP will be performed after all relevant study data have been processed and integrated into the analysis database, analysis populations have been finalized, and the database has been locked. Any post-hoc, exploratory

analysis completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in Section 9.8 of the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified as subject in the text of the CSR.

6.1 Visit Windows

Subjects who withdraw from the study will have their data collected at the premature withdrawal (PW) visit assigned to the closest scheduled visit (either prior or post PW) where the data was scheduled to have been collected based on the protocol schedule of events. The data collected closest in time and date to protocol scheduled timing will be used for analysis.

6.2 Data Adjustments, Handling, Conventions

All collected data will be presented in listings. Data not subject to analyses according to this plan will not appear in any tables or graphics but will be included only in the data listings.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1). Concomitant medications will be coded using World Health Organization Drug Dictionary (WHO-DD) (version March 1, 2013).

If partial dates occur, the convention for replacing missing dates for the purposes of calculating derived variables is as follows:

For partial start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then:
    - If the year matches the year of enrollment date, then impute the month and day of the randomization date.
    - Otherwise, assign 01 January
- If the day is unknown, then:
    - If the month and year match the month and year of the enrollment date, then impute the day of the first dose date.
    - Otherwise, assign 01

For partial end dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then assign the last day of the year, 31 December.

If the day is unknown, then assign the last day of the month.

If an AE has a missing severity, it will be imputed as ‘Severe’; any missing relationship to study drug of an AE will be imputed as ‘Related’. No other missing data will be imputed unless otherwise specified.

In general, for quantitative laboratory values reported as ‘<’ or ‘≤’, the lower limit of quantitation (LLOQ), or limit of detection (LOD), the reported value (i.e., LLOQ, LOD) will be used for analysis).

For quantitative laboratory values reported as ‘>’ or ‘≥’, the upper limit of quantitation (ULOQ), the reported value (i.e., ULOQ) will be used for analysis.

For analysis purposes, repeat laboratory test results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat

laboratory value will be used for data analysis.

6.3 Derived and Computed Variables

The following derived and computed variables have been initially identified as important for the analyses of Safety and Efficacy endpoints. It is expected that additional variables may be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files. If the SAP is not amended, further derivations related to primary and secondary target variables will be described in the CSR.

- 303 Baseline = The last non-missing measurement/assessment on the date of Week 26 Visit from HZNP-ACT-302. If this measurement is missing or otherwise unavailable, it will be the last non-missing measurement/assessment on or prior to first dose in HZNP-ACT-303.
- Study Day = Assessment Date – Date of Enrollment + 1
- Change from Baseline = Value at Post-Baseline – Value at Baseline
- Concomitant Medication is defined as any medication a subject has received concurrently with study treatment.
- Prior Medication is defined as any medication or therapies initiated prior to date of first dose of study drug. Medications that are started prior to the date of first dose of study drug and continue after the first dose of drug are considered to be both prior and concomitant medications.
- Treatment-Emergent Adverse Event (TEAE) – A TEAE is any adverse change from the subject's baseline condition that occurs on or after the date of the first dose of study drug through the duration of the clinical study.
- Related TEAE – Any TEAE with a reported relationship to study drug of 'possibly related'.
- Compliance = Calculated as the percentage of the number of vials used divided by the expected number of vials used, where the number of vials used is the number of used vials returned.

7. STUDY SUBJECTS AND DEMOGRAPHICS

7.1 Disposition of Subjects and Withdrawals

All subjects who provide informed consent/assent will be accounted for in this study. The number of subjects enrolled, completing, and withdrawing from the study, as well as reason for withdrawal, will be summarized by overall treatment. All disposition information will be included in a listing.

7.2 Protocol Violations and Deviations

Protocol deviations will be collected by the clinical team and provided to Premier biostatistics prior to database lock. Deviations will be reviewed on a case-by-case basis to be classified as major or minor by the project team prior to database lock. Major and minor deviations will be

included in a listing.

7.3 Demographics and Other Baseline Characteristics

Descriptive summaries and frequencies/percentages of demographic and other baseline characteristics will be completed for all enrolled subjects in the safety population for data collected in HZNP-ACT-301. These tabulations will include the following variables:

- Demographics (age, age categories (10-16 inclusive, and 17 and above), gender, race, ethnicity, height, weight, and Body Surface Area (BSA))

Tabulations of baseline HZNP-ACT-301 efficacy assessments will include the following in a separate table:

- FA Functional Stage
- FARS-mNeuro score
- ADL
- T25FW
- FARStot

Descriptive summaries and frequencies/percentages of demographic and other baseline conditions in separate tabulations will include the following:

- Medical History
- Prior Medications
- Baseline Physical Examination

Medical History: Incidences of findings in medical history will be summarized by System Organ Class and preferred term.

Prior Medications: The frequency and percentage of all prior medications will be summarized by Anatomical Therapeutic Chemical (ATC) classifications level 3 and preferred term for all subjects. Subjects will only be counted once within ATC and preferred term. These data will be grouped by overall treatment.

Baseline physical examination: Baseline physical examination will be summarized by body system and result by overall treatment.

8. EFFICACY ANALYSIS

All analyses are being conducted for an abbreviated safety CSR, and no efficacy analysis will be carried out.

9. SAFETY AND TOLERABILITY ANALYSIS

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Adverse Events
    - Summary of all Adverse Events
    - TEAEs, and Serious Adverse Events (SAEs)
    - TEAEs by severity
    - TEAEs by relationship to study drug
    - TEAEs leading to premature withdrawal

  - Any deaths
- Clinical Laboratory Investigations
  - Complete Blood Count
  - Chemistry panel
  - Urinalysis
- Electrocardiograms (ECG)
- Echocardiograms
- Physical Examinations
- Concomitant Medications
- Study Drug Exposure and Treatment Compliance

All tabulations and summaries for these categories will be performed on the safety population unless otherwise noted.

9.1 Adverse Events

Missing and partially missing AE start and/or stop dates will be imputed for the purpose of statistical analysis, according to the specifications described in Section 6.2.

A summary of overall TEAEs, TEAEs, SAEs, TEAEs leading to PW, TEAEs by relationship to study drug, and severity of TEAEs will be presented by overall treatment.

Summaries and incidence rates (frequencies and percentages) of individual TEAEs by MedDRA System Organ Class (SOC) and preferred term will be displayed by overall treatment received. Such summaries will be displayed for TEAEs, SAEs, TEAEs leading to early termination, TEAEs by relationship to study drug, and TEAEs by severity

Each subject will be counted only once within each preferred term. If a subject experiences more than one TEAE within a preferred term only the TEAE with the strongest relationship or the maximum intensity, as appropriate, will be included in the summaries of relationship and intensity. No inferential statistical tests will be performed.

In the AE data listings, all AEs will be displayed.

9.1.1 Deaths

A summary and data listing of deaths that occurred will be provided, displaying details of the event(s) captured on the CRF.

9.2 Clinical Laboratory Evaluations

Descriptive summaries of actual (absolute) values and changes from baseline will be presented for Chemistry, Urinalysis, and Complete Blood Count. These tables will be grouped by visit, and overall treatment.

The number and proportion of subjects with clinical laboratory values below, within, or above normal ranges, at each study visit will be tabulated (shift tables) for each clinical laboratory analyte by treatment group. Normal ranges will be provided by the central laboratory (Eurofins Central Laboratory) used in this study.

Laboratory values will be displayed in data listings and those that are outside the normal range will be flagged, along with the corresponding normal ranges.

9.3 Vital Signs

Descriptive summaries of actual (absolute) values and changes from baseline will be presented for all vital signs (temperature, systolic blood pressure, diastolic blood pressure, heart rate), weight, height, and BSA will be presented by visit and overall treatment. These data will be presented in a data listing by subject.

9.4 Electrocardiogram (ECG) and Echocardiogram

Descriptive summaries of actual (absolute) values and changes from baseline will be presented for ECG quantitative measures (heart rate, PR interval, QRS duration, QT interval and QTC interval). These data will be summarized by visit and overall treatment.

Additionally, the frequency and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECGs will be summarized by visit. Shift tables will also be presented and display the number of subjects who had values that shifted from their baseline result.

ECG and echocardiogram data will be presented by subject in separate data listings.

9.5 Concomitant Medication

Concomitant medications will be analyzed the same way as prior medications as noted in Section 7.3. The frequency and percentage of all concomitant medications will be summarized by ATC classification level 3 and preferred term for all subjects. Subjects will only be counted once within ATC and preferred term. These data will be grouped by overall treatment. A listing of prior and concomitant medications will be presented by subject.

9.6 Exposure and Compliance

For each subject, treatment compliance and exposure will be calculated and summarized for the entire study. Overall compliance and exposure will be summarized and grouped by overall treatment. Compliance is defined in Section 6.3. Drug accountability, exposure, and treatment compliance will also be provided in a subject listing.

10. CHANGES FROM PLANNED ANALYSIS

All efficacy analyses as described in the protocol will not be summarized since the clinical study report is an abbreviated safety report.

11. REFERENCES

US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.

ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999.http://www.amstat.org/about/ethicalguidelines.cfm

RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.

12. TABLES, LISTINGS, AND FIGURES

This section presents the list of shells for the planned Tables, Listings and Figures to be programmed in support of the planned analyses identified in the SAP. This section is intended to support the SAP and provides guidance on the programming specifications (shells) for the planned outputs and may be updated, independent of the SAP, with any updates appropriately documented, reviewed, and approved.

The following reporting conventions will be adopted for the presentation of study data. These conventions will enhance the review process and help to standardize the presentation with common notations.

General Reporting Conventions

- All tables and data listings will be developed in landscape orientation.
- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters should be used in tables and data listings. Special characters, such as nonprintable control characters, printer-specific characters, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ,α,β).
- All titles will be centered on a page. The ICH numbering convention is to be used for all outputs.
- All footnotes will be left justified and at the bottom of a page.
- Missing values for both numeric and character variables will be presented as blanks in a table or data listing. A value of zero may be used if appropriate to identify when the frequency of a variable is not observed.
- All date values will be presented as ddmmmyyyy (e.g., 29AUG2011) format. A 4-digit year is preferred for all dates.
- If applicable, all observed time values will be presented by using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.
- All tables and data listings will have the name of the program, the location, and a date stamp on the bottom of each output.

Population Summary Conventions

- Population sizes may be presented for each classification factor as totals in the column header as (N=xxxx), where appropriate.
- Population sizes shown with summary statistics are the samples sizes (n) of subjects with non-missing values.
- All population summaries for categorical variables will include all categories that were planned and for which the subjects may have had a response. Percentages corresponding to null categories (cells) will be suppressed; however counts and percentages of missing values may be needed.

- All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g., number missing, geometric mean, median, quartiles, 95% CIs, and coefficient of variation (CV) or % CV) may be used as appropriate.
- All percentages are rounded and reported to a single decimal point (xx.x %). A percentage of 100% will be reported as 100%.
- Population summaries that include P-values will report the P-value to 4 decimal places with a leading zero (0.0001). All P-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.0001 should be reported as <0.0001 not 0.0000.

13. [redacted]

14. PLANNED LISTINGS