



**CLINICAL STUDY PROTOCOL
FOR ACTIMMUNE®**

IND: 123947

**Protocol Number: HZNP-ACT-302
Version 2.0, incorporating Amendment 1**

**Multicenter, Safety and Efficacy, Open-Label Extension Study of
ACTIMMUNE® (interferon γ -1b) in Children and Young Adults with
Friedreich's Ataxia**

Short title: STEADFAST Open-Label Extension

**Safety, Tolerability and Efficacy of ACTIMMUNE® Dose Escalation in
Friedreich's Ataxia Study**

Date: 28 September 2016

**Collaborator:
Friedreich's Ataxia Research Alliance (FARA)**

**Sponsor:
Horizon Pharma Ireland Ltd.
Connaught House, 1st Floor
1 Burlington Road
Dublin 4, Ireland**

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This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written
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CONFIDENTIAL

PROTOCOL

1. TITLE PAGE

Study Title: Multicenter, Safety and Efficacy, Open-Label Extension Study of ACTIMMUNE® (interferon γ -1b) in Children and Young Adults with Friedreich's Ataxia

Protocol Number: HZNP-ACT-302

Version: 2.0, incorporating Amendment 1

Investigational Product: ACTIMMUNE

Indication: Friedreich's Ataxia (FA)

Sponsor: Horizon Pharma Ireland Ltd.
Connaught House, 1st Floor
1 Burlington Road
Dublin 4, Ireland

Development Phase: 3

Sponsor's Responsible Medical Officer: [REDACTED]
Senior Medical Director
Horizon Pharma, Inc.
150 South Saunders Road
Lake Forest, IL 60045

Sponsor Signatory: [REDACTED]
Chief Medical Officer
Horizon Pharma Ireland Ltd.

Approval Date: 28 September 2016

CONTACT IN THE EVENT OF AN EMERGENCY

Any death, life threatening event, or other Serious Adverse Event experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by telephone or fax to the contact numbers provided below.

Med Communications, Inc.
20 South Dudley, Ste. 700
Memphis, TN 38103
Telephone number: [REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

SPONSOR SIGNATURE PAGE

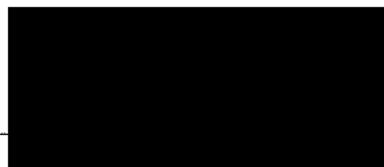
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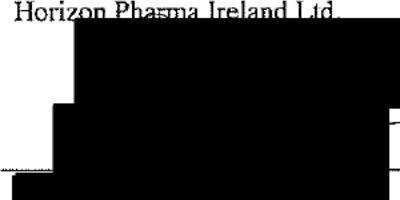
Version Date: 28 September 2016

Approved by:



29 SEP 2016
Date

Chief Medical Officer &
Executive Vice President, Research and Development
Horizon Pharma Ireland Ltd.



29 SEP 2016
Date

Coordinating Principal Investigator
Professor of Neurology
The Children's Hospital of Philadelphia



9/29/16
Date

Executive Director
Friedreich's Ataxia Research Alliance



29 SEP 2016
Date

Director, Biostatistics
Horizon Pharma, Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-ACT-302

Version: 2.0, incorporating Amendment 1

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Version Date: 28 September 2016

I agree to conduct the study according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a subject.

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the study drug supplied by the Sponsor will be used only as described in the protocol named above.

Name
Study Center
Address
City State

Date

SUMMARY OF CHANGES
Protocol HZNP-ACT-302
Version 2.0, incorporating Amendment 1

The original protocol was approved on 11 September 2015. This protocol is being further amended to collect additional safety data related to cardiac function (echocardiogram) and blood coagulation parameters (prothrombin time and activated partial thromboplastin time).

Since the initiation of this study, there has been a single case report of a study participant who developed cardiac hypertrophy (evidenced by respiratory distress and decreased left ventricular ejection fraction) and thrombosis in the ventricles, lung, and possibly the superior mesenteric artery that resulted in a fatal outcome approximately 5 months after initiating open-label treatment with ACTIMMUNE in this study. A detailed review of this event by the investigator and Sponsor did not reveal any causality with ACTIMMUNE, and given that Friedreich's Ataxia (FA) is associated with various forms of heart disease, such as hypertrophic cardiomyopathy [Weidemann et al, 2013], an acute process superimposed on chronic underlying heart disease must be considered. This single case report contrasts with a recently published case report showing improvement of cardiac hypertrophy and cardiomyopathy in a patient with FA who was treated with interferon γ -1b for one year [Wyller et al, 2016]. In addition, off-protocol physician-prescribed ACTIMMUNE therapy has not been identified to have adverse cardiac events, including 8 FA patients treated by the coordinating principal investigator (CPI) of this study for at least 6 months. In order to provide clarification regarding the effect of ACTIMMUNE on cardiac function and blood coagulation, echocardiogram and blood clotting parameters have been included in this amended protocol.

Echocardiograms, which were not scheduled in the original protocol, will be performed at Baseline and Week 26 (or premature withdrawal). In addition, the volume of individual blood samples for clinical laboratory safety analyses will be increased from 4.5 mL to 9.3 mL at each previously scheduled time point to accommodate the additional coagulation parameter testing.

In addition, the Sponsor's local address, employee titles, and signatories were updated, the contact person for the Academic Research Organization (ARO) was updated, and the contract organization performing statistical analyses was changed from the ARO to Premier Research.

The following sections of the protocol are affected: [2](#), [2.1](#), [4](#), [6](#), [9.1](#), [9.5.3](#), [9.5.3.5](#), [9.5.3.7](#), [9.5.5.1](#), [9.5.5.2](#), [9.5.5.3](#), [9.5.5.4](#), [9.6.1](#), and [17.1](#).

2. SYNOPSIS

Criteria for Evaluation:

Safety Assessments

- Vital signs, clinical safety laboratory evaluations (complete blood count, **prothrombin time [PT]**, **international normalized ratio [INR]**, **activated partial thromboplastin time [aPTT]**, chemistry, and urinalysis), and pregnancy testing (if applicable) at all on-treatment clinic visits.

- Echocardiogram at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).

Safety Endpoints

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, **echocardiogram data**, and ECG interval data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values.

2.1 Schedule of Assessments

Study Phase	Treatment Period				Follow-up Safety Visit
	Baseline ¹¹	1	2	3	
Visit #	Baseline ¹	4	13	26 (or PW)	28
Week	1				
Study Days (± visit window)	Day 1 (Week 26 of Study HZNP-ACT-301)	29 (± 3) days	92 (± 3) days	183 (± 3) days	197 (± 3) days
Safety Assessments					
TEAE, SAE assessment ¹¹	X	X	X	X	X
Immunogenicity testing ¹²	X	X	X	X	X
Echocardiogram	X			X	
ECG	X		X	X	
Physical examination ¹³	X	X ¹³	X	X	X ¹³
Vital Signs: blood pressure, pulse, temperature	X	X	X	X	
Urine pregnancy test ¹⁴	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X
Clinical laboratory evaluation ¹⁵ (hematology, chemistry, urinalysis)	X	X	X	X	
End treatment					X

¹¹ Adverse events occurring or worsening on or after the date of administration of the first dose of study drug at home through the end of the study will be considered treatment-emergent adverse events (TEAEs). All SAEs that occur on or after the date of administration of the first dose of study drug at home through two weeks after study discontinuation will be recorded.

¹² If a subject tests positive for anti-drug antibodies (ADA), he/she will be followed until ADA levels revert to baseline.

¹³ Brief physical examinations will be performed at the Week 4 and Follow-Up Safety Visits; all other examinations will be complete physical examinations.

¹⁴ Only for female subjects of childbearing potential.

¹⁵ Collect blood samples for clinical safety laboratory testing (total 9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for coagulation) and a urine sample for urinalysis.

4. LIST OF ABBREVIATIONS

PT, INR, and aPTT abbreviations were added.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Study site monitoring, project management, **and** data management, **and** statistical analyses will be performed by the Clinical Trials Coordination Center (CTCC), an Academic Research Organization (ARO) at the University of Rochester, Rochester, NY. **Statistical analyses will be performed by Premier Research International, LLC.**

Table 6.1 Table of Non-Sponsor Study Responsibilities

Clinical Trials Coordination Center (CTCC) (project management, clinical monitoring, and data management, and statistical analyses)	Academic Research Organization (ARO) Center for Human Experimental Therapeutics (CHET) University of Rochester 265 Crittenden Avenue Rochester, NY 14624
Statistical Analyses	Premier Research International, LLC One Park Drive, Suite 150 Durham, NC 27709

9.1 Overall Study Design and Plan

Safety Assessments

- Vital signs, clinical safety laboratory evaluations (complete blood count, **prothrombin time [PT]**, **international normalized ratio [INR]**, **activated partial thromboplastin time [aPTT]**, chemistry, and urinalysis), and pregnancy testing (if applicable) at all on-treatment clinic visits.
- **Echocardiogram at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).**

9.5.3 Safety Variables

- Safety will be assessed via AE and concomitant medication use monitoring, immunogenicity testing, physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, **PT**, **INR**, **aPTT**, chemistry, and urinalysis), pregnancy testing (if applicable), **echocardiograms**, and ECGs.

9.5.3.5 Echocardiograms (section added)

Echocardiograms are scheduled for Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).

9.5.3.7 Clinical Laboratory Tests

Samples of blood (**9.34.5 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT**) and urine are scheduled for collection at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW).

The following clinical laboratory tests will be performed:

- Complete blood count
- PT (and derivation of INR) and aPTT
- Chemistry panel
- Urinalysis

9.5.5.1 Baseline/Day 1 (Week 26 of Study HZNP-ACT-301)

- Collect blood (9.34.5 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]). The pregnancy test must be negative for those subjects to be eligible for participation in this study.
- Collect blood samples (2 mL) for immunogenicity testing.
- Collect blood samples (1 mL) for frataxin analyses.
- Measure height and weight to calculate dose volume.
- Educate subjects and caregivers on dosing technique and schedule.
- Between approximately 7 to 10 AM, administer the last dose of double-blind study drug for Study HZNP-ACT-301 or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.
- Perform physical examination, including vital signs.
- Enquire about AEs and concomitant medications.
- Perform ADL, and Physician's and Patient's Global Assessments.
- Perform echocardiogram.
- Perform ECG.

9.5.5.2 Week 4 and

9.5.5.3 Week 13

- Collect blood (9.34.5 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]).

9.5.5.4 Week 26 (Termination Visit or Premature Withdrawal Visit)

- Collect blood (9.34.5 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]).
- Collect blood samples (2 mL) for immunogenicity testing.
- Collect blood samples (1 mL) for frataxin analyses.
- Measure height and weight.

- Between approximately 7 to 10 AM, administer study drug or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.
- Perform physical examination, including vital signs.
- Enquire about AEs and concomitant medications.
- Perform ADL and Physician's and Patient's Global Assessments.
- **Perform echocardiogram.**
- Perform ECG.

9.6.1 Endpoints

Safety Endpoints

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, **echocardiogram data**, and ECG interval data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values.

17.1 Administrative Appendix

Medical Monitor

[REDACTED]
Senior Medical Director
Horizon Pharma, Inc.
[REDACTED]
150 South Saunders Road
[REDACTED] Lake Forest, IL [REDACTED] 60045

Sponsor Representative

[REDACTED]
Executive Director, Clinical Development &
Operations
Horizon Pharma, Inc.
[REDACTED]
150 South Saunders Road
[REDACTED] Lake Forest, IL [REDACTED] 60045

Academic Research Organization (ARO)

[REDACTED]
Center for Human Experimental Therapeutics (CHET)
Telephone number: [REDACTED]
Email: [REDACTED]

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2. SYNOPSIS

Protocol Title: Multicenter, Safety and Efficacy, Open-Label Extension Study of ACTIMMUNE® (interferon γ -1b) in Children and Young Adults with Friedreich's Ataxia

Protocol Number: HZNP-ACT-302	Phase: 3
Protocol Version: 2.0, incorporating Amendment 1	
Test Drug: ACTIMMUNE (interferon γ -1b)	Indication: Friedreich's Ataxia (FA)

Number and Country of Study Sites: Approximately 4 study centers in the United States.

Objectives:

Primary Study Objective

To evaluate the long-term safety of ACTIMMUNE in subjects with FA.

Primary Efficacy Objective

To evaluate the effect of ACTIMMUNE (interferon [IFN]- γ 1b) on the change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in neurological outcome as measured by Friedreich's Ataxia Rating Scale (FARS) excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score (FARS-mNeuro score).

Secondary Efficacy Objectives

To evaluate the effect of ACTIMMUNE (interferon [IFN]- γ 1b) on the change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies for the following:

- Activities of Daily Living (ADL)
- The timed 25-foot-walk test (T25FW)
- Responder rate (≥ 3 point improvement in the FARS-mNeuro score)
- Neurological outcome as measured by the total FARS score (FARStot)

Study Design:

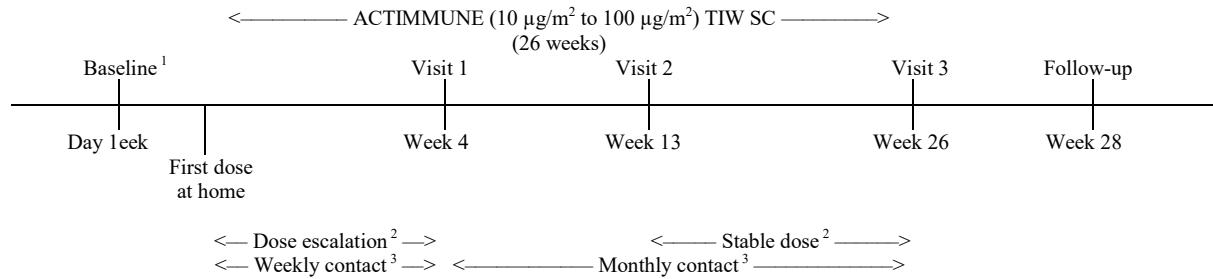
This is a multi-center, dose-escalation, open-label extension study of HZNP-ACT-301 examining the safety and efficacy of ACTIMMUNE in the treatment of FA in children and young adults. Subjects who complete 26 weeks of blinded treatment in HZNP-ACT-301 will be eligible to enter this 6-month study. All subjects who choose to participate will receive ACTIMMUNE three times a week (TIW) for 26 weeks. In order to maintain the study blind in HZNP-ACT-301, all subjects in this open-label extension study will undergo ACTIMMUNE titration, regardless if they received ACTIMMUNE or placebo in HZNP-ACT-301. The study drug dose is planned to be escalated on a weekly basis over the first 4 weeks of treatment (from $10 \mu\text{g}/\text{m}^2$ to $100 \mu\text{g}/\text{m}^2$), however, the dose may be reduced, interrupted, or held based on tolerability. By Week 13, all subjects are to be on a stable tolerated dose of study drug in order to continue study participation; the dose may not be further increased after Week 13, however, it may be reduced on a case-by-case basis to manage subsequent drug-related adverse events (AEs) (e.g., elevated liver function tests).

The Week 26 Visit from HZNP-ACT-301 will serve as the Baseline Visit (Day 1) for this study. All subjects will undergo Baseline assessments and be assigned to the lowest dose ($10 \mu\text{g}/\text{m}^2$) of ACTIMMUNE. The first dose of study drug will be administered at home before bedtime according to the subject's TIW dosing schedule. During the treatment period, additional clinic visits are scheduled at Weeks 4, 13, and 26; in between clinic visits, subjects (and/or caregivers) will be monitored via emails/phone calls on a weekly basis until subjects reach their maximum tolerated dose and on a monthly basis thereafter.

Subjects will return to the clinic two weeks after the last dose of study drug for a Follow-Up Safety Visit.

An overview of the study design is presented in the schematic below, and details of study activities are provided in [Section 2.1, Schedule of Assessments](#).

Schematic of Study Design



¹ Week 26 of HZNP-ACT-301 will serve as the Baseline Visit (Day 1) for this study. Subjects will receive the last dose of the randomized drug from HZNP-ACT-301 in a double-blind fashion, and the first dose of study drug for the open-label extension study (10 $\mu\text{g}/\text{m}^2$) will be distributed for administration at home according to the planned TIW dosing schedule.

² The planned dose escalation consists of two doses of ACTIMMUNE 10 $\mu\text{g}/\text{m}^2$ in the first week, followed by weekly escalation to 25, 50, and 100 $\mu\text{g}/\text{m}^2$ TIW on Days 8, 15, and 22, respectively; however, the dose may be reduced, interrupted, or held based on tolerability. All subjects are to be on a stable tolerated dose of study drug by Week 13 in order to continue study participation.

³ Subjects and/or caregivers will be contacted by email or phone to monitor safety and dosing logistics on a weekly basis from Day 1 (Week 26 of HZNP-ACT-301) through Week 4 (or until stable tolerated dose is achieved) and on a monthly basis after Week 4 (or after dose stabilization) through Week 26.

Subject Population:

Male and non-pregnant female subjects who completed 26 weeks of blinded treatment in Study HZNP-ACT-301 will be enrolled.

Inclusion Criteria:

Eligible subjects must meet **all** of the following criteria:

1. Written informed consent and child assent, if applicable.
2. Completed 26 weeks of blinded treatment in Study HZNP-ACT-301.
3. If female, the subject is not pregnant or lactating or intending to become pregnant during the study, or within 30 days after the last dose of study drug. Female subjects of child-bearing potential must have a negative urine pregnancy test result at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and agree to use a reliable method of contraception throughout the study and for 30 days after the last dose of study drug.

Exclusion Criteria:

Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

Dose Regimen/Route of Administration:

Subjects will receive SC doses of ACTIMMUNE TIW for 26 weeks. The volume of study drug will be determined using the subject's body surface area (BSA) at the appropriate clinic visit. The planned dose escalation consists of two doses of ACTIMMUNE 10 $\mu\text{g}/\text{m}^2$ in the first week, followed by weekly escalation to 25, 50, and 100 $\mu\text{g}/\text{m}^2$ TIW on Days 8, 15, and 22, respectively; however, dose escalation will only occur if the previous dose is tolerated. If, in the opinion of the investigator, severe reactions occur during dose escalation, the dose will be reduced to the previous dose level or will be interrupted until the adverse reaction resolves and then restarted at the previous or a lower dose level. By Week 13 of the study, subjects must be receiving a stable tolerated dose of study drug; the dose should not be further increased but should be maintained for the remaining 13 weeks of the study, however, dose reductions will be allowed on a case-by-case basis to manage subsequent drug-related AEs.

Dosage Form and Strength Formulation:

The commercial formulation of ACTIMMUNE will be used in this study. Each 0.5 mL of ACTIMMUNE contains 100 μg (2 million international units [IU]) of IFN- γ 1b.

Duration of Treatment and Follow-Up:

The planned treatment duration is 26 weeks (6 months), with a Follow-Up Safety Visit two weeks following the last dose of study drug.

Criteria for Evaluation:

Safety Assessments

- Adverse event (AE) monitoring, concomitant medication monitoring, and physical examinations throughout the study.
- Immunogenicity testing pre-dose at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, 26 (or premature withdrawal [PW]), and 28.
- Vital signs, clinical safety laboratory evaluations (complete blood count, prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], chemistry, and urinalysis), and pregnancy testing (if applicable) at all on-treatment clinic visits.
- Echocardiogram at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).
- Electrocardiogram (ECG) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), with additional ECGs at Weeks 13 and 26 (or PW).

Efficacy Assessments

- FARS, ADL assessment, T25FW, and 9-hole peg test (9-HPT) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and 4 to 6 hours post-dose at Weeks 13 and 26 (or PW).
- Low-contrast Sloan letter chart (LCSLC) Vision Test at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Week 26 (or PW).
- For all subjects with a normal audiogram result at Screening in Study HZNP-ACT-301, Listening in Spatialized Noise-Sentences Auditory Test (LiSN-S) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Week 26 (or PW).
- Frataxin protein levels in whole blood, muscle biopsies (optional), and buccal cells at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Weeks 13 and 26 (or PW).
- Functional staging of ataxia at Baseline/Day 1 (Week 26 of study HZNP-ACT-301), and post-dose at Weeks 13 and 26 (or PW).
- Physician Global Assessment and Patient Global Assessment at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Weeks 13 and 26 (or PW).

Quality of Life Assessments

- Quality of life assessments (Modified Fatigue Impact Score [MFIS], and Pediatric Quality of Life [PedsQL] questionnaire or 36-item short-form health survey [SF-36]) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 13 and 26 (or PW). The MFIS will be completed for all subjects. Subjects who completed the PedsQL during Study HZNP-ACT-301 will continue to complete the PedsQL in this study. Subjects who completed the SF-36 during Study HZNP-ACT-301 will continue to complete the SF-36 in this study.

Statistical Analyses:

All summaries will be presented by both the treatment received in HZNP-ACT-301 as well as overall.

Safety Endpoints

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, echocardiogram data, and ECG interval data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values. Shift tables will be presented for clinical laboratory values and ECG categorical results from Baseline to each post-dose visit. Physical examination findings will be listed by subject. Results of immunogenicity testing will be presented in tabular format.

Efficacy Endpoints

The primary efficacy endpoint is the observed change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in the FARS-mNeuro score. Results will be summarized descriptively.

Secondary Efficacy Endpoints

The observed mean change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in ADL, T25FW, FARS-mNeuro responder rate, and FARStot results will be summarized descriptively.

Exploratory Efficacy/Quality of Life Endpoints

The observed mean changes from Baseline will be summarized descriptively for the following endpoints:

- Change from Baseline to Week 13 in the FARS-mNeuro, ADL, T25FW, and FARStot scores.
- Change from Baseline to Weeks 13 and 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in 9-HPT, remaining FARS subscale scores, FA stage, frataxin protein levels, MFIS, SF-36, PedsQL, and Physician and Patient Global Assessments.
- Change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in LCSLC and LiSN-S.

Sample Size Estimate:

Subjects who complete 26 weeks of blinded treatment in Study HZNP-ACT-301 will be eligible for enrollment. The sample size is not based on statistical considerations.

2.1 Schedule of Assessments

Study Phase	Visit #	Treatment Period				Follow-up Safety Visit
		Baseline ¹	1	2	3	
Week	1	4	13	26 (or PW)	28	
Study Days (\pm visit window)	Day 1 (Week 26 of Study HZNP-ACT-301)		29 (\pm 3) days	92 (\pm 3) days	183 (\pm 3) days	197 (\pm 3) days
Informed consent/assent	X					
Review of inclusion/exclusion criteria	X					
Weight/height, BSA ²	X	X	X	X		
Educate on dosing technique and schedule ³	X	X	X			
Dose given at study visit ⁴		X	X	X		
Dispense study drug ⁵	X	X	X			
Drug compliance		X	X	X		
Phone (email) contact for safety and dosing logistics ⁶	X	X	X			
Efficacy assessments ⁷						
Functional staging of FA ⁷	X		X	X		
FARS ⁷	X		X	X		
T25FW ⁷	X		X	X		
9-HPT ⁷	X		X	X		
Vision testing (LCSLC)	X				X	
Auditory testing (LiSN-S) ⁸	X				X	
Frataxin protein: whole blood, muscle biopsy (optional) ⁹ , and buccal cells	X		X	X		
Physician and Patient Global assessments	X		X	X		
ADL	X		X	X		
Quality of Life (QOL) Assessments						
PedsQL or SF-36 ¹⁰	X		X	X		
MFIS	X		X	X		
Safety Assessments						
TEAE, SAE assessment ¹¹	X	X	X	X	X	
Immunogenicity testing ¹²	X	X	X	X	X	
Echocardiogram	X				X	
ECG	X			X	X	
Physical examination ¹³	X	X ¹³	X	X	X ¹³	
Vital Signs: blood pressure, pulse, temperature	X	X	X	X	X	
Urine pregnancy test ¹⁴	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X
Clinical laboratory evaluation ¹⁵ (hematology, chemistry, urinalysis)	X	X	X	X	X	
End treatment					X	

9-HPT=9-hole peg test, ADL=activities of daily living, BSA=body surface area, ECG=electrocardiogram, FA=Friedreich's Ataxia, FARS=Friedreich's Ataxia Rating Scale, IFN=interferon, LCSLC=Low-contrast Sloan letter chart, LiSN-S=Listening in Spatialized Noise-Sentences Auditory Test, MFIS=Modified Fatigue Impact Scale, PedsQL=Pediatric Quality of Life, PW=premature withdrawal, QOL=quality of life, SAE=serious adverse event, SF-36=36-item short form health survey, T25FW=timed 25-foot walk, TEAE=treatment-emergent adverse event.

Footnotes are presented on the next page.

- ¹ On Day 1 (Baseline), subjects will receive the last dose of assigned study drug (ACTIMMUNE or placebo) for HZNP-ACT-301, and undergo assessments; these assessments will serve as the Week 26 assessments for HZNP-ACT-301 and the Baseline assessments for HZNP-ACT-302.
- ² Height and weight will be measured at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 to determine BSA; dosing will be based on BSA at Baseline/Day1, and Weeks 4 and 13.
- ³ Study drug will be initiated at home following the Baseline/Day 1 visit at 10 $\mu\text{g}/\text{m}^2$ according to the subject's TIW dosing schedule. The planned dose escalation consists of two doses of ACTIMMUNE 10 $\mu\text{g}/\text{m}^2$ in the first week, followed by weekly escalation to 25, 50, and 100 $\mu\text{g}/\text{m}^2$ TIW on Days 8, 15, and 22, respectively; however, the dose may be reduced, interrupted, or held based on tolerability. All subjects are to be on a stable tolerated dose of study drug by Week 13 in order to continue study participation
- ⁴ At the Baseline/Day 1 visit (Week 26 of Study HZNP-ACT-301), subjects will receive the last dose of study drug from the double-blind Study HZNP-ACT-301 (ACTIMMUNE or placebo). The first dose for this open-label extension study (ACTIMMUNE 10 $\mu\text{g}/\text{m}^2$) will be administered at home before bedtime according to the subject's TIW dosing schedule. Dosing at Weeks 4, 13, and 26 will be performed at the clinic. All other doses will be administered at home before bedtime.
- ⁵ Subjects will be given a 4-week supply of study drug prior to clinic discharge at the Baseline/Day 1 Visit (Week 26 of Study HZNP-ACT-301). At the Week 4 and 13 Visits, subjects will be given a 6-week supply of study drug, and additional study drug will be directly shipped to the subjects' homes as needed; if direct shipment is not feasible, subjects may receive a full supply at Weeks 4 and 13 (9-week supply at Week 4 and 13-week supply at Week 13).
- ⁶ Subjects and/or caregivers will be contacted by email or phone to monitor safety and dosing logistics on a weekly basis during the dose-escalation period (from Day 1 through at least Week 4 [or later until a stable tolerated dose is reached]) and on a monthly basis after dose stabilization (from Week 4 or when dose is stabilized) through Week 26.
- ⁷ Functional staging, FARS, T25W, and 9-HPT will be performed at approximately the same time of day at each visit and by the same examiner.
- ⁸ The LiSN-S will only be performed for subjects who had a normal audiogram prior to enrollment in HZNP-ACT-301. The LiSN-S will be performed at the Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 visits.
- ⁹ Muscle biopsies will be optional for each subject, and consent will be signed prior to biopsy collection. Biopsies will be the last efficacy assessment of the day at Weeks 13 and 26.
- ¹⁰ The PedsQL (study subject and parent/caregiver assessments) will be administered throughout the study for subjects who received the PedsQL at their Baseline Visit of the HZNP-ACT-301 study (even if subjects turn 18 during their participation in either Study HZNP-ACT-301 or HZNP-ACT-302). The SF-36 will continue to be administered throughout the study for subjects who completed the SF-36 during their HZNP-ACT-301 study participation.
- ¹¹ Adverse events occurring or worsening on or after the date of administration of the first dose of study drug at home through the end of the study will be considered treatment-emergent adverse events (TEAEs). All SAEs that occur on or after the date of administration of the first dose of study drug at home through two weeks after study discontinuation will be recorded.
- ¹² If a subject tests positive for anti-drug antibodies (ADA), he/she will be followed until ADA levels revert to baseline.
- ¹³ Brief physical examinations will be performed at the Week 4 and Follow-Up Safety Visits; all other examinations will be complete physical examinations.
- ¹⁴ Only for female subjects of childbearing potential.
- ¹⁵ Collect blood samples for clinical safety laboratory testing (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and a urine sample for urinalysis.

3. TABLE OF CONTENTS

1. TITLE PAGE.....	2
2. SYNOPSIS.....	11
2.1 Schedule of Assessments	15
3. TABLE OF CONTENTS.....	17
4. LIST OF ABBREVIATIONS.....	21
5. ETHICS.....	23
5.1 Institutional Review Board.....	23
5.2 Ethical Conduct of the Study	23
5.3 Subject Information and Consent/Assent.....	23
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE.....	23
7. INTRODUCTION	25
7.1 Scientific Background.....	25
7.2 Rationale for the Study.....	26
7.3 Rationale for Dose Selection.....	27
8. STUDY OBJECTIVES.....	29
8.1 Primary Study Objective	29
8.2 Primary Efficacy Objective.....	29
8.3 Secondary Efficacy Objectives	29
9. INVESTIGATIONAL PLAN	30
9.1 Overall Study Design and Plan	30
9.2 Discussion of Study Design	32
9.3 Selection of Study Population.....	33
9.3.1 Inclusion Criteria	33
9.3.2 Exclusion Criteria	33
9.3.3 Removal of Subjects from Therapy or Assessment	33
9.4 Treatments.....	34
9.4.1 Treatments Administered.....	34
9.4.1.1 Dose Adjustment Guidelines.....	35
9.4.2 Identity of Investigational Products.....	35
9.4.2.1 ACTIMMUNE	35

9.4.3	Labeling	36
9.4.4	Storage	36
9.4.5	Study Drug Quality Issues	36
9.4.6	Drug Accountability.....	37
9.4.7	Study Drug Administration and Timing of Dose for each Subject.....	37
9.4.7.1	Description of Clinical Supplies	37
9.4.7.2	Determination of Dose Volume	37
9.4.7.3	Details Concerning Timing and Dose Administration.....	38
9.4.8	Method of Assigning Subjects to Treatment Group	39
9.4.9	Blinding.....	39
9.4.10	Concomitant Therapy and Restricted Medications.....	39
9.4.11	Treatment Compliance.....	39
9.5	Efficacy, Quality-of-Life, and Safety Variables	40
9.5.1	Efficacy Variables.....	40
9.5.1.1	Functional Stage of Friedreich's Ataxia.....	40
9.5.1.2	Friedreich's Ataxia Rating Scale (FARS).....	40
9.5.1.3	Activities of Daily Living	41
9.5.1.4	Timed 25-Foot Walk	41
9.5.1.5	Nine-Hole Peg Test	41
9.5.1.6	Low-Contrast Sloan Letter Chart (LCSLC) Vision Test	42
9.5.1.7	Listening in Spatialized Noise – Sentences Test (LiSN-S).....	42
9.5.1.8	Frataxin.....	43
9.5.1.9	Physician's and Patient's Global Assessments	43
9.5.2	Quality-of-Life Assessments	43
9.5.2.1	Pediatric Quality of Life Inventory (PedsQL).....	43
9.5.2.2	36-Item Short-Form Health Survey (SF-36)	44
9.5.2.3	Modified Fatigue Impact Scale (MFIS)	44
9.5.3	Safety Variables	44
9.5.3.1	Adverse Events.....	44
9.5.3.1.1	Definitions	45
9.5.3.1.2	Documentation of Adverse Events	46

9.5.3.1.3 Grading of Adverse Events.....	47
9.5.3.1.4 Relationship to Study Drug	47
9.5.3.1.5 Reporting and Documenting SAEs.....	48
9.5.3.1.6 Follow-Up of Adverse Events	49
9.5.3.1.7 Medication Error and Overdose	49
9.5.3.1.8 Review of Adverse Events and Emerging New Safety Information	49
9.5.3.1.9 Reporting of IND Safety Reports	50
9.5.3.2 Pregnancy Reporting	50
9.5.3.3 Vital Signs.....	50
9.5.3.4 Physical Examinations, Height, and Weight.....	50
9.5.3.5 ECGs	51
9.5.3.6 Clinical Laboratory Tests	51
9.5.3.7 Immunogenicity Testing	51
9.5.4 Appropriateness of Measurements.....	51
9.5.5 Study Procedures	52
9.5.5.1 Baseline/Day 1 (Week 26 of study HZNP-ACT-301)	52
9.5.5.2 Week 4.....	53
9.5.5.3 Week 13.....	54
9.5.5.4 Week 26 (Termination Visit or Premature Withdrawal Visit).....	55
9.5.5.5 Follow-Up Safety Visit	56
9.6 Statistical Methods and Determination of Sample Size.....	56
9.6.1 Endpoints	56
9.6.2 Populations for Analysis	57
9.6.3 Baseline Characteristics	57
9.6.4 Sample Size and Power Considerations.....	57
9.7 Changes in the Conduct of the Study	57
10. SOURCE DOCUMENTATION AND INVESTIGATOR FILES	57
11. CASE REPORT FORMS	58
12. STUDY MONITORING	59
13. DATA MANAGEMENT.....	60
14. RETENTION OF RECORDS	60

15. PUBLICATION	60
16. REFERENCES	61
17. APPENDICES	64
17.1 Administrative Appendix	64
17.2 Approved US Labeling for ACTIMMUNE	65
17.3 FARS Neurological Assessment	76
17.4 ADL Assessment.....	83
17.5 PedsQL Inventory (Child Report for Ages 8-12).....	84
17.6 SF-36 Assessment	86
17.7 MFIS Assessment.....	93

LIST OF TABLES

Table 6.1 Table of Non-Sponsor Study Responsibilities.....	24
Table 7.1 Approved Dosing for ACTIMMUNE versus Proposed Clinical Dosing in This Study	28
Table 9.1 Dosing Allowance for Acetaminophen, Ibuprofen, and Diphenhydramine	39
Table 9.2 Functional Stage of Ataxia Scale.....	40

LIST OF FIGURES

Figure 9.1 Schematic of Study Design.....	31
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4. LIST OF ABBREVIATIONS

ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
aPTT	activated partial thromboplastin time
ARO	Academic Research Organization
ATP	adenosine triphosphate
BLA	Biologics License Application
BSA	body surface area
CFR	Code of Federal Regulations
CGD	chronic granulomatous disease
CHET	Center for Human Experimental Therapeutics
CPI	coordinating principal investigator
CSM	Clinical Supplies Management, Inc
CTCC	Clinical Trials Coordination Center
DNA	deoxyribonucleic acid
DRG	dorsal root ganglion
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
ECG	electrocardiogram
FA	Friedreich's Ataxia
FARA	Friedreich's Ataxia Research Alliance
FARS	Friedreich's Ataxia Rating Scale
FARS-mNeuro	FARS excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score
FARStot	FARS total score
FDA	Food and Drug Administration
FLS	flu-like symptoms
<i>FXN</i>	frataxin gene
GAA	guanine-adenine-adenine
GCP	Good Clinical Practice
HDAC	histone deacetylase
HEENT	head, eyes, ears, nose, throat
HIPAA	Health Insurance Portability and Accountability Act
9-HPT	9-Hole Peg Test
ICH	International Conference on Harmonization
IIS	Investigator-Initiated Study
IFN- γ	interferon gamma
IM	intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IU	international units

IV	intravenous
K ₂ -EDTA	potassium ethylene diamine tetraacetic acid
LCSLC	Low-contrast Sloan letter chart
LiSN-S	Listening in Spatialized Noise-Sentences
MedDRA	Medical Dictionary for Regulatory Activities
MFIS	Modified Fatigue Impact Score
mRNA	messenger RNA
PBMC	peripheral blood mononuclear cells
PedsQL	Pediatric Quality of Life
PW	premature withdrawal
PT	prothrombin time
QOL	Quality of Life
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	36-item short-form health survey
SMO	severe, malignant osteopetrosis
SRT	speech reception threshold
T25FW	Timed 25-foot walk
TEAE	treatment-emergent adverse event
TIW	three times per week
URL	uniform resource locator
URMC	University of Rochester Medical Center
US	United States
VAS	visual analog scale
WHODrug	World Health Organization Drug Dictionary

5. ETHICS

5.1 Institutional Review Board

The Principal Investigator (Investigator) will submit this protocol, any protocol modifications, and the subject Consent/Accent Form to be used in this study to the appropriate Institutional Review Board (IRB) for review and approval. A letter confirming the IRB approval of the protocol and the subject Consent/Accent Form, as well as a statement that the IRB is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the Sponsor or its designee **prior to** the enrollment of subjects into the study. A copy of the approved Consent/Accent Form will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the study will be made to the IRB and the Sponsor or its designee by the Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

5.2 Ethical Conduct of the Study

The Investigator will ensure that the study will be conducted in accordance with the Declaration of Helsinki and GCP in accordance to International Conference on Harmonisation (ICH) E6 guidelines. Specifically, the study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by an IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; and each subject and caregiver, if applicable, will give his/her informed consent/assent before any tests or evaluations are performed.

5.3 Subject Information and Consent/Accent

The Investigator or his/her designee must explain to the subject and caregiver, if applicable, the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent before enrolling that subject in the study. A properly executed, written Informed Consent and if necessary, Assent Form, in compliance with the Declaration of Helsinki, ICH GCP E6, and the United States (US) Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR Parts 50 and 56), will be obtained from each subject and his/her caregiver as applicable prior to entering the study. The Investigator will provide a copy of the signed Consent and Assent Form to each subject and his/her caregiver, as applicable. The originals will be maintained at the study site. It is the Investigator's (or designee's) responsibility to obtain written Informed Consent and if required, Assent from each subject and his/her caregiver.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Pharma Ireland Ltd (Horizon). Horizon personnel will serve as the Medical Monitor and the Sponsor's regulatory representative (see [Section 17.1](#) for details). The Sponsor's regulatory representative will be responsible for timely reporting of serious adverse events (SAEs) to US regulatory authorities as required. The Sponsor will be

responsible for timely reporting of SAEs and any other new pertinent safety information to all investigators as required.

The study will be conducted at approximately 4 study centers located in the US, with [REDACTED] at the Children's Hospital of Philadelphia (CHOP) serving as the coordinating principal investigator (CPI) (Table 6.1). Prior to initiation of the study, each principal investigator will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all sub-investigators listed on the Form 1572. It is the responsibility of the investigators or sub-investigators to advise the Sponsor of any change in the relevant financial interests that occur during the study and the one year period following its completion.

Study site monitoring, project management, and data management will be performed by the Clinical Trials Coordination Center (CTCC), an Academic Research Organization (ARO) at the University of Rochester, Rochester, NY. Statistical analyses will be performed by Premier Research International, LLC. Clinical Supplies Management, Inc ([CSM] in Fargo, ND) will label the study drug, package the study drug into kits, and provide kits of study drug to the clinical sites as well as direct-to-subject shipments. The study will be monitored by a Data Safety Monitoring Board (DSMB), which will advise the Sponsor regarding the continuing safety of study subjects and potential subjects as well as the continuing validity and scientific merit of the trial. The decision to modify or halt the study will be made collectively by the CPI, the Sponsor (Horizon), and FARA after review with the FDA. SAE intake will be performed by Med Communications, Inc (Memphis, TN).

Table 6.1 Table of Non-Sponsor Study Responsibilities

Study Responsibility	Organization
Coordinating Principal Investigator (CPI)	[REDACTED] Professor of Neurology The Children's Hospital of Philadelphia (CHOP)
SAE intake	Med Communications, Inc. 20 South Dudley, Ste. 700 Memphis, TN 38103
Data Safety Monitoring Board (DSMB)	[REDACTED], DSMB Chair, [REDACTED]
Clinical Trials Coordination Center (CTCC) (project management, clinical monitoring, and data management)	Academic Research Organization (ARO) Center for Human Experimental Therapeutics (CHET) University of Rochester 265 Crittenden Avenue Rochester, NY 14624
Statistical Analyses	Premier Research International, LLC One Park Drive, Suite 150 Durham, NC 27709

Study Responsibility	Organization
Clinical drug supply	Clinical Supplies Management, Inc. 342 42nd Street South Fargo, ND 58103
Immunogenicity laboratory	Intertek Pharmaceutical Services Immunochemistry 10420 Wateridge Circle San Diego, CA 92121
Central safety laboratory	University of Rochester Medical Center (URMC) 77 Ridgeland Road Rochester, NY 14623 USA
Frataxin analysis	CHOP Clinical and Translational Research Center 502 Abramson Research Center Philadelphia, PA 19104 USA

7. INTRODUCTION

7.1 Scientific Background

ACTIMMUNE (interferon [IFN]- γ 1b) is an orphan drug product currently approved and indicated for reducing the frequency and severity of serious infections associated with chronic granulomatous disease (CGD) and for delaying the time to disease progression in patients with severe, malignant osteopetrosis (SMO); it is approved under Biologics License Application (BLA) 103836, and is now being studied by Horizon in the treatment of FA.

FA is an autosomal recessive disorder associated with progressive ataxia, cardiomyopathy, scoliosis, diabetes, and loss of visual and sensorineural hearing function at later stages of the disease [Harding, 1981; Lynch et al, 2002a]. FA has a prevalence of about 1 in 50,000 persons in the US [Tsou et al, 2009]. Patients develop difficulty walking, loss of coordination, and dysarthria. Degeneration of the dorsal root ganglion (DRG) neurons, their axons in the dorsal columns, and the dorsal spinocerebellar pathways gives rise to loss of proprioception and associated ataxia. A few other nuclei (including the dentate of the cerebellum) within the central nervous system are affected and contribute to the ataxia [Simon et al, 2004]. The abnormal gene in FA and its product (frataxin) provide insight into pathophysiological mechanisms in this disease. In 98% of individuals, FA is caused by homozygous expanded guanine – adenine – adenine (GAA) repeats in the frataxin gene (*FXN*). This triplet repeat is located within an intron, leading to decreased ribonucleic acid (RNA) transcription and levels of the mitochondrial frataxin protein. Decreased frataxin expression is implicated in the assembly and repair of mitochondrial iron-sulfur-cluster containing enzymes and the ability to produce adenosine triphosphate (ATP) [Babcock et al, 1997; Koeppen, 2011; Rotig et al, 1997]. Frataxin deficiency leads to mitochondrial iron accumulation. This may initiate or propagate free radical reactions leading to cell death, consistent with mitochondrial dysfunction as a pathophysiological mechanism in FA.

Patients with FA have frataxin protein levels in peripheral tissues that range from 2-30% of control levels. The level of frataxin protein correlates with age of onset and inversely with the length of the GAA repeat. In carriers, who do not develop symptoms of FA, frataxin protein levels range from 30-80% of control levels [Deutsch et al, 2010]. The lack of symptoms observed in carriers suggests that restoration of frataxin levels in patients to those observed in carriers may lead to substantial improvement of symptoms.

At present, no therapy is approved for use in FA [Corben et al, 2014; Delatycki et al, 2014]. Many of the therapies being developed are designed to increase levels of frataxin, either by reversal of its transcriptional depression or by other means [Arpa et al, 2014; Lynch et al, 2010; Lynch et al, 2012]. Frataxin-depleted cells have an increased sensitivity to oxidative stress. Subtype-selective histone deacetylase (HDAC) inhibition has been successful *in vitro* at increasing levels of transcription of frataxin, and is beginning early stage trials in humans [Rai et al, 2008; Sandi et al, 2011]. Erythropoietin and its derivatives raise frataxin levels in peripheral tissues by non-transcriptional means, but the effect has been too small to observe efficacy in human trials [Boesch et al, 2014; Mariotti et al, 2012].

IFN- γ , a protein produced by the immune system in response to infections, increases both frataxin messenger RNA (mRNA) and protein levels in a variety of different cell types, including cell lines derived from FA patients. In addition, an FA mouse model treated with subcutaneous (SC) injections of IFN- γ for 14 weeks showed improvements in motor coordination, an effect that was mirrored by accumulation of frataxin protein in the DRG tissue in these mice [Tomassini et al, 2012]. Its mechanism of action is as a transcriptional activator of multiple genes. From a therapeutic perspective, IFN- γ 1b (ACTIMMUNE[®]) is approved for use in the US in patients with CGD and SMO (see prescribing information in Section 17.2), and has been investigated in other conditions, including oncology, infectious diseases, and inflammatory disorders.

7.2 Rationale for the Study

In an Investigator-Initiated Study (IIS) in FA conducted by [REDACTED], 12 subjects between the ages of 5 and 17 years (mean age of 12 years) with genetically-confirmed FA were treated with ACTIMMUNE by SC injection three times per week (TIW) over the course of a 12-week treatment period. The starting dose was 10 $\mu\text{g}/\text{m}^2$ for the first two weeks of the study, then escalated to 25 $\mu\text{g}/\text{m}^2$ for weeks three and four, and then escalated to 50 $\mu\text{g}/\text{m}^2$ for the final eight weeks of treatment. All subjects followed the same dose-escalation schedule, with adjustments made in the event of clinically significant adverse events (AEs). Ten of the subjects completed 12 weeks of treatment, with the remaining 2 subjects discontinuing prior to 8 weeks of treatment due to transportation issues.

As reported by the authors, ACTIMMUNE was well-tolerated with no SAEs, with only two subjects reporting severe dose-related AEs and subsequent dose reductions. Efficacy results showed small changes in frataxin levels observed in red blood cells, peripheral blood mononuclear cells (PBMC), and platelets after 12 weeks of treatment; however, the results

varied between tissues. Frataxin tissue samples were not timed to drug administration, potentially contributing to the variability of the results [\[Seyer et al, 2014\]](#).

The mean improvement in FARS score was significant after 12 weeks of treatment ($p = 0.008$). The magnitude of improvement in FARS score when contrasted with the natural history of FA deterioration was equivalent to almost 18 months of disease progression prevention and the absolute improvement in FARS may suggest not only prevention of disease progression but potential subject salvage and absolute disease improvement. No statistically significant relationships were observed between frataxin protein levels, FARS scores, and in vivo IFN- γ levels [\[Seyer et al, 2014\]](#). On withdrawal of ACTIMMUNE during the follow-up period, there was a trend for the FARS scores to worsen, suggesting a loss of therapy-related benefit.

Other secondary endpoints included timed performance tests, such as the timed 25-foot walk (T25FW), failed to show any significant treatment-related changes, but this may reflect the small sample size in this IIS.

Overall, the safety profile of ACTIMMUNE in FA subjects in this IIS mirrors the typical profile and frequency of AEs in the prescribing information for ACTIMMUNE. In two cases, the maintenance dose of ACTIMMUNE was lower than planned in response to either raised liver function tests and/or flu-like symptoms (FLS). Subjects were able to continue in the study following dose reduction.

Based on the results of the IIS, Horizon is currently conducting a randomized, multicenter, double-blind, placebo-controlled study evaluating the efficacy and safety of ACTIMMUNE in children and young adults with FA (HZNP-ACT-301). This study (HZNP-ACT-302) is designed to be an open-label extension of HZNP-ACT-301, in which all subjects who complete 26 weeks of blinded treatment in HZNP-ACT-301 will be offered the opportunity to receive ACTIMMUNE for an additional 26 weeks.

FA is a rare, debilitating, autosomal recessive deoxyribonucleic acid (DNA)-inherited, mitochondrial disease that causes progressive damage to the nervous system. The rationale for use of IFN- γ 1b for the treatment of FA is based on *in vitro* and animal data, and clinical experience in FA subjects. Currently, there is no FDA-approved therapy for FA. ACTIMMUNE was granted Orphan Drug Designation for the treatment of FA on October 1, 2014.

7.3 Rationale for Dose Selection

In humans, ACTIMMUNE is rapidly cleared after intravenous (IV) administration and slowly absorbed after intramuscular (IM) or SC administration. After IM or SC injection, the apparent fraction of the dose absorbed was greater than 89%. Peak plasma concentrations occurred approximately 4 hours (1.5 ng/mL) after IM dosing and 7 hours (0.6 ng/mL) after SC dosing. In healthy male subjects, the mean elimination half-lives after IV, IM, and SC dosing with 0.1 mg/m² were 38 minutes, 2.9 hours, and 5.9 hours, respectively. ACTIMMUNE administered by the IV, IM, and SC routes (0.1 mg/m²) was not detected in the urine of healthy volunteers.

ACTIMMUNE is currently approved and indicated for reducing the frequency and severity of serious infections associated with CGD and for delaying the time to disease progression in subjects with SMO, both orphan indications (BLA 103836). The current recommended dosage of ACTIMMUNE for the treatment of subjects with CGD and SMO is $50 \mu\text{g}/\text{m}^2$ (1 million international units [IU]/ m^2) for subjects whose body surface area (BSA) is greater than 0.5 m^2 and $1.5 \mu\text{g}/\text{kg}/\text{dose}$ for subjects whose BSA is equal to or less than 0.5 m^2 , administered SC TIW. Please refer to the ACTIMMUNE prescribing information in [Section 17.2](#) for the well-established safety profile of ACTIMMUNE. This includes FLS upon initiation of ACTIMMUNE dosing that can be mitigated with medication, such as acetaminophen, and/or ibuprofen, and/or diphenhydramine, and dose titration [\[Devane et al, 2014\]](#). FLS is defined as the presence of fever, chills, muscle aches, and tiredness. Transient elevation in liver transaminases can also occur; this was seen in the OLIGA-FA study, where one subject with severe FLS experienced elevated transaminases that returned to normal after dose reduction from $50 \mu\text{g}/\text{m}^2$ to $10 \mu\text{g}/\text{m}^2$, and has been reported in the literature in a trial administering recombinant interferon γ (rIFN- γ) to subjects with systemic sclerosis [\[Polisson et al, 1996\]](#).

In this clinical trial, FA subjects will be dose-escalated weekly (10, 25, 50, and $100 \mu\text{g}/\text{m}^2$ SC TIW). If severe reactions occur during dose escalation, the dosage will be reduced to the previous dose level or therapy will be interrupted until the adverse reaction resolves and then restarted at the previous or lower dose level. By Week 13 of the study, the dose will not be further adjusted and will be maintained for the remainder of the study (an additional 13 weeks of dosing), unless dose reductions are required for drug-related AE management. The dosing of ACTIMMUNE in this protocol is fairly consistent with that already approved for ACTIMMUNE ([Table 7.1](#)). The difference is that in this study, the dose will be titrated to a maximum of $100 \mu\text{g}/\text{m}^2$ compared to the dose of $50 \mu\text{g}/\text{m}^2$ recommended in the current ACTIMMUNE prescribing information ([Section 17.2](#)). Although the pilot study showed promising results in the FARS assessment, the lack of clinically meaningful effects on other outcomes indicate a higher dose may be necessary in the treatment of FA.

Table 7.1 Approved Dosing for ACTIMMUNE versus Proposed Clinical Dosing in This Study

	Approved ACTIMMUNE Dosing Regimen	Proposed ACTIMMUNE Dosing Regimen in Protocol HZNP-ACT-302
Age	All ages	10 to 25 years of age at start of HZNP-ACT-301
Route of administration	SC	SC
Individual dose	Per m^2 (or /kg if $<0.5 \text{ m}^2$)	Per m^2 (or /kg if $<0.5 \text{ m}^2$)
Maximum daily dose	$50 \mu\text{g}/\text{m}^2$ or $1.5 \mu\text{g}/\text{kg}$	$100 \mu\text{g}/\text{m}^2$ or $3 \mu\text{g}/\text{kg}$
Initial dose	No titration	Titration weekly from $10 \mu\text{g}/\text{m}^2$ to 25 , 50 , and $100 \mu\text{g}/\text{m}^2$
Frequency	TIW	TIW

There are several well-documented Investigational New Drug (IND)-reported, randomized, controlled clinical trials providing experience in large, late-stage subject populations such as liver disease (fibrosis) and idiopathic pulmonary fibrosis (IPF) at doses, frequency, and duration equivalent to those proposed for this study (i.e., 200 µg SC or approximately 100 µg/m²; Sponsor data on file). There are also reports from Europe on the use of higher doses of IFN- γ 1b in the treatment of FA [<https://fafysio.wordpress.com/>]. The clinical safety and tolerability at the 200 µg SC dose TIW appeared consistent with the safety described in the current package insert ([Section 17.2](#)).

While the approved ACTIMMUNE dose regimen does not involve initial dose escalation or titration, a recently completed study in healthy volunteers demonstrated a potential reduction in the severity of acute FLS when dose escalation to the standard dose was utilized [[Devane et al, 2014](#)]. This mirrors the clinical experience with other IFNs, particularly the interferon-betas (IFN- β s) used by multiple sclerosis patients where initial dose escalation using an acute titration regimen has been adopted. Natural tolerance to FLS develops relatively quickly in the majority of patients receiving IFNs and the dose escalation/titration minimizes the initial poor tolerability and treatment dropouts. It is expected that the use of the acute dose escalation as proposed in this protocol will facilitate subject retention during the early phase in the trial, particularly with dose escalation to 100 µg/m².

8. STUDY OBJECTIVES

8.1 Primary Study Objective

The primary objective is to evaluate the long-term safety of ACTIMMUNE (IFN- γ 1b) in subjects with FA.

8.2 Primary Efficacy Objective

To evaluate the effect of ACTIMMUNE (interferon [IFN]- γ 1b) on the change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in neurological outcome as measured by Friedreich's Ataxia Rating Scale (FARS) excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score (FARS-mNeuro score).

8.3 Secondary Efficacy Objectives

The secondary efficacy objectives are:

To evaluate the effect of ACTIMMUNE (interferon [IFN]- γ 1b) on the change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies for the following:

- Activities of Daily Living (ADL)
- The timed 25-foot-walk test (T25FW)
- Responder rate (≥ 3 point improvement in the FARS mNeuro score)
- Neurological outcome as measured by the total FARS score (FARStot)

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

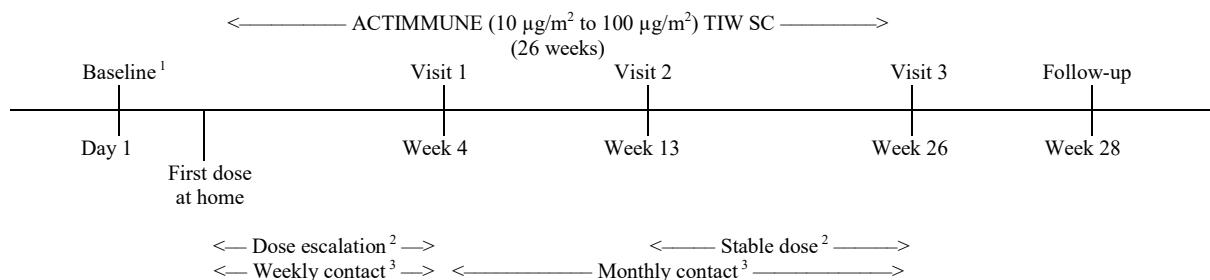
This is a multi-center, dose-escalation, open-label extension study of HZNP-ACT-301 examining the safety and efficacy of ACTIMMUNE in the treatment of FA in children and young adults. Subjects who complete 26 weeks of blinded treatment in HZNP-ACT-301 will be eligible to enter this 6-month study. All subjects who choose to participate will receive ACTIMMUNE three times a week (TIW) for 26 weeks. In order to maintain the study blind in HZNP-ACT-301, all subjects in this open-label extension study will undergo ACTIMMUNE titration, regardless if they received ACTIMMUNE or placebo in HZNP-ACT-301.

The study drug dose is planned to be escalated on a weekly basis over the first four weeks of treatment (from $10 \mu\text{g}/\text{m}^2$ to 25, 50, and $100 \mu\text{g}/\text{m}^2$); however, the dose may be reduced, interrupted, or held based on tolerability. During the dose-escalation phase (i.e., through at least Week 4 or until the subject is receiving a stable tolerated dose), subjects will be contacted on a weekly basis either by email or telephone to monitor safety and dosing logistics. By Week 13, all subjects are to be on a stable tolerated dose of study drug in order to continue study participation; the dose may not be further increased after Week 13, however, it may be reduced on a case-by-case basis to manage subsequent drug-related AEs (e.g., elevated liver function tests).

An overview of the study is provided in [Figure 9.1](#). The Week 26 Visit from HZNP-ACT-301 will serve as the Baseline Visit (Day 1) for this study. Subjects will receive the last dose of the randomized drug from HZNP-ACT-301 (ACTIMMUNE or placebo) in a double-blind fashion, and the first dose of study drug for the open-label extension study ($10 \mu\text{g}/\text{m}^2$) will be distributed for administration at home according to the planned TIW dosing schedule. During the treatment period, additional clinic visits are scheduled at Weeks 4, 13, and 26; in between clinic visits, subjects (and/or caregivers) will be monitored via emails/phone calls on a weekly basis until subjects reach their maximum tolerated dose and on a monthly basis thereafter.

Subjects will return to the clinic two weeks after the last dose of study drug for a Follow-Up Safety Visit.

Figure 9.1 Schematic of Study Design



¹ Week 26 of HZNP-ACT-301 will serve as the Baseline Visit (Day 1) for this study. Subjects will receive the last dose of the randomized drug from HZNP-ACT-301 in a double-blind fashion, and the first dose of study drug for the open-label extension study (10 µg/m²) will be distributed for administration at home according to the planned TIW dosing schedule.

² The planned dose escalation consists of two doses of ACTIMMUNE 10 µg/m² in the first week, followed by weekly escalation to 25, 50, and 100 µg/m² TIW on Days 8, 15, and 22, respectively; however, the dose may be reduced, interrupted, or held based on tolerability. All subjects are to be on a stable tolerated dose of study drug by Week 13 in order to continue study participation.

³ Subjects and/or caregivers will be contacted by email or phone to monitor safety and dosing logistics on a weekly basis from Day 1 through Week 4 (or until stable tolerated dose is achieved) and on a monthly basis after Week 4 (or after dose stabilization) through Week 26.

The following assessments will be performed during the study:

Safety Assessments

- Adverse event (AE) monitoring, concomitant medication monitoring, and physical examinations throughout the study.
- Immunogenicity testing pre-dose at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, 26 (or premature withdrawal [PW]), and 28.
- Vital signs, clinical safety laboratory evaluations (complete blood count, prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], chemistry, and urinalysis), and pregnancy testing (if applicable) at all on-treatment clinic visits.
- Echocardiogram at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).
- ECG at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), with additional ECGs at Weeks 13 and 26 (or PW).

Efficacy Assessments

- FARS, ADL assessment, T25FW, and 9-hole peg test (9-HPT) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and 4 to 6 hours post-dose at Weeks 13 and 26 (or PW).
- Low-contrast Sloan letter chart (LCSLC) Vision Test at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Week 26 (or PW).

- For all subjects with a normal audiogram result at Screening in Study HZNP-ACT-301, Listening in Spatialized Noise-Sentences Auditory Test (LiSN-S) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Week 26 (or PW).
- Frataxin protein levels in whole blood, muscle biopsies (optional), and buccal cells at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Weeks 13 and 26 (or PW).
- Functional staging of ataxia at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and post-dose at Weeks 13 and 26 (or PW).
- Physician Global Assessment and Patient Global Assessment at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Weeks 13 and 26 (or PW).

Quality of Life Assessments

Quality of life assessments (Modified Fatigue Impact Score [MFIS], and Pediatric Quality of Life [PedsQL] questionnaire or 36-item short-form health survey [SF-36]) will be completed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 13 and 26 (or PW). The MFIS will be completed for all subjects. Subjects who completed the PedsQL during Study HZNP-ACT-301 will continue to complete the PedsQL in this study. Subjects who completed the SF-36 during Study HZNP-ACT-301 will continue to complete the SF-36 in this study.

9.2 Discussion of Study Design

The study population consists of subjects who completed Study HZNP-ACT-301; this population was well-defined and consistent with the expected target population for whom ACTIMMUNE will be indicated (pediatric and young adult subjects with a FA functional stage of >1 to <5).

The most common adverse experiences occurring with ACTIMMUNE therapy are FLS or constitutional symptoms such as fever, headache, chills, myalgia, or fatigue that may decrease in severity as treatment continues (see product prescribing information in [Section 17.2](#)). It is hoped that the weekly dose-escalation scheme and the allowable dose adjustments in this study will alleviate the severity of these symptoms. In addition, previous experience with this drug indicates these FLS may be minimized with bedtime administration of ACTIMMUNE and the use of acetaminophen, and/or ibuprofen, and/or diphenhydramine. Therefore, subjects in this study will be instructed to self-administer study drug at bedtime on days when they are not being seen in the clinic for neurological assessments, and the use of acetaminophen, and/or ibuprofen, and/or diphenhydramine (see [Table 9.1](#) for allowable doses) will be allowed throughout the study. On clinic days when neurological assessments are being performed, study drug dosing will occur on site.

The primary efficacy endpoint (change in FARS-mNeuro from Baseline to Week 26) has been agreed upon with the FDA as part of a pre-IND study submission. The measurements used in this study for the primary efficacy endpoint (FARS) are established and well-validated endpoints that have been shown to correlate significantly with functional disability in FA patients [[Friedman et al, 2010](#); [Lynch et al, 2006](#); [Lynch et al, 2005](#)].

In order to maintain the study blind in HZNP-ACT-301, all subjects in this open-label extension study will undergo ACTIMMUNE titration, regardless if they received ACTIMMUNE or placebo in HZNP-ACT-301. The doses planned for dose escalation of ACTIMMUNE in this study are 10, 25, 50, and 100 $\mu\text{g}/\text{m}^2$. The approved dosage of ACTIMMUNE for the treatment of CGD and SMO is 50 $\mu\text{g}/\text{m}^2$ for patients whose BSA is greater than 0.5 m^2 and the highest dose administered in the OLIGA-FA pilot study was also 50 $\mu\text{g}/\text{m}^2$. Although the pilot study showed promising results in the FARS assessment, the lack of clinically meaningful effects on other outcomes indicate a higher dose may be necessary in the treatment of FA. During the ACTIMMUNE development program, the 100 $\mu\text{g}/\text{m}^2$ dose was administered to healthy adult subjects in PK studies, and doses $>100 \mu\text{g}/\text{m}^2$ were administered to subjects with disease states other than the approved indications. As expected, the AE profile of ACTIMMUNE at $>100 \mu\text{g}/\text{m}^2$ in other disease states was broader than that seen among patients with CGD at the 50 $\mu\text{g}/\text{m}^2$ dose. Since the safety profile of the 100 $\mu\text{g}/\text{m}^2$ dose is unknown among pediatric subjects with FA, the study will be monitored by a DSMB, which will advise the Sponsor or its delegate regarding the continuing safety of study subjects and potential subjects as well as the continuing validity and scientific merit of the trial. The decision to modify or halt the study will be made collectively by the CPI, the Sponsor (Horizon), and FARA after review with the FDA.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Eligible subjects must meet all of the following criteria:

1. Written informed consent and child assent, if applicable.
2. Completed 26 weeks of blinded treatment in Study HZNP-ACT-301.
3. If female, the subject is not pregnant or lactating or intending to become pregnant during the study, or within 30 days after the last dose of study drug. Female subjects of child-bearing potential must have a negative urine pregnancy test result at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and agree to use a reliable method of contraception throughout the study and for 30 days after the last dose of study drug.

9.3.2 Exclusion Criteria

Subjects will be ineligible if, in the opinion of the Investigator, they are unlikely to comply with the study protocol or have a concomitant disease or condition that could interfere with the conduct of the study or potentially put the subject at unacceptable risk.

9.3.3 Removal of Subjects from Therapy or Assessment

All subjects are free to withdraw from study participation at any time, for any reason, and without prejudice to their further medical care. In addition, the investigator may terminate a subject from the study at any time. The primary reason for discontinuation should be recorded on the case report form using one of the following categories:

- Adverse event. The subject experiences an AE that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of an AE.
- Lack of therapeutic effect. The investigator has determined that study drug administration is not benefitting the subject, and continued participation poses an unacceptable risk to the subject.
- Inclusion/exclusion criteria violation. The investigator discovers that the subject did not meet all of the inclusion/exclusion criteria after study enrollment.
- Protocol noncompliance. The subject has a significant protocol deviation, does not comply with study drug administration schedule, or fails to adhere to other study requirements as stated in the protocol.
- Lost to follow-up. The subject does not return to the clinic for scheduled assessments, and does not respond to the site's attempts to contact the subject.
- Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF; if the underlying reason is documented as an AE or lack of efficacy, the category of withdrawal should be marked in the corresponding category and not as voluntary withdrawal.
- Study termination. The Sponsor, DSMB, IRB, or regulatory agency terminates the study.
- Pregnancy.

Following early discontinuation from the study, the subject or his/her legally acceptable representative will be informed regarding the additional study evaluations that are necessary to monitor his/her safety. These subjects or their representatives will be encouraged to complete the PW and Follow-Up Safety Visits.

Discontinued or withdrawn subjects will not be replaced. Subject identification numbers are unique and will not be reassigned.

9.4 Treatments

9.4.1 Treatments Administered

In order to maintain the study blind in HZNP-ACT-301, all subjects in this open-label extension study will undergo ACTIMMUNE titration, regardless if they received ACTIMMUNE or placebo in HZNP-ACT-301.

Subjects will receive SC doses of ACTIMMUNE TIW for 26 weeks. The planned dose escalation consists of two doses of ACTIMMUNE $10 \mu\text{g}/\text{m}^2$, followed by weekly-escalated doses of 25, 50, and $100 \mu\text{g}/\text{m}^2$ TIW on Days 8, 15, and 22, respectively. The first dose of study drug will be administered after the Baseline/Day 1 Visit at home before bedtime according to the subject's TIW dosing schedule.

9.4.1.1 Dose Adjustment Guidelines

The dose of ACTIMMUNE is based on the subject's BSA; therefore, height and weight will be measured at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 4 and 13, and the dosing volume will be determined using the formula presented in [Section 9.4.7.2](#).

The planned 4-week dose escalation schedule will be implemented if it is tolerated by the subject. If, however, in the opinion of the investigator, the subject experiences severe reactions during dose escalation, the dose will be reduced to the previous dose level, or will be interrupted until the adverse reaction resolves and then restarted at the previous or a lower dose level. Once the previous/lower dose level is tolerated, the dose may then be titrated upwards again to the next dose level as tolerated.

During the dose-escalation period, the clinical site will contact the subjects (or caregivers/legal representatives) via phone calls or email on a weekly basis to monitor AEs and dosing logistics. In addition, subjects may contact the clinical site at any time with dosing or possible drug reaction concerns throughout the study. Dose adjustments may be continued through Week 13, but at Week 13, all subjects should be on a stable tolerated dose and remain at that dose through Week 26. During the stable dosing period, subjects will be contacted by the site via phone calls or emails on a monthly basis to monitor AEs and dosing logistics. Although the dose may not be further increased after Week 13, it may be reduced on a case-by-case basis to manage subsequent drug-related AEs (e.g., elevated liver function tests).

9.4.2 Identity of Investigational Products

9.4.2.1 ACTIMMUNE

ACTIMMUNE (IFN- γ 1b) is a single-chain polypeptide containing 140 amino acids with a molecular weight of approximately 16,465 Daltons. IFN- γ 1b differs from natural human IFN- γ by the substitution of an additional N-terminal methionine, deletion/loss of seven amino acids and lack of glycosylation.

The commercial formulation of ACTIMMUNE is a sterile, clear, colorless solution filled in a single-use vial for SC injection. Each 0.5 mL of ACTIMMUNE contains: 100 μ g (2 million IU) of IFN- γ 1b formulated in 20 mg mannitol, 0.37 mg disodium succinate hexahydrate, 0.14 mg succinic acid, 0.05 mg polysorbate 20, and sterile water for injection.

The Sponsor will provide unlabeled, commercial ACTIMMUNE to CSM, Inc. The commercial formulation will be utilized, with each unlabeled vial containing ACTIMMUNE in a concentration of 200 μ g/mL. Each vial permits the extraction of up to 0.5 mL of ACTIMMUNE with additional volume to facilitate solution withdrawal. The study drug vials will be shipped to CSM, who will be responsible for labeling of the vials in accordance with regulatory guidelines (see [Section 9.4.3](#)). CSM will assemble kits containing three vials each, which will provide a sufficient quantity of study drug for one week of dosing until two vials per dose may be needed to deliver 100 μ g/m² depending on the BSA of the subject. When subjects reach the 100 μ g/m² TIW dose level, and two vials per dose are required, the same volume should be removed from

each vial and delivered in individual syringes. For example, if the dose should be 0.8 mL, then 0.4 mL should be withdrawn from each vial into separate syringes and two injections given.

9.4.3 Labeling

Subjects will maintain the unique 6-digit subject ID number assigned in Study HZNP-ACT-301; the first three digits are the site number and the last three digits are the sequential number assigned by the site to subjects who consented to the double-blind study beginning with 001. So for example, the first subject consented at site 222 in Study HZNP-ACT-301 would have been assigned subject ID 222001.

CSM will label the ACTIMMUNE vials, assemble the study drug into kits containing three vials each, and ship kits to the study sites and directly to study subjects. Each kit will have a label that includes a unique 4-digit kit number. At the Baseline/Day 1 visit, study staff will contact the ARO at the University of Rochester in order to enroll eligible subjects and identify the kit number to dispense to the subject. Before dispensing study drug to the subject, study site staff will record the subject's unique 6-digit subject ID number on the label.

Labels on all vials of study drug and study drug kits will clearly indicate the study number, Sponsor's name and location, storage conditions, and appropriate precautionary labeling required by US Federal law. Carton labels will also include the unique 4-digit kit number. Dosing instructions will be provided separately to the subject/caregiver.

9.4.4 Storage

Study drug kits are to be stored in a 2°C to 8°C (36°F to 46°F) refrigerator at the site, and subjects and their caregivers will be instructed to store all study drug in their home refrigerators.

At the clinic, all study medications must be stored in a secure area with limited access, and a daily temperature log of the drug storage area will be maintained every working day; deviations from the specified temperature range will be reported as protocol deviations.

Vials must be placed in a 2°C to 8°C (36°F to 46°F) refrigerator immediately upon receipt to ensure optimal retention of physical and biochemical integrity. The vials must not be frozen. Excessive or vigorous agitation should be avoided. Exposure of vials to temperatures greater than 25°C (77°F) should be strictly avoided. The sponsor should be contacted for disposition instructions for vials left at room temperature (>8°C) for a total time exceeding 8 hours. Vials should not be used beyond the expiration date.

9.4.5 Study Drug Quality Issues

ACTIMMUNE is a sterile, clear, colorless solution. If any vials of study drug are not colorless or contain particulate matter, study drug MUST NOT be administered. In the event that any of the vials stored at home are considered suspect by the subject/caregiver, the clinic is to be notified immediately for instructions regarding dosing and possible re-supply.

9.4.6 Drug Accountability

The Principal Investigator at each site is responsible for the control of all study medication. The site must maintain adequate records of the receipt and disposition of all study medication shipped to the study center. Records will include receipt dates, quantities received, quantities dispensed, quantities returned or destroyed, and the ID numbers of the subjects who received study medication.

All empty, partially empty, and full vials of study drug must be retained by the study center under locked storage, until drug accountability has been completed. Periodically throughout the study and at the conclusion of the study, inventory checks and accountability of study materials will be conducted by a representative of the Sponsor. Once accountability is completed, the Sponsor's representative will authorize the return of study medication (all used, partially used, and unused vials) to CSM. The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the Sponsor. The investigator's copy of the Drug Accountability and Drug Return/Destruction Record(s) must document accurately the return of all study drug supplies. Records will also include disposition dates and quantities returned to the designated facility.

In addition, subjects or their caregivers can return biohazard containers supplied by study staff with all used syringes and needles from the study to study staff at the follow-up visit(s). Study staff will dispose of these containers appropriately.

9.4.7 Study Drug Administration and Timing of Dose for each Subject

9.4.7.1 Description of Clinical Supplies

CSM will supply study drug kits and packages containing ancillary supplies for dosing (i.e., syringes, alcohol swabs, gauze pads, bandages, and biohazard containers for safe storage of used needles and syringes) to the study sites.

9.4.7.2 Determination of Dose Volume

The volume of study drug to be administered will be determined by the site and will be based on the subject's BSA. Height and weight will be measured at all clinic visits. The BSA will be calculated at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 4 and 13 using the Mosteller [\[Mosteller, 1987\]](#) formula:

$$BSA (m^2) = \sqrt{\frac{Height (in) * Weight (lb)}{3131}}$$

Given that each 0.5 mL of study drug solution contains 100 µg IFN- γ 1b (0.005 mL/µg), the following calculation will be used to determine the volume of study drug to be administered.

Dose level ($\mu\text{g}/\text{m}^2$) \times BSA \times 0.005 mL/ μg = ___ mL to be dosed

10	(m^2)	(drug
25		concentration)
50		
100		

For example, a subject who is 62 inches tall and weighs 100 pounds will have a BSA of 1.41 m^2 . At the 25 $\mu\text{g}/\text{m}^2$ dose level, the subject will receive **0.18 mL** of study drug.

$25 \mu\text{g}/\text{m}^2 \times 1.41 \text{ m}^2 \times 0.005 \text{ mL}/\mu\text{g} = 0.176 \text{ mL}$, rounded to **0.18 mL** of study drug

9.4.7.3 Details Concerning Timing and Dose Administration

All doses of study drug will be administered by SC injection. Subjects and/or their caregivers will be instructed on their individualized dosing volume and proper dosing techniques; they will also be instructed to administer the study drug on the right and left deltoid, anterior thigh, and upper and lower abdomen and to rotate the injection sites.

Subjects or their caregivers will also be instructed in safe handling and storage of used syringes and needles. The clinical staff will demonstrate proper technique for withdrawing the appropriate volume of study drug from the vial. When two vials are needed to achieve the dose, an equal volume should be removed from each vial. For example, if the dose should be 0.8 mL, then 0.4 mL should be withdrawn from each vial into separate syringes and two injections given. The injection site will be cleaned with an alcohol swab and allowed to air dry. About an inch of skin and fat tissue will be pinched between the thumb and forefinger, the needle will be inserted all the way into the pinched skin, and the entire volume of study drug will be injected under the skin.

The first dose of study drug is after the Baseline/Day 1 Visit and will be administered at home before bedtime according to the subject's TIW dosing schedule. Subjects and their caregivers will be instructed to administer study drug on an outpatient basis TIW before bedtime; and to adhere to a dosing schedule of Monday, Wednesday and Friday or Tuesday, Thursday, and Saturday for the duration of the study as agreed to by the clinic staff. Subjects and their caregivers will also be instructed concerning the use of acetaminophen, and/or ibuprofen, and/or diphenhydramine to alleviate injection site and study drug reactions (see [Table 9.1](#) for allowable doses).

After Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), subjects are scheduled to return to the clinic at Weeks 4, 13, and 26 during the treatment period. Study drug will be administered in the morning at the clinic at each of these visits. If the subject's next scheduled dose is the same day as the clinic visit, the dose will simply be given in the morning as opposed to bedtime for that particular day. If the subject is scheduled to dose the evening prior to the visit, the dose will be held and administered the next morning at the clinic. Bedtime dosing will be resumed after the clinic visit according to the subject's regular dosing schedule. For the TIW schedule, dosing should be Monday, Wednesday and Friday or alternatively Tuesday, Thursday and Saturday.

At Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), subjects will be dispensed a 4-week supply of study drug for the dose-escalation period (up to 6 kits), and at Weeks 4 and 13, subjects and/or their caregivers will be dispensed a 6-week supply of study drug (up to 12 kits). Additional kits will be shipped to the subject's house between Weeks 4 and 13, and between Weeks 13 and 26, as needed. Subjects/caregivers may be dispensed the full supply at Weeks 4 and 13 if interim direct-to-subject shipments are not feasible. At Weeks 4, 13, and 26, subjects and/or their caregivers will return all unused kits and study drug vials.

9.4.8 Method of Assigning Subjects to Treatment Group

All subjects will receive ACTIMMUNE in this open-label extension study.

9.4.9 Blinding

This is an open-label extension study.

9.4.10 Concomitant Therapy and Restricted Medications

All concomitant medications (including over-the-counter medications) should be at stable doses beginning at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and for the duration of the study. Nicotinamide is limited to doses ≤ 1 g/day. Throughout the study, all possible efforts will be made to maintain stable doses of all concomitant medications, vitamins, and supplements. However, occasional use of acetaminophen, and/or ibuprofen, and/or diphenhydramine (per dosing label instructions, see [Table 9.1](#)) and other medications to treat AEs will be allowed throughout the study. The use of prednisone at a stable dose throughout the study will be allowed, but occasional use is not generally permitted.

Table 9.1 Dosing Allowance for Acetaminophen, Ibuprofen, and Diphenhydramine

Age	Acetaminophen Regular Strength	Ibuprofen	Diphenhydramine
10 years	325 mg every 4-6 hours ≤ 1625 mg/24 hours	200 mg every 6-8 hours ≤ 800 mg/day	25 mg every 4-6 hours ≤ 150 mg/24 hours
11 years	325 mg every 4-6 hours ≤ 1625 mg/24 hours	300 mg every 6-8 hours ≤ 1200 mg/day	25 mg every 4-6 hours ≤ 150 mg/24 hours
≥ 12 years	650 mg every 4-6 hours ≤ 3250 mg/24 hours	200 to 400 mg every 4-6 hours ≤ 1200 mg/day	25 to 50 mg every 4-6 hours ≤ 300 mg/24 hours

9.4.11 Treatment Compliance

Study medication will be dispensed at clinic visits, and re-supplies of study drug may be shipped in temperature-controlled containers to the subject's home. All unused study drug received by the subjects since the previous visit will be returned at the subsequent visit for drug accountability.

An inventory of the study medication supplies will be performed by the site or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

9.5 Efficacy, Quality-of-Life, and Safety Variables

The Schedule of Assessments was previously provided in [Section 2.1](#).

9.5.1 Efficacy Variables

Efficacy variables include the following: functional stage of FA, FARS, ADL, T25FW, 9-HPT, LCSLC vision test, LiSN-S auditory test, frataxin protein levels, and Physician's and Patient's Global Assessments.

9.5.1.1 Functional Stage of Friedreich's Ataxia

The functional stage of FA will be assessed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 13 and 26 (or PW), and on each assessment day, it will be performed at approximately the same time of day and by the same examiner. The functional stage will be rated on a 7-point scale, with increments of 0.5 allowed if the status is about the middle between two stages ([Table 9.2](#)).

Table 9.2 Functional Stage of Ataxia Scale

Stage	Description
0	Normal.
1.0	Minimal signs detected by physician during screening. Can run or jump without loss of balance. No disability.
2.0	Symptoms present, recognized by patient, but still mild. Cannot run or jump without losing balance. The patient is physically capable of leading an independent life, but daily activities may be somewhat restricted. Minimal disability.
3.0	Symptoms are overt and significant. Requires regular or periodic holding onto wall/furniture or use of a cane for stability and walking. Mild disability. (Note: many patients postpone obtaining a cane by avoiding open spaces and walking with the aid of walls/ people etc. These patients are graded as stage 3.0.)
4.0	Walking requires a walker, Canadian crutches or two canes. Or other aids such as walking dogs. Can perform several activities of daily living. Moderate disability.
5.0	Confined but can navigate a wheelchair. Can perform some activities of daily living that do not require standing or walking. Severe disability.
6.0	Confined to wheelchair or bed with total dependency for all activities of daily living. Total disability.

9.5.1.2 Friedreich's Ataxia Rating Scale (FARS)

The FARS will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW), and on each assessment day, it will be performed at approximately

the same time of day and by the same examiner. The FARS includes neurological signs that specifically reflect neural substrates affected in FA. Based on a neurological examination, bulbar, upper limb, lower limb, peripheral nerve, and upright stability/gait functions are assessed [Friedman et al, 2010; Lynch et al, 2006; Subramony et al, 2005].

The FARStot score has a maximum of 125 points (see assessment in [Section 17.3](#)). The primary efficacy endpoint in this study is based on the FARS-mNeuro score, which excludes peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score and has a maximum of 93 points.

9.5.1.3 Activities of Daily Living

The ADL assessment will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW). Subjects and/or their caregivers will rate 9 areas of daily living skills (speech, swallowing, cutting food and handling utensils, dressing, personal hygiene, falling, walking, quality of sitting position, and bladder function) on a 5-point scale (0=normal, 4=greatest loss of function) with allowable increments of 0.5 if the subject or caregiver strongly feels that a task falls between two scores ([Section 17.4](#)). The maximum score for this assessment is 36 [Lynch et al, 2006; Subramony et al, 2005].

9.5.1.4 Timed 25-Foot Walk

The T25FW, which is a quantitative measure of lower extremity function, has been shown to accurately reflect real-world ambulation in subjects with FA [Fahey et al, 2007] and has been established as a reliable outcome measure in clinical trials in FA [Friedman et al, 2010; Lynch et al, 2006; Lynch et al, 2005]. It will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW); on each assessment day, it will be performed at approximately the same time of day and whenever possible, by the same examiner. Subjects will be instructed to wear shoes suitable for walking at each study visit, and will be encouraged to wear the same shoes or the same style of shoes for the T25FW assessments on Day 1, and Weeks 13 and 26. Subjects will be directed to one end of a clearly marked 25-foot course and instructed to walk 25 feet as quickly as possible, but safely. The task is immediately administered again by having the subject walk back the same distance, and the score for the test is the average of the two walks (after reciprocal transformation). Subjects may use assistive devices when performing this task, with the same assistive device used at each assessment.

9.5.1.5 Nine-Hole Peg Test

The 9-HPT, which is a quantitative measure of upper extremity (arm and hand) function, has been established as a useful clinical outcome measure for subjects with FA [Friedman et al, 2010; Lynch et al, 2006; Lynch et al, 2005]. It will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW); and on each assessment day, it will be performed at approximately the same time of day and whenever possible, by the same examiner. At each assessment, two trials will be performed with each arm consecutively, starting with the dominant arm, and the average score of the two trials (after reciprocal transformation) will be reported for each arm separately. Using one hand only, the subject is instructed to take a

total of 9 pegs, one at a time, from a container and insert them into a pegboard, and then remove them from the pegboard, one at a time, and place them back in the container.

The time of each test will be recorded in seconds, starting from the time the subject touches the first peg, and stopping when the last removed peg hits the container. If a peg drops on the floor, the examiner may retrieve it and put it back in the peg box; however, if a peg drops onto the table, the subject is instructed to retrieve it.

9.5.1.6 Low-Contrast Sloan Letter Chart (LCSLC) Vision Test

A quantitative binocular vision assessment will be performed using the LCSLC (100%, 2.5%, and 1.25% contrasts) at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).

Sloan letter charts contain 14 rows of letters (five letters per row for a total of 70 letters) with each successive row logarithmically decreasing in size. The letters are shaded gray on a white/retroilluminated background at different contrast levels; the 100%, 2.5%, and 1.25% contrast levels will be used in this study. The total score for each chart is the number of letters correctly read until five letters in succession are not identified (maximum score of 70) from a standard distance of six meters (approximately 20 feet). The LCSLC has been shown to be a useful clinical outcome measure for subjects with FA [Lynch et al, 2002b] and other neurological disorders [Balcer et al, 2003; Bodis-Wollner et al, 1976].

9.5.1.7 Listening in Spatialized Noise – Sentences Test (LiSN-S)

The LiSN-S is only required for subjects who had normal audiogram results in Study HZNP-ACT-301. The LiSN-S assesses the ability to understand speech when noise is arriving from different directions, and changes in this assessment have been shown to mirror disease progression in individuals with FA [Rance et al, 2012]. It will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW). The subject will listen to a computer program with specialized headphones that creates a three-dimensional acoustic space. The computer program will have a target speaker saying sentences in the presence of competing noises. Scores are obtained under four conditions:

<u>Condition</u>	<u>Type of voice for competing noise</u>	<u>Direction of competing noise</u>	<u>Direction of target speaker</u>
1: Different voices \pm 90 degrees	Different from target speaker	Left and right	Front
2: Same voice \pm 90 degrees	Same as target speaker	Left and right	Front
3: Different voices 0 degrees	Different from target speaker	Front	Front
4: Same voice 0 degrees	Same as target speaker	Front	Front

The spatial advantage score is the difference in scores between conditions 2 and 4, the talker advantage score is the difference in scores between conditions 3 and 4, and the total advantage score is the difference in scores between conditions 1 and 4.

9.5.1.8 Frataxin

Individual whole blood (1 mL) and buccal cells, and optionally muscle biopsies, will be collected at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and post-dose at Weeks 13 and 26 (or PW) for analysis of frataxin protein levels. When performed, muscle biopsies should be the last efficacy assessment at Weeks 13 and 26 (or PW) and the last procedure prior to dosing at Baseline.

Samples will be shipped to the central safety laboratory (URMC), which will batch samples and then ship them to CHOP for analysis.

9.5.1.9 Physician's and Patient's Global Assessments

The Physician's Global Assessment of disease status and the Patient's Global Assessment of overall well-being will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 13 and 26 (or PW).

The Physician's Global Assessment of disease status is independent of the patient's self-assessment, and will be measured using a visual analog scale (VAS) from 0 to 100 where 0 = very good and 100 = very poor.

The Patient's Global Assessment of overall well-being will also be measured using a 100 mm VAS by responding to the question "Considering all the ways in which your FA affects you, how are you doing?" with 0 = doing very well and 100 = doing very poorly.

9.5.2 Quality-of-Life Assessments

The MFIS will be completed for all subjects. For subjects <18 years of age at Baseline (Day 1) of Study HZNP-ACT-301, the PedsQL (study subject and parent/caregiver assessments) will be completed throughout the study, regardless if the subject turns 18 during the HZNP-ACT-301 study or the HZNP-ACT-302 extension study. For subjects ≥18 years of age at Baseline (Day 1) of study HZNP-ACT-301, the SF-36 will be completed throughout the HZNP-ACT-301 and HZNP-ACT-302 studies.

9.5.2.1 Pediatric Quality of Life Inventory (PedsQL)

For subjects <18 years of age at Baseline (Day 1) of Study HZNP-ACT-301, the PedsQL will be completed by the subjects and their caregivers at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and at Weeks 13 and 26 (or PW). The PedsQL is a 23-item assessment including scales for physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items) [Friedman et al, 2010; Paulsen et al, 2010; Varni et al, 1999]. Each item is rated as to how much of a problem the item has been over the past month on a 5-point scale (0=it is never a problem → 4=it is almost always a problem) (see [Section 17.5](#)).

The total score is the sum of all items, the physical health score is the sum of the Physical Functioning items, and the psychosocial score is the summary of the Emotional Functioning, Social Functioning, and School Functioning scores.

9.5.2.2 36-Item Short-Form Health Survey (SF-36)

The SF-36 is one of the most widely-accepted generic health status measures [Ware et al, 1992] and has been shown to be a useful clinical outcome measure for subjects with FA [Epstein et al, 2008]. For study subjects ≥ 18 years of age at Baseline of Study HZNP-ACT-301, the SF-36 will be completed by the subjects at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and at Weeks 13 and 26 (or PW) in this study (HZNP-ACT-302).

The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section (Section 17.6). Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score, the more disability. The higher the score, the less disability (i.e., a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability).

9.5.2.3 Modified Fatigue Impact Scale (MFIS)

The MFIS, which has been shown to be a useful clinical outcome measure for subjects with FA [Epstein et al, 2008; Friedman et al, 2010], will be completed by all subjects or their caregivers at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and at Weeks 13 and 26 (or PW). The MFIS is a 21-item assessment, with each item rated on a 5-point scale (0=never \rightarrow 4=almost always) (Section 17.7). It can be aggregated into three subscales (physical, cognitive, and psychosocial), as well as into a total MFIS score. All items are scaled so that higher scores indicate a greater impact of fatigue on a subject's activities (i.e., no items are reverse scored).

9.5.3 Safety Variables

Safety will be assessed via AE and concomitant medication use monitoring, immunogenicity testing, physical examinations, vital signs, clinical safety laboratory evaluations (complete blood count, PT, INR, aPTT, chemistry, and urinalysis), pregnancy testing (if applicable), echocardiograms, and ECGs.

9.5.3.1 Adverse Events

Comprehensive assessments of any apparent AE experienced by the subject will be performed throughout the course of this study. Study center personnel will record all AEs, whether observed by the Investigator/designee or reported by the subject/caregiver, in the source document and on the eCRF. A physician (either the Principal Investigator or a physician/nurse practitioner/physician's assistant designated by the Principal Investigator) will manage and treat any treatment-emergent AE (TEAE).

AE information will be elicited from each subject/caregiver by indirect questioning using a non-leading question, such as "Has anything bothered you since your last visit or is anything bothering you now?" AE data also may be volunteered by the parent/caregiver to the Investigator (or designee). A physician (either the Principal Investigator or a physician/nurse practitioner/physician's assistant designated by the Principal Investigator) will assess the seriousness, severity, and causality of each AE based on the following definitions and documentation requirements.

9.5.3.1.1 Definitions

Adverse Event: An AE is defined in 21 CFR 312.32(a) as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

A TEAE is any adverse change from the subject's baseline condition, including any laboratory test value abnormality judged as clinically significant by the investigator, that occurs on or after the date of the first dose of study drug administered at home and throughout the duration of the clinical study, whether the AE is considered related to the treatment or not. Adverse events include the following types of occurrences:

- Adverse reaction: an adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse events for which there is reason to conclude that the drug caused the event.
- Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug. Suspected adverse reactions are the subset of all AEs for which there is a reasonable possibility that the drug caused the event.
- Other medical experiences, regardless of their relationship to the study drug, such as injury, accidents, increased severity of pre-existing symptoms, apparently unrelated illness, and clinically significant abnormalities in clinical laboratory values, physiological testing, or physical examination findings.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, an interaction with another drug or substance, or toxicity.

Serious Adverse Event (SAE): An AE is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drug (e.g., car accidents).
- Life-threatening adverse experience. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity.
- Inpatient hospitalization or prolongation of an existing hospitalization.

- Congenital anomaly or birth defect.
- Other medically important event which, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

Of note: Surgical procedures or other therapeutic interventions themselves are not adverse events, but the condition for which the surgery/intervention is required is an adverse event and should be documented accordingly.

Elective surgeries and/or treatments requiring hospitalization (e.g., cosmetic surgery), and treatment received at an emergency room or similar facility, will not be considered as SAEs unless one of the definitions of an SAE listed above is met.

Non-Serious Adverse Event: A non-serious AE includes any AE that is not described in the previous SAE category.

Unexpected: An AE or suspected adverse reaction is considered unexpected if it is not listed in the Investigator Brochure or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.5.3.1.2 Documentation of Adverse Events

Adverse events that are ongoing from Study HZNP-ACT-301 will be considered baseline signs/symptoms. The TEAE reporting period begins with the date of the first dose of study drug at home and continues until completion of the Follow-Up Safety Visit, performed two weeks after administration of the final dose of study medication. All baseline signs/symptoms and TEAEs must be recorded in the source documents and on the subject's eCRF.

If the Investigator observes an SAE after study completion that he/she believes was possibly caused by the study medication, the Investigator will report this SAE using the procedures described in [Section 9.5.3.1.5](#).

Unchanged, chronic conditions are **NOT** considered AEs and should not be recorded on the AE pages of the eCRF unless there is an exacerbation of a chronic condition.

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied (i.e., FA). It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of worsening ataxia may be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug.

In addition, hospitalizations for planned procedures are not considered an AE unless they are prolonged hospitalizations, and emergency room visits less than 24 hours in duration are not considered hospitalizations.

Detailed information regarding all SAEs must also be recorded on the Serious Adverse Event Reporting Form. Whenever possible, the Investigator should group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis, and sneezing might be grouped together as “upper respiratory infection” if the Investigator is confident of the diagnosis.

9.5.3.1.3 Grading of Adverse Events

The severity of all AEs, including all treatment-emergent clinically significant laboratory test results and all treatment-emergent clinically significant changes in laboratory test results, will be assessed in accordance with the following criteria:

- Mild (Grade 1): awareness of signs or symptoms that are easily tolerated, are of minor irritant type, cause no loss of time from usual activities, do not require medication or further medical evaluation, and/or are transient.
- Moderate (Grade 2): signs or symptoms sufficient to interfere with function but not activities of daily living.
- Severe (Grade 3): signs or symptoms sufficient to interfere with activities of daily living; signs and symptoms may be of a systemic nature or may require further medical evaluation and/or treatment.
- Life-Threatening (Grade 4): disabling or with life-threatening consequences. This definition does not include any event that might have caused death if it had occurred in a more severe form.
- Fatal (Grade 5): death related to an AE.

9.5.3.1.4 Relationship to Study Drug

The relationship of the study drug to each AE will be determined by the Investigator based on the following definition:

- No reasonable causal relationship (probably not related): There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.
- Yes, reasonable causal relationship (possibly related): There is evidence in favor of a causal relationship; i.e., there is a plausible time course, and at least one of the following criteria apply:

- There is a reasonable pharmacological relationship (or known class effect)
- There is no other more plausible explanation
- There is a positive de-challenge (without active treatment of the event)
- There is a positive re-challenge
- There is a distinguishable dose effect

Within the reporting requirement under 21 CFR 312.32(c)(1)(i), the FDA provides the following examples of types of evidence that would suggest a causal relationship between the drug and the adverse event.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.5.3.1.5 Reporting and Documenting SAEs

All SAEs beginning with the time of signing IC and continuing until two weeks after administration of the final dose of study medication must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to the study medication:

- 1) Report the SAE to Med Communications, Inc. **by telephone or fax within 24 hours** after becoming aware that a subject has experienced an SAE (see [Appendix 17.1](#) for contact information).
- 2) Record the SAE accurately in the source documents and on the AE page of the subject's eCRF, as described in [Section 9.5.3.1.2](#). Using the Serious Adverse Event Reporting Form, submit all known subject information to Med Communications, Inc. (as specified in separate instructions provided to the study center) on the SAE reporting form **within 24 hours of learning of the SAE occurrence**.

- 3) Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the Sponsor's representative.
- 4) Respond in a timely manner to any queries from Sponsor regarding the SAE.
- 5) Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator.
- 6) Review each SAE report and evaluate the relationship of the SAE to study treatment. The Sponsor will determine whether the SAE is unexpected in nature.
- 7) The Investigator must report all AEs or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB.

9.5.3.1.6 Follow-Up of Adverse Events

Any ongoing study drug-related AE present at the time of study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

In the event of unexplained, treatment-emergent, clinically significant abnormal laboratory test results or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed until the values have returned to within the reference range or to baseline for that subject.

9.5.3.1.7 Medication Error and Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to, or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

If the subjects/caregivers accidentally administer the wrong dose of study drug, they are to **immediately** contact the site to discuss possible safety concerns and receive instructions regarding future doses. All cases of medication errors and overdose (with or without associated AEs) will be documented on the eCRF in order to capture this important safety information consistently in the database. AEs associated with an overdose and SAEs of overdose are to be reported according to the procedures outlined in [Sections 9.5.3.1.2](#) and [9.5.3.1.5](#), respectively.

In the event of drug overdose, the subject is to be treated.

9.5.3.1.8 Review of Adverse Events and Emerging New Safety Information

The Sponsor's Medical Monitor or designee in Pharmacovigilance will perform an ongoing review of all AEs and all other emerging new information relevant to the safety of the drug.

9.5.3.1.9 Reporting of IND Safety Reports

The sponsor will notify the US FDA and all investigators on any new serious risks associated with the drug.

9.5.3.2 Pregnancy Reporting

All female subjects of childbearing potential will undergo urine pregnancy tests at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW) and will be instructed to use effective contraceptive measures in line with the inclusion and exclusion criteria. In case a female subject becomes pregnant during the study observation period (from Baseline to Week 26) or pregnancy is confirmed within 30 days after the final study visit, the Investigator will immediately inform the Sponsor of the clinical trial using the Pregnancy Reporting Form. Pregnant subjects still ongoing in the trial will be withdrawn. Information regarding the outcome of the pregnancy must be provided shortly after the birth of the child or the termination of the pregnancy. Pregnancies will be followed whether or not an AE in the mother or the unborn child has been observed.

Male subjects should refrain from fathering a child or donating sperm during the study and for 30 days following the last dose of study drug. Pregnancy of the subject's partner is not considered to be an AE; however, the outcome of all pregnancies should (if possible) be followed up and documented.

9.5.3.3 Vital Signs

Vital signs (resting systolic and diastolic blood pressure in the non-dominant arm, pulse, and temperature) will be assessed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW). Blood pressure and pulse measurements will be obtained with the subject's arm unconstrained by clothing or other material and while the subject is sitting up. When possible, the same arm will be used for measurements in all study visits. Temperature will be obtained orally or via the ear.

9.5.3.4 Physical Examinations, Height, and Weight

Complete physical examinations (including evaluation of general appearance/mental status, HEENT [head, eyes, ears, nose, throat], and the following body systems: skin, heart, lungs, abdomen, extremities) will be performed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 13 and 26 (or PW). Brief physical examinations will be performed at the Week 4 and Follow-Up Safety Visits.

Height and weight will be assessed at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW); dosing will be based on the calculated BSA at Baseline/Day 1, and Weeks 4 and 13.

9.5.3.5 Echocardiograms

Echocardiograms are scheduled for Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Week 26 (or PW).

9.5.3.6 ECGs

ECGs are scheduled for Baseline/Day 1 (Week 26 of Study HZNP-ACT-301) and Weeks 13 and 26 (or PW).

9.5.3.7 Clinical Laboratory Tests

Samples of blood (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine are scheduled for collection at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and Weeks 4, 13, and 26 (or PW). Additional follow-up samples for clinical laboratory testing should be obtained as clinically indicated.

All clinical laboratory testing, with the exception of on-site urine pregnancy tests during the treatment period for females of childbearing potential, will be performed by the central clinical safety laboratory (URMC).

The following clinical laboratory tests will be performed:

- Complete blood count
- PT (and derivation of INR) and aPTT
- Chemistry panel
- Urinalysis

9.5.3.8 Immunogenicity Testing

Individual blood samples (2 mL) for immunogenicity testing will be collected from all subjects at Baseline/Day 1 (Week 26 of Study HZNP-ACT-301), and prior to dosing at Weeks 4, 13, 26 (or PW), and 28. Samples will be collected in red top tubes, centrifuged, and serum will be collected and stored at $\geq -70^{\circ}\text{C}$ at the site until shipment to the central safety laboratory (URMC). URMC will store the samples at $\geq -70^{\circ}\text{C}$ until shipment to Intertek (San Diego, CA) for immunogenicity testing.

If a subject tests positive for anti-drug antibodies (ADA), he/she will be followed until ADA levels revert to baseline.

9.5.4 Appropriateness of Measurements

The study population consists of subjects who completed Study HZNP-ACT-301; this population was well-defined and consistent with the expected target population for whom ACTIMMUNE will be indicated (pediatric and young adult subjects with a FA functional stage of >1 to <5).

The primary efficacy endpoint (change in FARS-mNeuro from Baseline to Week 26) has been agreed upon with the FDA. The measurements used in this study for the primary and secondary endpoints (ADL, FARStot, and T25FW) are established and well-validated endpoints that have been shown to correlate significantly with functional disability in FA patients [Lynch et al, 2006].

9.5.5 Study Procedures

Subjects who provide Informed Consent/Assent and who meet all the entry criteria for participation in this study will be enrolled in the open-label extension study. Subjects may participate in this study for up to 28 consecutive weeks in total. The order and timing of the assessments at each study visit should be followed so that assessments are performed at consistent times relative to dosing at each visit.

9.5.5.1 Baseline/Day 1 (Week 26 of Study HZNP-ACT-301)

The Week 26 Visit from HZNP-ACT-301 will serve as Baseline/Day 1 for this study. At the Baseline Visit, subjects will receive the last dose of the randomized drug from HZNP-ACT-301(ACTIMMUNE or placebo) in a double-blind fashion, and the first dose of study drug for the open-label extension study ($10 \mu\text{g}/\text{m}^2$) will be distributed for administration at home according to the planned TIW dosing schedule. Baseline assessments should be performed in the order presented below to ensure that the neurological tests are performed at approximately the same time on testing days.

- Collect all used, partially used, and unused study medication kits and vials from Study HZNP-ACT-301.
- Obtain signed, written Informed Consent/Assent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act [HIPAA]) for Study HZNP-ACT-302. Refusal to provide this permission excludes an individual from eligibility for study participation. Record date Informed Consent/Assent was given and who conducted the process on the appropriate source documentation.
- Perform review of inclusion/exclusion criteria.
- Collect blood (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]). The pregnancy test must be negative for those subjects to be eligible for participation in this study.
- Collect blood samples (2 mL) for immunogenicity testing.
- Collect blood samples (1 mL) for frataxin analyses.
- Measure height and weight to calculate dose volume.
- Educate subjects and caregivers on dosing technique and schedule.
- Between approximately 7 to 10 AM, administer the last dose of double-blind study drug for Study HZNP-ACT-301 or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.
- Perform physical examination, including vital signs.

- Enquire about AEs and concomitant medications.
- Perform ADL, and Physician's and Patient's Global Assessments.
- Perform echocardiogram.
- Perform ECG.
- Perform vision testing (LCSLC) and auditory testing (LiSN-S) if normal audiogram results at Screening Visit of Study HZNP-ACT-301.
- Perform QOL assessments (PedsQL, SF-36, MFIS).
- Perform functional staging of FA and neurological assessments (FARS, T25FW, 9-HPT) at approximately 4 to 6 hours post-dose.
- Collect buccal samples and muscle biopsies (optional) for frataxin analysis (muscle biopsies, if performed, will be the last activity prior to dosing activities).
- Use CTCC's electronic system to obtain the enrollment number and study drug kit assignment.
- Dispense a 4-week supply of study drug.

Subjects will be discharged from the study center after all of the Study Day 1 procedures have been completed.

9.5.5.2 Week 4

- Collect all used, partially used, and unused study medication kits and vials.
- Collect blood (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]). The pregnancy test must be negative for those subjects to continue participation in this study.
- Collect blood samples (2 mL) for immunogenicity testing.
- Measure height and weight to calculate dose volume.
- Educate subjects and caregivers on dosing technique and schedule.
- Between approximately 7 to 10 AM, administer study drug or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.

- Perform brief physical examination, including vital signs.
- Enquire about AEs and concomitant medication use.
- Dispense a 6- or 9-week supply of study drug, as applicable.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return to the clinic at Week 13.

9.5.5.3 Week 13

- Collect all used, partially used, and unused study medication kits and vials.
- Collect blood (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]). The pregnancy test must be negative for those subjects to continue participation in this study.
- Collect blood samples (2 mL) for immunogenicity testing.
- Collect blood samples (1 mL) for frataxin analyses.
- Measure height and weight to calculate dose volume.
- Educate subjects and caregivers on dosing technique and schedule.
- Between approximately 7 to 10 AM, administer study drug or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.
- Perform physical examination, including vital signs.
- Enquire about AEs and concomitant medications.
- Perform ADL and Physician's and Patient's Global Assessments.
- Perform ECG.
- Perform QOL assessments (PedsQL, SF-36, MFIS).
- Perform functional staging of FA and neurological assessments (FARS, T25FW, 9-HPT) at approximately 4 to 6 hours post-dose.
- Collect buccal samples and muscle biopsies (optional) for frataxin analysis.
- Dispense a 6- or 13-week supply of study drug, as applicable.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return to the clinic at Week 26.

9.5.5.4 Week 26 (Termination Visit or Premature Withdrawal Visit)

- Collect all used, partially used, and unused study medication kits and vials.
- Collect blood (9.3 mL; 1.0 mL for hematology, 3.5 mL for chemistry, 3.0 mL discard, and 1.8 mL for PT/INR/aPTT) and urine samples from all subjects for safety clinical laboratory values (including urine pregnancy test [if applicable]).
- Collect blood samples (2 mL) for immunogenicity testing.
- Collect blood samples (1 mL) for frataxin analyses.
- Measure height and weight.
- Between approximately 7 to 10 AM, administer study drug or supervise administration of the study drug by either the subject or the subject's caregiver and record date/time of dosing.
- Perform physical examination, including vital signs.
- Enquire about AEs and concomitant medications.
- Perform ADL and Physician's and Patient's Global Assessments.
- Perform echocardiogram.
- Perform ECG.
- Perform Vision testing (LCSLC) and auditory testing (LiSN-S) if audiogram results were normal at Screening Visit of Study HZNP-ACT-301.
- Perform QOL assessments (PedsQL, SF-36, MFIS).
- Perform functional staging of FA and neurological assessments (FARS, T25FW, 9-HPT) at approximately 4 to 6 hours post-dose.
- Collect buccal samples and muscle biopsies (optional) for frataxin analysis.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return in approximately two weeks for the Follow-Up Safety Visit.

9.5.5.5 Follow-Up Safety Visit

Subjects will return to the clinic approximately two weeks after administration of their final dose of study medication. They will undergo a brief physical examination and report any changes in concomitant medication and AEs. Any ongoing study drug-related AE present at the time of study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained. In addition, individual blood samples (2 mL) will be collected for immunogenicity testing; if subjects test positive for ADA, they will be followed until the ADA levels revert to baseline.

9.6 Statistical Methods and Determination of Sample Size

Detailed statistical analyses will be presented in a separate statistical analysis plan. Some key points identified for statistical analyses are outlined below.

9.6.1 Endpoints

Safety Endpoints

Adverse event and concomitant medication data will be summarized. Clinical laboratory safety data, vital sign data, echocardiogram data, and ECG interval data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values. Shift tables will be presented for clinical laboratory values and ECG categorical results from Baseline to each post-dose visit. Physical examination findings will be listed by subject. Results of immunogenicity testing will be presented in tabular format.

Efficacy Endpoints

The primary efficacy endpoint is the observed change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in the FARS-mNeuro score. Results will be summarized descriptively.

Secondary Efficacy Endpoints

The observed mean change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in ADL, T25FW, FARS-mNeuro responder rate, and FARStot scores will be summarized descriptively.

Exploratory Efficacy/Quality of Life Endpoints

The observed mean changes from Baseline will be summarized descriptively for the following endpoints:

- Change from Baseline to Week 13 in the FARS-mNeuro, ADL, T25FW, and FARStot scores.
- Change from Baseline to Weeks 13 and 26 for all subjects, and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in 9-HPT, remaining FARS subscale scores, FA

stage, frataxin protein levels, MFIS, SF-36, PedsQL, and Physician and Patient Global Assessments.

- Change from Baseline to Week 26 for all subjects and from Baseline of HZNP-ACT-301 to Week 26 of HZNP-ACT-302 (52-week treatment duration) for subjects receiving active treatment in both studies in LCSLC and LiSN-S.

9.6.2 Populations for Analysis

All analyses will be based on the Safety Population. The safety population will be all subjects who receive at least one dose of open-label study drug after the Baseline Visit for HZNP-ACT-302).

9.6.3 Baseline Characteristics

Baseline and demographic characteristics will be summarized by standard descriptive summaries (e.g., means and standard deviations for continuous variables such as age and percentages for categorical variables such as gender).

9.6.4 Sample Size and Power Considerations

Subjects who complete 26 weeks of blinded treatment in Study HZNP-ACT-301 will be eligible for enrollment. The sample size is not based on statistical considerations.

9.7 Changes in the Conduct of the Study

If any modifications in the experimental design, dosages, parameters, subject selection, or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before any such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approved from the appropriate IRB.

The Sponsor's Medical Monitor will consider any requests for exceptions to protocol entry criteria on a case-by-case basis. The Investigator or other health professional in attendance must contact CTCC as soon as possible to discuss the associated circumstances; CTCC in turn, will notify the Sponsor. All protocol deviations and the reasons for such deviations **must** be documented in eClinical. In the event of a protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB and Sponsor.

10. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The Investigator must maintain adequate and accurate records to document fully the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified in two separate categories: (1) Investigator study file and (2) subject clinical source

documents that corroborate data collected in the eCRFs. Subject clinical source documents would include, as applicable, original hospital/clinic subject records; physicians' and nurses' notes; appointment book; original laboratory, ECG, electroencephalogram, radiology, pathology, and special assessment reports; dispensing records; signed Informed Consent/Assent Forms; consultant letters; and subject screening and enrollment logs.

In order to comply with regulatory requirements, it is the policy of the Sponsor that, at a minimum, the following be documented in source documents at the study center:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify that the subject meets protocol entry criteria, including genetic testing results.
- Study number, assigned subject number, and verification that written Informed Consent/Assent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each study visit including each study assessment and the identity of the staff member performing the assessment.
- Study drug dispensing and return.
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- Adverse events (start and stop date, description, action taken, and resolution).
- Investigator or sub-investigator's signed assessment of each AE.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or PW from, the study.

11. CASE REPORT FORMS

An electronic case report form (eCRF) is required for every subject who signs the informed consent/assent or for whom the caregiver has signed informed consent. Required data must be entered on the eCRF within three days after data collection or the availability of test results. Separate source records are required to support all eCRF entries. Data captured on the eCRF, and requested anonymized copies of supporting documents, will be transferred to the Sponsor at study completion.

The Investigator will ensure that the eCRFs are accurate, complete, legible, and timely, and will review and provide an electronic signature for the eCRF according to the standard operating procedure of the ARO Data Management System. Final eCRFs will be provided to the Investigator and Sponsor by ARO Data Management.

12. STUDY MONITORING

The Investigator will ensure that the study is conducted in accordance with all regulations governing the protection of human subjects. The Investigator will adhere to the basic principles of GCP as outlined in Title 21 of the CFR, Part 312, Subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators"; and the ICH guideline entitled "Good Clinical Practice: Consolidated Guidance". Additionally, this study will be conducted in compliance with the Declaration of Helsinki and with all local laws and regulations.

The Investigator will ensure that all work and services described in or associated with this protocol are conducted in accordance with the investigational plan, applicable regulations, and the highest standards of medical and clinical research practice. The Investigator will provide copies of the study protocol and Investigator Brochure to all Sub-Investigators, pharmacists, and other staff responsible for study conduct.

All aspects of the study will be monitored by qualified individuals designated by the Sponsor. The Sponsor will ensure that the study is monitored adequately in accordance with GCP guidelines.

Prior to initiation of the study, the Sponsor's representatives will review with study center personnel information regarding the investigational drug, protocol requirements, monitoring requirements, and reporting of SAEs.

At intervals during the study, as well as after the completion of subject enrollment, the study center will be monitored by the ARO for compliance. During these visits, the monitor will discuss study progress, verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies, and check on various aspects of study conduct (e.g., drug accountability, sample storage). The Investigator agrees to allow these monitors access to the clinical supplies, dispensing and storage areas, and clinical records of the study subjects, and, if requested, agrees to assist the monitors. The Investigator must cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

A secondary audit may be conducted by Quality Assurance designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the US FDA and/or representatives of other regulatory authorities may also conduct an inspection of the study at the investigative site. If informed of such an inspection, the Investigator should notify the Sponsor immediately.

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical study. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all

subjects enrolled in this study. A statement to this effect should be included in the Informed Consent/Assent Form.

13. DATA MANAGEMENT

Data will be entered into a clinical database as specified in the ARO's Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections will be documented in an audit trail.

The coding of an adverse event, medical history and concomitant medication terms will be performed by the ARO and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) and adverse event/medical history/surgery/non drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

14. RETENTION OF RECORDS

No study documents at the study site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed Informed Consent Forms, IRB correspondence, and correspondence with the Sponsor must be kept by the Investigator for at least two years following the date of the last approval of a marketing application in an ICH region (including the US) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all study-related files must be retained for at least two years following the date of discontinuation of the clinical development program for ACTIMMUNE and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any study-related files. If the Investigator leaves the practice or institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the study was conducted.

15. PUBLICATION

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications) as detailed in the Clinical Trial Agreement.

16. REFERENCES

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17. APPENDICES

17.1 Administrative Appendix

This appendix provides names and contact information for the study administrative structure. The IRB must be notified of changes that are made to this section, but IRB review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment number.

Medical Monitor

[REDACTED]
Senior Medical Director
Horizon Pharma, Inc.
150 South Saunders Road
Lake Forest, IL 60045
Mobile telephone number: [REDACTED]
Business telephone number: [REDACTED]
Fax number: [REDACTED]
Email: [REDACTED]

Sponsor
Representative

[REDACTED]
Executive Director, Clinical Development & Operations
Horizon Pharma, Inc.
150 South Saunders Road
Lake Forest, IL 60045
Mobile telephone number: [REDACTED]
Business telephone number: [REDACTED]
Fax number: [REDACTED]
Email: [REDACTED]

Sponsor Contact for
Serious Adverse Event Reporting

Med Communications, Inc.
20 South Dudley, Ste. 700
Memphis, TN 38103
Telephone number: [REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

Academic Research
Organization (ARO)

[REDACTED]
Center for Human Experimental Therapeutics (CHET)
University of Rochester
265 Crittenden Avenue
Rochester, NY 14624
Telephone number: [REDACTED]
Fax: [REDACTED]
Email: [REDACTED]

17.2 Approved US Labeling for ACTIMMUNE

Interferon γ -1b was approved in 1990 in the US under the trade name ACTIMMUNE as a treatment to reduce the frequency and severity of serious infections associated with CGD, an inherited disorder characterized by deficient phagocyte oxidative metabolism (BLA 103836, approved for orphan indication). In February 2000, approval was obtained to market the product in SMO, a rare (and often fatal) bone disorder (BLA 103836/1001, approved for orphan indication).

The current version of the approved US labeling (02 June 2015) is included in this appendix; any subsequent updates to the labeling can be found at
http://actimmune.com/pdf/10889_Actimmune-PI_8_5x11.pdf

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACTIMMUNE® safely and effectively. See full prescribing information for ACTIMMUNE.

ACTIMMUNE® (interferon gamma-1b) injection, for subcutaneous use.
Initial U.S. Approval: 1990

INDICATIONS AND USAGE

ACTIMMUNE is an interferon gamma indicated for:

- Reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD) (1)
- Delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO) (1)

DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1)

- The recommended dose is 50 mcg/m² for patients whose body surface area is greater than 0.5 m² and 1.5 mcg/kg/dose for patients whose body surface area is equal to or less than 0.5 m² three times weekly. (2.1)
- Monitor hematology, blood chemistries and urinalysis prior to the beginning of treatment and at 3-month intervals. (2.1)
- If severe reactions occur, reduce dose by 50 percent or discontinue therapy until the adverse reaction abates. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mcg (2 million International Units) of Interferon gamma-1b in 0.5 mL solution in a single use vial. (3)

CONTRAINDICATIONS

Known hypersensitivity to interferon gamma, *E. coli* derived products, or any component of the product (4)

WARNINGS AND PRECAUTIONS

- Cardiovascular Disorders:** Pre-existing cardiac conditions may be exacerbated. (5.1)

- Neurologic Disorders:** Reduce dose or discontinue if decreased mental status, gait disturbance, dizziness occur. (5.2)
- Bone Marrow Toxicity:** Monitor for neutropenia and thrombocytopenia particularly when administering ACTIMMUNE in combination with other potentially myelosuppressive agents. (5.3)
- Hepatic Toxicity:** Reduce dose or discontinue to reverse severe elevations of aspartate transaminase (AST) and/or alanine transaminase (ALT); monitor liver function monthly in patients less than 1 year old. (5.4)
- Hypersensitivity Reactions:** If serious hypersensitivity reactions occur, discontinue and institute appropriate medical therapy. (5.5)
- Renal Toxicity:** Monitor renal function regularly when administering ACTIMMUNE to patients with severe renal insufficiency (5.6)

DRUG INTERACTIONS

- Concomitant use of drugs with neurotoxic, hematotoxic or cardiotoxic effects may increase the toxicity of interferons. (7.2)
- Avoid simultaneous administration of ACTIMMUNE with other heterologous serum protein or immunological preparations (e.g., vaccines). (7.3)

ADVERSE REACTIONS

Common adverse reactions (incidence rate 2% or greater) for ACTIMMUNE include fever, headache, rash, chills, injection site erythema or tenderness, fatigue, diarrhea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Horizon Pharma USA, Inc. at 1-866-479-6742 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 8/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

1	INDICATIONS AND USAGE
2	DOSAGE AND ADMINISTRATION
2.1	Dosing Information
2.2	Important Administration Instructions
2.3	Dose Modification
3	DOSAGE FORMS AND STRENGTHS
4	CONTRAINDICATIONS
5	WARNINGS AND PRECAUTIONS
5.1	Cardiovascular Disorders
5.2	Neurologic Disorders
5.3	Bone Marrow Toxicity
5.4	Hepatic Toxicity
5.5	Hypersensitivity Reactions
5.6	Renal Toxicity
5.7	Allergic Reactions to Natural Rubber
6	ADVERSE REACTIONS
6.1	Clinical Trials Experience
6.2	Postmarketing Experience
6.3	Immunogenicity
7	DRUG INTERACTIONS
7.1	Myelosuppressive Agents
7.2	Drugs with Neurotoxic, Hematotoxic or Cardiotoxic Effects
7.3	Immunological Preparations

7.4 Effects on Cytochrome P-450 Pathways

8	USE IN SPECIFIC POPULATIONS
8.1	Pregnancy
8.2	Lactation
8.3	Females and Males of Reproductive Potential
8.4	Pediatric Use
8.5	Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Effects in Chronic Granulomatous Disease (CGD)

14.2 Effects in Severe, Malignant Osteopetrosis (SMO)

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- ACTIMMUNE is indicated for reducing the frequency and severity of serious infections associated with Chronic Granulomatous Disease (CGD).
- ACTIMMUNE is indicated for delaying time to disease progression in patients with severe, malignant osteopetrosis (SMO).

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

- The recommended dosage of ACTIMMUNE administered subcutaneously, for the treatment of patients with CGD and SMO is shown in Table 1 below:

Table 1: Recommended Dosage for ACTIMMUNE for the Treatment of Patients with CGD and SMO

Body Surface Area (m ²)	Dose (mcg/m ²)	Dose (International Units/m ²) ^a	Frequency
Greater than 0.5 m ²	50 mcg/m ²	1 million International Units/m ²	Three times weekly (For example, Monday, Wednesday and Friday)
Equal to or less than 0.5 m ²	1.5 mcg/kg/dose	-----	Three times weekly (For example, Monday, Wednesday and Friday)

^a Note that the above activity is expressed in International Units (1 million International Units/50 mcg). This is equivalent to what was previously expressed as units (1.5 million units/50 mcg).

- Prior to the beginning of treatment and at three-month intervals during treatment the following laboratory tests are recommended for all patients on ACTIMMUNE (interferon gamma-1b) therapy [see *Warnings and Precautions (5.3, 5.4, 5.6)*]:
 - Hematologic tests – including complete blood counts, differential and platelet counts
 - Blood chemistries – including renal and liver function tests. In patients less than 1 year of age, liver function tests should be measured monthly [see *Adverse Reactions (6.2)*].
 - Urinalysis

2.2 Important Administration Instructions

- The optimum sites of subcutaneous injection are the right and left deltoid and anterior thigh.
- ACTIMMUNE can be administered by a physician, nurse, family member or patient when appropriately counseled in the administration of subcutaneous injections.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. ACTIMMUNE is a clear, colorless solution.
- ACTIMMUNE is for a single use only. Discard any unused portion. ACTIMMUNE does not contain a preservative.
- ACTIMMUNE should not be mixed with other drugs in the same syringe.
- Administer ACTIMMUNE using either sterilized glass or plastic disposable syringes.

2.3 Dose Modification

- If severe reactions occur, the dosage should be reduced by 50 percent or therapy should be interrupted until the adverse reaction abates.

- Safety and efficacy has not been established for ACTIMMUNE given in doses greater or less than the recommended dose of 50 mcg/m². Higher doses (i.e., greater than 50 mcg/m²) are not recommended. The minimum effective dose of ACTIMMUNE has not been established.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mcg (2 million International Units) per 0.5 mL solution in a single-use vial. ACTIMMUNE (interferon gamma-1b) is a sterile, clear, colorless solution filled in a single-use vial for subcutaneous injection.

4 CONTRAINDICATIONS

ACTIMMUNE is contraindicated in patients who develop or have known hypersensitivity to interferon gamma, *E. coli* derived products, or any component of the product.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Disorders

Acute and transient "flu-like" symptoms such as fever and chills induced by ACTIMMUNE at doses of 250 mcg/m²/day (greater than 10 times the weekly recommended dose) or higher may exacerbate pre-existing cardiac conditions. Patients with pre-existing cardiac conditions, including ischemia, congestive heart failure or arrhythmia on ACTIMMUNE should be monitored for signs/symptoms of exacerbation. Some of the "flu-like" symptoms may be minimized by bedtime administration of ACTIMMUNE. Acetaminophen may also be used to ameliorate these effects.

5.2 Neurologic Disorders

Decreased mental status, gait disturbance and dizziness have been observed, particularly in patients receiving ACTIMMUNE doses greater than 250 mcg/m²/day (greater than 10 times the weekly recommended dose). Most of these abnormalities were reversible within a few days upon dose reduction or discontinuation of therapy. Monitor patients when administering ACTIMMUNE to patients with seizure disorders or compromised central nervous system function.

5.3 Bone Marrow Toxicity

Reversible neutropenia and thrombocytopenia that can be severe and may be dose related have been observed during ACTIMMUNE therapy. Monitor neutrophil and platelet counts in patients with myelosuppression during treatment with ACTIMMUNE.

5.4 Hepatic Toxicity

Repeated administration of ACTIMMUNE to patients with advanced hepatic disease may result in accumulation of interferon gamma-1b. Frequent assessment of liver function in these patients is recommended.

Elevations of aspartate transaminase (AST) and /or alanine transaminase (ALT) (up to 25-fold) have been observed during ACTIMMUNE therapy. The incidence appeared to be higher in patients less than 1 year of age compared to older children. The transaminase elevations were reversible with reduction in dosage or interruption of ACTIMMUNE treatment. Patients begun on ACTIMMUNE before age one year should receive monthly assessments of liver function. If severe hepatic enzyme elevations develop, ACTIMMUNE dosage should be modified [see *Dosage and Administration (2.3)*].

5.5 Hypersensitivity Reactions

Isolated cases of acute serious hypersensitivity reactions have been observed in patients receiving ACTIMMUNE. If such an acute reaction develops the drug should be discontinued immediately and appropriate medical therapy instituted. Transient cutaneous rashes have occurred in some patients following injection of ACTIMMUNE that have necessitated treatment interruption.

5.6 Renal Toxicity

Monitor renal function regularly when administering ACTIMMUNE in patients with severe renal insufficiency because the possibility exists that with repeated administration, accumulation of interferon gamma-1b may occur. Renal toxicity has been reported in patients receiving ACTIMMUNE.

5.7 Allergic Reactions to Natural Rubber

The stopper of the glass vial for ACTIMMUNE contains natural rubber (a derivative of latex) which may cause allergic reactions.

6 ADVERSE REACTIONS

The following adverse reactions are described below and elsewhere in the warnings and precautions section of the labeling:

- *Cardiovascular Disorders [see Warnings and Precautions (5.1)]*
- *Neurologic Disorders [see Warnings and Precautions (5.2)]*
- *Bone Marrow Toxicity [see Warnings and Precautions (5.3)]*
- *Hepatic Toxicity [see Warnings and Precautions (5.4)]*
- *Hypersensitivity Reactions [see Warnings and Precautions (5.5)]*
- *Renal Toxicity [see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The following data on adverse reactions are based on the subcutaneous administration of ACTIMMUNE at a dose of 50 mcg/m², three times weekly, in patients with CGD during a clinical trial in the United States and Europe.

The most common adverse reactions observed in patients with CGD are shown in the following table:

Table 2: Adverse Reactions Occurring in 2 % or Greater of CGD Patients Receiving ACTIMMUNE in Clinical Trials

Adverse Reactions	Percent of Patients	
	ACTIMMUNE CGD (n=63)	Placebo CGD (n=65)
Fever	52	28
Headache	33	9
Rash	17	6
Chills	14	0
Injection site erythema or tenderness	14	2
Fatigue	14	11
Diarrhea	14	12
Vomiting	13	5
Nausea	10	2
Myalgia	6	0
Arthralgia	2	0

Similar safety data were observed in 34 patients with SMO.

The clinical and laboratory toxicity associated with multiple dose studies of ACTIMMUNE is dose, route and schedule-dependent.

The most common adverse reactions include constitutional symptoms such as fever, headache, chills, myalgia or fatigue which may decrease in severity as treatment continues.

Less Common Adverse Reactions

The following adverse reactions are assessed as potentially related to ACTIMMUNE (interferon gamma-1b) therapy:

Blood and Lymphatic System—neutropenia (reversible), febrile neutropenia, leukopenia, and thrombocytopenia.

Cardiovascular—angina pectoris, arrhythmia, atrial fibrillation, atrioventricular block, cardiac failure (including congestive cardiac failure), tachyarrhythmia, heart block, (acute) myocardial infarction, myocardial ischemia, syncope, and tachycardia.

Gastrointestinal—abdominal pain, dyspepsia, gastrointestinal bleeding, granulomatous colitis, hepatic insufficiency, and pancreatitis, including pancreatitis with fatal outcome.

General Disorders and Administration Site Conditions—asthenia, chest pain/discomfort, influenza-like illness/flu-like symptoms, injection site hemorrhage, injection site pain, malaise, rigors, and weakness.

Hepatobiliary Disorders—hepatic insufficiency and hepatomegaly.

Immunological—hypersensitivity, increased autoantibodies, lupus-like syndrome (including systemic lupus erythematosus-flares and drug-induced lupus erythematosus), and Stevens-Johnson syndrome.

Infections and Infestations—upper respiratory tract infection.

Investigations—blood alkaline phosphatase increased, liver function tests abnormal/ elevation of hepatic enzymes, increased triglycerides, and weight decreased.

Metabolic—hyponatremia, hypokalemia, hyperglycemia, and hypertriglyceridemia.

Musculoskeletal—back pain, clubbing, and muscle spasms.

Nervous System—dizziness (excluding vertigo), gait disturbance, headache, Parkinsonian symptoms, convulsion/seizure (including grand mal convulsions), and transient ischemic attacks.

Psychiatric—confusion, depression, disorientation, hallucinations, mental status changes, and mental status decreased.

Pulmonary—tachypnea, bronchospasm, pulmonary edema, and interstitial pneumonitis.

Renal—acute renal failure (which may be reversible) and proteinuria.

Skin and Subcutaneous Tissue Disorders—atopic dermatitis, (exacerbation of) dermatomyositis, transient cutaneous rash, and urticaria.

Vascular Disorder—deep venous thrombosis, hypotension, pulmonary embolism.

Abnormal Laboratory Test Values: Elevations of ALT and AST have been observed [*see Warnings and Precautions (5.4)*].

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of ACTIMMUNE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Children with CGD less than 3 years of age:

Data on the safety and activity of ACTIMMUNE in 37 patients under the age of 3 years was pooled from four uncontrolled postmarketing studies. The rate of serious infections per patient-year in this uncontrolled group was similar to the rate observed in the ACTIMMUNE treatment groups in controlled trials. Developmental parameters (height, weight and endocrine maturation) for this uncontrolled group conformed to national normative scales before and during ACTIMMUNE therapy.

In 6 of the 10 patients receiving ACTIMMUNE therapy before age one year 2-fold to 25-fold elevations from baseline of AST and/or ALT were observed. These elevations occurred as early as 7 days after starting treatment. Treatment with ACTIMMUNE was interrupted in all 6 of these patients and was restarted at a reduced dosage in 4. Liver transaminase values returned to baseline in all patients and transaminase elevation recurred in one patient upon ACTIMMUNE rechallenge. An 11-fold alkaline phosphatase elevation and hypokalemia in one patient and neutropenia (ANC = 525 cells/mm³) in another patient resolved with interruption of ACTIMMUNE treatment and did not recur with rechallenge.

In the postmarketing safety database clinically significant adverse reactions observed during ACTIMMUNE therapy in children under the age of three years (n=14) included: two cases of hepatomegaly, and one case each of Stevens-Johnson syndrome, granulomatous colitis, urticaria, and atopic dermatitis.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. In clinical trials, 8 out of 33 ACTIMMUNE-treated patients developed non-neutralizing antibodies to interferon gamma-1b. No neutralizing antibodies to ACTIMMUNE have been detected in patients. In a Phase 1 study, none of the 38 ACTIMMUNE-treated healthy volunteers developed non-neutralizing antibodies to interferon gamma-1b.

The detection of antibody formation, including neutralizing antibody, in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ACTIMMUNE with the incidence of antibodies to other products may be misleading.

7 DRUG INTERACTIONS

7.1 Myelosuppressive Agents

When administering ACTIMMUNE in combination with other potentially myelosuppressive agents, monitor neutrophil and platelet counts [*see Warnings and Precautions (5.3)*].

7.2 Drugs with Neurotoxic, Hematotoxic or Cardiotoxic Effects

The concurrent use of drugs having neurotoxic (including effects on the central nervous system), hematotoxic, or cardiotoxic effects may increase the toxicity of interferons in these systems. It is theoretically possible that hepatotoxic and/or nephrotoxic drugs might have an effect on the clearance of ACTIMMUNE.

7.3 Immunological Preparations

Simultaneous administration of ACTIMMUNE with other heterologous serum protein preparations or immunological preparations (e.g., vaccines) should be avoided due to the risk of an unexpected, or amplified, immune response.

7.4 Effects on Cytochrome P-450 Pathways

Preclinical studies in rodents using species-specific interferon gamma have demonstrated a decrease in hepatic microsomal cytochrome P-450 concentrations. This could potentially lead to a depression of the hepatic metabolism of certain drugs that utilize this degradative pathway.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women. ACTIMMUNE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

ACTIMMUNE has shown an increased incidence of abortions in primates when given from gestation day 20 to 80 in doses approximately 100 times the human dose. A study in pregnant primates treated with subcutaneous doses 2–100 times the human dose failed to demonstrate teratogenic activity for ACTIMMUNE.

Female mice treated subcutaneously with recombinant murine IFN-interferon gamma (rmuIFN-gamma) at 280 times the maximum recommended clinical dose of ACTIMMUNE from shortly after birth through puberty but not during pregnancy had offspring which exhibited decreased body weight during the lactation period. The clinical significance of this finding observed following treatment of mice with rmuIFN-gamma is uncertain. For lower doses, there is no evidence of maternal toxicity, embryotoxicity, fetotoxicity or teratogenicity in preclinical studies.

8.2 Lactation

Risk Summary

It is not known whether ACTIMMUNE is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ACTIMMUNE, a decision should be made whether to discontinue nursing or to discontinue the drug, dependent upon the importance of the drug to the mother.

8.3 Females and Males of Reproductive Potential

Infertility

Based on the information available, it cannot be excluded that the presence of higher levels of interferon gamma may impair male fertility and that in certain cases of female infertility increased levels of interferon gamma may have played a role [*see Nonclinical Toxicology (13.1)*].

In younger patients, the long-term effect on fertility is also not known.

8.4 Pediatric Use

The safety and effectiveness of ACTIMMUNE has been established in pediatric patients aged 1 year and older in CGD patients and 1 month and older in SMO patients [see *Clinical Studies (14)*]. There are no data available for pediatric patients below the age of 1 month.

8.5 Geriatric Use

Clinical studies of ACTIMMUNE did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Central nervous system adverse reactions including decreased mental status, gait disturbance and dizziness have been observed, particularly in patients receiving doses greater than 100 mcg/m²/day by intravenous or intramuscular administration. These abnormalities were reversible within a few days upon dose reduction or discontinuation of therapy. Reversible neutropenia, elevation of hepatic enzymes and of triglycerides, and thrombocytopenia have also been observed.

11 DESCRIPTION

ACTIMMUNE (Interferon gamma-1b), an interferon gamma, is a single-chain polypeptide containing 140 amino acids. Production of ACTIMMUNE is achieved by fermentation of a genetically engineered *Escherichia coli* bacterium containing the DNA which encodes for the recombinant protein. Purification of the product is achieved by conventional column chromatography. ACTIMMUNE is a highly purified sterile solution consisting of non-covalent dimers of two identical 16,465 Dalton monomers; with a specific activity of 20 million International Units/mg (2x10⁶ International Units/0.5 mL) which is equivalent to 30 million units/mg.

ACTIMMUNE is a sterile, clear, colorless solution filled in a single-use vial for subcutaneous injection. Each 0.5 mL of ACTIMMUNE contains: 100 mcg (2 million International Units) of interferon gamma-1b formulated in disodium succinate hexahydrate (0.37 mg), mannitol (20 mg), polysorbate 20 (0.05 mg), succinic acid (0.14 mg) and Sterile Water for Injection. Note that the above activity is expressed in International Units (1 million International Units/50 mcg). This is equivalent to what was previously expressed as units (1.5 million units/50 mcg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Interferons bind to specific cell surface receptors and initiate a sequence of intracellular events that lead to the transcription of interferon-stimulated genes. The three major groups of interferons (alpha, beta, gamma) have partially overlapping biological activities that include immunoregulation such as increased resistance to microbial pathogens and inhibition of cell proliferation. Type 1 interferons (alpha and beta) bind to the alpha/ beta receptor. Interferon gamma binds to a different cell surface receptor and is classified as Type 2 interferon. Specific effects of interferon gamma include the enhancement of the oxidative metabolism of macrophages, antibody dependent cellular cytotoxicity (ADCC), activation of natural killer (NK) cells, and the expression of Fc receptors and major histocompatibility antigens.

CGD is an inherited disorder of leukocyte function caused by defects in the enzyme complex responsible for phagocyte superoxide generation. ACTIMMUNE does not increase phagocyte superoxide production even in treatment responders.

In SMO (an inherited disorder characterized by an osteoclast defect, leading to bone overgrowth, and by deficient phagocyte oxidative metabolism), a treatment-related enhancement of superoxide production by phagocytes was observed. ACTIMMUNE was found to enhance osteoclast function in vivo.

In both disorders, the exact mechanism(s) by which ACTIMMUNE has a treatment effect has not been established. Changes in superoxide levels during ACTIMMUNE therapy do not predict efficacy and should not be used to assess patient response to therapy.

12.3 Pharmacokinetics

Pharmacokinetic studies in patients with CGD have not been performed. The intravenous, intramuscular, and subcutaneous pharmacokinetics of ACTIMMUNE have been investigated in 24 healthy male subjects following single-dose administration of 100 mcg/m² (twice the recommended dose for CGD and SMO patients). ACTIMMUNE is rapidly cleared after intravenous

administration (1.4 Liters/minute) and slowly absorbed after intramuscular or subcutaneous injection. After intramuscular or subcutaneous injection, the apparent fraction of dose absorbed was greater than 89%. The mean elimination half-life after intravenous administration of 100 mcg/m² in healthy male subjects was 38 minutes. The mean elimination half-lives for intramuscular and subcutaneous dosing with 100 mcg/m² were 2.9 and 5.9 hours, respectively. Peak plasma concentrations, determined by ELISA, occurred approximately 4 hours (1.5 ng/mL) after intramuscular dosing and 7 hours (0.6 ng/mL) after subcutaneous dosing. Multiple dose subcutaneous pharmacokinetic studies were conducted in 38 healthy male subjects. There was no accumulation of ACTIMMUNE after 12 consecutive daily injections of 100 mcg/m².

Interferon gamma was not detected in the urine of healthy human volunteers following administration of 100 mcg/m² of ACTIMMUNE by the intravenous, intramuscular and subcutaneous routes. In vitro perfusion studies utilizing rabbit livers and kidneys demonstrate that these organs are capable of clearing interferon gamma from perfusate.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: ACTIMMUNE has not been tested for its carcinogenic potential.

Mutagenesis: Ames tests using five different tester strains of bacteria with and without metabolic activation revealed no evidence of mutagenic potential. ACTIMMUNE was tested in a micronucleus assay for its ability to induce chromosomal damage in bone marrow cells of mice following two intravenous doses of 20 mg/kg. No evidence of chromosomal damage was noted.

Impairment of Fertility: Female cynomolgus monkeys treated with daily subcutaneous doses of 30 or 150 mcg/kg ACTIMMUNE (approximately 20 and 100 times the human dose) exhibited irregular menstrual cycles or absence of cyclicity during treatment. Similar findings were not observed in animals treated with 3 mcg/kg ACTIMMUNE.

Female mice receiving recombinant murine IFN-interferon gamma (rmuIFN-gamma) at 32 times the maximum recommended clinical dose of ACTIMMUNE for 4 weeks via intramuscular injection exhibited an increased incidence of atretic ovarian follicles.

Male cynomolgus monkeys treated intravenously for 4 weeks with 8 times the maximum recommended clinical dose of ACTIMMUNE exhibited decreased spermatogenesis. Male mice receiving rmuIFN-gamma at 32 times the maximum recommended clinical dose of ACTIMMUNE for 4 weeks via intramuscular injection exhibited decreased spermatogenesis. The impact of this finding on fertility is not known.

Male mice treated subcutaneously with rmuIFN-gamma from shortly after birth through puberty, with 280 times the maximum recommended clinical dose of ACTIMMUNE exhibited profound yet reversible decreases in sperm counts and fertility, and an increase in the number of abnormal sperm.

The clinical significance of these findings observed following treatment of mice with rmuIFN-gamma is uncertain.

14 CLINICAL STUDIES

14.1 Effects in Chronic Granulomatous Disease (CGD)

A randomized, double-blind, placebo-controlled trial of ACTIMMUNE (interferon gamma-1b) in patients with CGD, was performed to determine whether ACTIMMUNE administered subcutaneously on a three times weekly schedule could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions in patients with CGD. One hundred twenty-eight eligible patients were enrolled in this trial including patients with different patterns of inheritance. Most patients received prophylactic antibiotics. Patients ranged in age from 1 to 44 years with the mean age being 14.6 years. The study was terminated early following demonstration of a highly statistically significant benefit of ACTIMMUNE therapy compared to placebo with respect to time to serious infection ($p=0.0036$), the primary endpoint of the investigation. Serious infection was defined as a clinical event requiring hospitalization and the use of parenteral antibiotics. The final analysis provided further support for the primary endpoint ($p=0.0006$). There was a 67 percent reduction in relative risk of serious infection in patients receiving ACTIMMUNE ($n=63$) compared to placebo ($n=65$). Additional supportive evidence of treatment benefit included a twofold reduction in the number of primary serious infections in the ACTIMMUNE group (30 on placebo versus 14 on ACTIMMUNE, $p=0.002$) and the total number and rate of serious infections including recurrent events (56 on placebo versus 20 on ACTIMMUNE, $p=<0.0001$). Moreover, the length of hospitalization for the treatment of all clinical events provided evidence highly supportive of an ACTIMMUNE treatment benefit. Placebo patients required three times as many inpatient hospitalization days for treatment of clinical events compared to patients receiving ACTIMMUNE (1493 versus 497 total days, $p=0.02$). An ACTIMMUNE treatment benefit with respect to time to serious infection was consistently demonstrated in all subgroup analyses according to stratification factors, including pattern of inheritance, use of prophylactic antibiotics, as well as age. There was a 67 percent reduction in relative risk of serious infection in

patients receiving ACTIMMUNE compared to placebo across all groups. The beneficial effect of ACTIMMUNE therapy was observed throughout the entire study, in which the mean duration of ACTIMMUNE administration was 8.9 months/patient.

14.2 Effects in Severe, Malignant Osteopetrosis (SMO)

A controlled, randomized trial in patients with SMO was conducted with ACTIMMUNE administered subcutaneously three times weekly. Sixteen patients were randomized to receive either ACTIMMUNE plus calcitriol (n=11), or calcitriol alone (n=5). Patients ranged in age from 1 month to 8 years, mean 1.5 years. Treatment failure was considered to be disease progression as defined by 1) death, 2) significant reduction in hemoglobin or platelet counts, 3) a serious bacterial infection requiring antibiotics, or 4) a 50 dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the ACTIMMUNE plus calcitriol arm versus calcitriol alone. In the treatment arm, the median was not reached. Based on the observed data, however, the median time to progression in this arm was at least 165 days versus a median of 65 days in the calcitriol alone arm. In an analysis which combined data from a second study, 19 of 24 patients treated with ACTIMMUNE plus or minus calcitriol for at least 6 months had reduced trabecular bone volume compared to baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ACTIMMUNE (interferon gamma-1b) is a sterile, clear, colorless solution filled in a single-use vial for subcutaneous injection. Each vial permits the extraction of up to 0.5 mL of ACTIMMUNE with additional volume to facilitate solution withdrawal. Each 0.5 mL of ACTIMMUNE contains: 100 mcg (2 million International Units) of interferon gamma-1b.

<u>NDC Number</u>	<u>Size</u>
42238-111-01	One vial
42238-111-12	Cartons of 12 vials

16.2 Storage and Handling

Store vials in the refrigerator at 2 to 8 °C (36 °F – 46 °F). *Do Not Freeze*. Avoid excessive or vigorous agitation. *Do Not Shake*. An unused vial of ACTIMMUNE can be stored at room temperature up to 12 hours prior to use. Discard vials if not used within the 12 hour period. Do not return to the refrigerator.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or their parents or caregivers to read the FDA-approved patient labeling (Information for Patient/Caregiver).

- Inform patients and/or their parents or caregiver regarding the potential benefits and risks associated with treatment. If home use is determined to be desirable by the physician, instructions on appropriate use should be given, including review of the contents of the Information for Patient/ Caregiver. This information is intended to aid in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.
- If home use is prescribed, a puncture resistant container for the disposal of used syringes and needles should be used by the patient and/or parents or caregivers. Instruct patients thoroughly on the importance of proper disposal and caution the patient and/or patient or caregiver against any reuse of needles and syringes. The full container should be disposed of according to the directions provided by the physician.
- Advise the patients and/or their parents or caregivers that the most common adverse reactions occurring with ACTIMMUNE therapy are “flu-like” or constitutional symptoms such as fever, headache, chills, myalgia or fatigue [see *Adverse Reactions (6.1)*] which may decrease in severity as treatment continues. Some of the “flu-like” symptoms may be minimized by bedtime administration of ACTIMMUNE. Acetaminophen may also be used to prevent or partially alleviate the fever and headache.
- Advise patients and/or their parents or caregivers that they may experience undesirable effects such as fatigue, convulsion, confusional state, disorientation or hallucination during treatment. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery. This effect may be enhanced by alcohol.

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Dublin, Ireland
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Distributed by:
HZNP USA Inc.
Roswell, GA 30076

17.3 FARS Neurological Assessment

STEADFAST
NEUROLOGICAL EXAMINATION

1	5	9		3	2
SUBJECT ID			VISIT NO		
<input type="text"/>			<input type="text"/>		
INITIALS		<input type="text"/>	SITE NO	<input type="text"/>	VISIT DATE
		<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
		MM	DD	YYYY	
Time exam was conducted: (24 hr clock)					
			<input type="text"/>	:	<input type="text"/>
			HH	mm	

D. If the subject could not complete this test indicate why: D.

- 1 = Unable to complete trial due to physical limitations – not related to FA.
- 3 = Subject was too fatigued to complete trial.
- 4 = Subject refused to complete trial.

NEUROLOGICAL EXAMINATION (rate each item on the basis of the subject status during examination. To the extent possible, sequential subject examinations should be carried out at the same time of the day. Increments of 0.5 may be used if examiner feels an item falls between 2 defined severities).

A. BULBAR

Most subjects with FA do not have significant facial or tongue atrophy. If mild facial or tongue atrophy is noted score as per instructions. Speech and Cough assessment is self-explanatory.

1. **Facial Atrophy, Fasciculation, Action Myoclonus, and Weakness:** 1. .
 - 0 = None.
 - 1 = Fasciculations or action myoclonus, but no atrophy.
 - 2 = Atrophy present but not profound or complete.
 - 3 = Profound atrophy and weakness.
2. **Tongue Atrophy, Fasciculation, Action Myoclonus and Weakness:** 2. .
 - 0 = None.
 - 1 = Fasciculations or action myoclonus, but no atrophy.
 - 2 = Atrophy present but not profound or complete.
 - 3 = Profound atrophy and weakness.
3. **Cough: (Subject asked to cough forcefully 3 times)** 3. .
 - 0 = Normal.
 - 1 = Depressed.
 - 2 = Totally or nearly absent.
4. **Speech (ask the subject to read or repeat the sentences A “The President lives in the White House.” and B “The traffic is heavy today.”):** 4. .
 - 0 = Normal.
 - 1 = Mild (all or most words understandable).
 - 2 = Moderate (most words not understandable).
 - 3 = Severe (no or almost no useful speech).

Taken from Subramony et al., Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. Neurology 2005; 64(7):1261-2 and as modified by Lynch et al., Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology 2006; 66(11):1711-6.

STEADFAST
NEUROLOGICAL EXAMINATION

1	5	9	SUBJECT ID	3	2	
			VISIT NO			
			VISIT DATE	MM	DD	YYYY

B. UPPER LIMB COORDINATION

Upper limb coordination: Most of the items are self-explanatory. For items 3 through 5, ask the subject to count as they do the task. Example: "Move your hand back and forth 10 times as fast as you can. Please count each time to yourself". You can time the activity with either a watch or a stopwatch.

1. **Finger to Finger Test (The index fingers are placed in front of each other with flexion at the elbow about 25 cm. from the sternum. Observe for 10 seconds. Score amplitude of oscillations):**
0 = Normal.
1 = Mild oscillations of finger (less than 2 cm.).
2 = Moderate oscillations of finger (2-6 cm.).
3 = Severe oscillations of finger (greater than 6 cm.).
1a. Right .
1b. Left .
2. **Nose-Finger Test (Assess kinetic or intention tremor during and towards the end of movement: examiner holds index finger at 90% reach of subject; test at least 3 nose-finger-nose trials; movement slow greater than 3 sec.):**
0 = None.
1 = Mild (less than 2 cm. amplitude).
2 = Moderate (2-6 cm. amplitude or persisting through movement).
3 = Severe (greater than 6 cm. & persisting through movement).
4 = Too poorly coordinated to perform task.
2a. Right .
2b. Left .
3. **Dysmetria Test : The subject touches tip of examiner's finger then subject's chin 8 times as rapidly as possible while the examiner moves his finger to four corners of a one foot square and at about 90% reach of the subject. Assess dysmetria - (i.e. inaccuracy of reaching the target- tip of examiner's finger):**
0 = None.
1 = Mild (misses 2 or fewer times).
2 = Moderate (misses 3-5 times).
3 = Severe (misses 6-8 times.).
4 = Too poorly coordinated to perform task.
3a. Right .
3b. Left .
4. **Rapid Alternating Movements of Hands (Subject should be seated. Forearm pronation/supination 15 cm. above thigh; 10 full cycles as fast as possible; assess rate, rhythm, accuracy; practice 10 cycles before rating, if time greater than 7 sec. add .5 to score. Use stopwatch):**
0 = Normal.
1 = Mild (slightly irregular or slowed).
2 = Moderate (irregular and slowed).
3 = Too poorly coordinated to perform task.
4a. Right .
4b. Left .

Taken from Subramony et al., Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. Neurology 2005; 64(7):1261-2 and as modified by Lynch et al., Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology 2008; 68(11):1711-6.

1 5 9	STEADFAST NEUROLOGICAL EXAMINATION	3 2					
SUBJECT ID	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	VISIT NO	<input type="text"/>	<input type="text"/>
	VISIT DATE		<input type="text"/>				
			MM	DD	YYYY		

B. UPPER LIMB COORDINATION (CONT)

5. **Finger Taps (index fingertip-to-thumb crease; 15 reps as fast as possible; practice 15 reps once before rating; if time greater than 6 sec., add 1 to rating. Use stopwatch):** 5a. Right . .
0 = Normal.
1 = Mild (misses 1-3 times).
2 = Moderate (misses 4-9 times).
3 = Severe (misses 10-15 times).
4 = Cannot perform the task.
5b. Left . .

C. LOWER LIMB COORDINATION

Lower limb coordination: the items are self-explanatory. The heel shin slide is scored 1 if there is an abnormality but contact is steady along the top of the shin. If the heel starts going off the shin to one or other side score 2 or 3 as noted. For heel to shin tap instruct the subject to count 8 taps with heel raised about 8" each time. It is preferable to do this section with subject seated. If this is not followed for a particular subject, it should be done in the same position each time.

1. **Heel Along Shin Slide (Perform while seated, under visual control, slide heel on the contralateral tibia from the patella to the ankle up and down with contralateral leg extended, 3 cycles at moderate speed, one leg at a time):**

0 = Normal (stay on shin).
1 = Mild (abnormally slow, tremulous but contact maintained).
2 = Moderate (goes off shin a total of 3 or fewer times during 3 cycles).
3 = Severe (goes off shin 4 or more times during 3 cycles).
4 = Too poorly coordinated to perform task.

1a. Right .
1b. Left .

2. **Heel-to-Shin Tap (Subject taps heel on midpoint of contralateral shin 8 times on each side from about 6-10", one at a time. Perform seated with contralateral leg extended):**

0 = Normal (stays on target).
1 = Mild (misses shin 2 or less times).
2 = Moderate (misses shin 3-5 times).
3 = Severe (misses shin greater than 5 times).
4 = Too poorly coordinated to perform task.

2a. Right .
2b. Left .

1 5 9	STEADFAST NEUROLOGICAL EXAMINATION	3 2						
SUBJECT ID	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	VISIT NO	<input type="text"/>	<input type="text"/>
	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	VISIT DATE	<input type="text"/>	<input type="text"/>
						MM	<input type="text"/>	<input type="text"/>
						DD	<input type="text"/>	<input type="text"/>
						YYYY	<input type="text"/>	<input type="text"/>

D. PERIPHERAL NERVOUS SYSTEM

Peripheral nervous system: these items are self-explanatory. Check deltoids and intrinsic hand muscles in the upper limbs; iliopsoas and tibialis anterior in the lower limbs. Atrophy and weakness are scored on the basis of the worst muscle in this group. One does not have to do extensive muscle testing. Vibration sense is recorded as noted in seconds and then given a score depending on the extent of impairment. DTR are recorded in the given space as noted and then any hypoareflexia is given a numerical score as noted.

1. **Muscle Atrophy (score most severe atrophy in either upper or lower limb):**

0 = None
 1 = Present - mild/moderate
 2 = Severe/total wasting

1c. If question 1a or 1b is either 1 or 2 indicate location of atrophy:

2. **Muscle Weakness (Test deltoids, interossei, iliopsoas and tibialis anterior. Score most severe weakness in either upper or lower limb):**

0 = Normal (5/5).
 1 = Mild (movement against resistance but not full power 4/5).
 2 = Moderate (movement against gravity but not with added resistance 3/5).
 3 = Severe (movement of joint but not against gravity 2/5).
 4 = Near paralysis (muscular activity without movement 1/5).
 5 = Total paralysis (0/5).

3. **Vibratory Sense** (Educate subject regarding the sensation at the elbow. Tested with 128 cps tuning fork set to near full vibration; eyes closed; test over index finger and top of great toe (most distal joint not nail). Abnormal less than 15 seconds for toes and less than 25 seconds for hands):

3a. Time felt for <i>toes</i> (Right)	3a. Right	<input type="checkbox"/>	<input type="checkbox"/>
3b. Time felt for <i>toes</i> (Left)	3b. Left	<input type="checkbox"/>	<input type="checkbox"/>
3c. Time felt for <i>fingers</i> (Right)	3c. Right	<input type="checkbox"/>	<input type="checkbox"/>
3d. Time felt for <i>fingers</i> (Left)	3d. Left	<input type="checkbox"/>	<input type="checkbox"/>
3e. 0 = Normal. 1 = Impaired at toes or fingers. 2 = Impaired at toes and fingers.	3e.1 Right	<input type="checkbox"/>	<input type="checkbox"/>
	3e.2 Left	<input type="checkbox"/>	<input type="checkbox"/>

4. **Position Sense (test using minimal random movement of distal interphalangeal joints of index finger and big toe)**

0 = Normal.
 1 = Impaired at toes or fingers.
 2 = Impaired at toes and fingers.

4a. Right	<input type="checkbox"/>	<input type="checkbox"/>
4b. Left	<input type="checkbox"/>	<input type="checkbox"/>

Taken from Subramony et al., Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. *Neurology*. 2005; 64(7):1261-2 and as modified by Lynch et al., Measuring Friedreich ataxia: complementary features of examination and performance measures. *Neurology*. 2006; 68(11):1711-8.

5/28/15

Page 4 of 7

1	5	9	STEADFAST	3	2
NEUROLOGICAL EXAMINATION					
SUBJECT ID			VISIT NO		
VISIT DATE			MM	DD	YYYY

E. UPRIGHT STABILITY

Upright stability: For sitting posture subject can sit in a chair or examination table. For standing and walking assessment instruct subject to wear best walking shoes and record below if barefoot, footwear or AFOs [plastic brace] used. Stance assessment begins with feet 20 cm apart. Place marker tapes in the exam room 20 cm apart and the insides of the feet are lined up against these. Subsequent stance tests get more difficult. For feet together the entire inside of the feet should be close together as much as possible. For tandem stance, the dominant foot is in the back and the heel of the other foot is lined with the toes of the dominant foot but not in front of the toes (because this makes it even more difficult). For one foot stance, the subject is asked to stand on dominant foot and the other leg is elevated by bringing it forward with knee extended; this gives some advantage to the subject. If a subject can stand in a particular position for 1 minute or longer in trial 1 for tests 2a, 2b, 3a, 3b, 4 and 5, then trials 2 and 3 are abandoned. Otherwise each of 3 trials is timed and then averaged. Grading scores are then given as noted. Tandem walk and gait are performed in a hallway. Preferably no carpet but at least serial examinations should be on the same surface. Subject walks the distance turns around and comes back and the activity is not timed. **Note** if the gait was achieved with or without device and serial examinations should be done with the same device as in the first examination.

Ea. Is subject: (1 = barefoot, 2 = footwear) Ea.

Eb. Indicate if AFOs [plastic brace] are used: (0 = No, 1 = Yes) Eb.

Ec. Test performed on Carpet? (0 = No, 1 = Yes) Ec.

1. **Sitting Posture (Subject seated in chair with thighs together, arms folded across chest, back unsupported; observe for 30 sec.):** 1.

0 = Normal.

1 = Mild oscillations of head/trunk without touching chair back or side.

2 = Moderate oscillations of head/trunk; needs contact with chair back or side for stability.

3 = Severe oscillations of head/trunk; needs contact with chair back or side for stability.

4 = Support on all 4 sides for stability.

Taken from Subramony et al., Measuring Friedreich ataxia: Interrater reliability of a neurologic rating scale. Neurology. 2005; 64(7):1261-2 and as modified by Lynch et al., Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology. 2008; 68(11):1711-8. 5/28/15 Page 5 of 7

STEADFAST
NEUROLOGICAL EXAMINATION

1	5	9		3	2
SUBJECT ID			VISIT NO		
VISIT DATE			MM	DD	YYYY

E. UPRIGHT STABILITY (CONT)

2a. Stance feet apart – Inside of feet 20 cm apart marked on floor. Use stopwatch; 3 attempts; time in seconds. If greater than 60 seconds on trial 1 stop, if less than 60 seconds do all three trials):

Length of time:

0 = 1 minute or longer

1 = Less than 1 minute, greater than 45 seconds

2 = Less than 45 seconds, greater than 30 seconds

3 = Less than 30 seconds, greater than 15 seconds

4 = Less than 15 sec. or needs hands held by assistant/device

2a.1 Trial One

2a.2 Trial Two

2a.3 Trial Three

2b. Same as above but with eyes closed.

Length of time:

0 = 1 minute or longer

1 = Less than 1 minute, greater than 45 seconds

2 = Less than 45 seconds, greater than 30 seconds

3 = Less than 30 seconds, greater than 15 seconds

4 = Less than 15 sec. or needs hands held by assistant/device

2b.1 Trial One

2b.2 Trial Two

2b.3 Trial Three

3a. Stance – Feet Together (use stopwatch; 3 attempts; time in seconds):

Length of time:

0 = 1 minute or longer

1 = Less than 1 minute, greater than 45 seconds

2 = Less than 45 seconds, greater than 30 seconds

3 = Less than 30 seconds, greater than 15 seconds

4 = Less than 15 sec. or needs hands held by assistant/device

3a.1 Trial One

3a.2 Trial Two

3a.3 Trial Three

3b. Same as above but with eyes closed.

Length of time:

0 = 1 minute or longer

1 = Less than 1 minute, greater than 45 seconds

2 = Less than 45 seconds, greater than 30 seconds

3 = Less than 30 seconds, greater than 15 seconds

4 = Less than 15 sec. or needs hands held by assistant/device

3b.1 Trial One

3b.2 Trial Two

3b.3 Trial Three

17.4 ADL Assessment

Category	Score ¹				
	0	1	2	3	4
Speech	Normal.	Mildly affected. No difficulty being understood.	Moderately affected. Sometimes asked to repeat statements.	Severely affected. Frequently asked to repeat statements.	Unintelligible most of the time.
Swallowing	Normal.	Rare choking (less than once a month).	Frequent choking (less than once a week, greater than once a month).	Requires modified food or chokes multiple times a week. Or subject avoids certain foods.	Requires NG tube or gastrostomy feedings.
Cutting Food and Handling Utensils	Normal.	Somewhat slow and clumsy, but no help needed.	Clumsy and slow, but can cut most foods with some help needed. Or needs assistance when in a hurry.	Food must be cut by someone, but can still feed self slowly.	Needs to be fed.
Dressing	Normal.	Somewhat slow, but no help needed.	Occasional assistance with buttoning, getting arms in sleeves, etc or has to modify activity in some way (e.g., having to sit to get dressed, use velcro for shoes, stop wearing ties, etc).	Considerable help required, but can do some things alone.	Helpless.
Personal Hygiene	Normal.	Somewhat slow, but no help needed.	Very slow hygienic care or has need for devices such as special grab bars, tub bench, shower chair, etc.	Requires personal help with washing, brushing teeth, combing hair or using toilet.	Fully dependent (bed-bound).
Falling ²	Normal.	Rare falling (less than once a month).	Occasional falls (once a week to once a month).	Falls multiple times a week or requires device to prevent falls.	Unable to stand or walk.
Walking ²	Normal.	Mild difficulty, perception of imbalance.	Moderate difficulty, but requires little or no assistance.	Severe disturbance of walking, requires assistance or walking aids.	Cannot walk at all even with assistance (wheelchair bound).
Quality of Sitting Position	Normal.	Slight imbalance of the trunk, but needs no back support.	Unable to sit without back support.	Can sit only with extensive support (geriatric chair, posy, etc).	Unable to sit.
Bladder Function ³	Normal.	Mild urinary hesitance, urgency or retention (less than once a month).	Moderate hesitance, urgency, rare retention/incontinence (greater than once a month, but less than once a week).	Frequent urinary incontinence (greater than once a week).	Loss of bladder function requiring intermittent catheterization/indwelling catheter.

¹ Increments of 0.5 may be used if subject or caregiver strongly feels that a task falls between two scores.

² If assistive device is used, score = 3.

³ If using drugs for bladder control, automatic score of 3.

17.5 PedsQL Inventory (Child Report for Ages 8-12)

ID#	_____
Date:	_____

PedsQLTM

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages 8-12)

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past ONE month** by circling:

- 0 if it is **never** a problem
- 1 if it is **almost never** a problem
- 2 if it is **sometimes** a problem
- 3 if it is **often** a problem
- 4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL 2

*In the past **ONE month**, how much of a **problem** has this been for you ...*

ABOUT MY HEALTH AND ACTIVITIES (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL (problems with...)	Never	Almost Never	Sometimes	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

17.6 SF-36 Assessment

1	5	9	STEADFAST	6	8
HEALTH STATUS QUESTIONNAIRE (SF-36)					
SUBJECT ID			VISIT NO		
INITIALS		SITE NO	VISIT DATE	MM	DD
					YYYY

OFFICE USE ONLY

D. If the subject could not complete this test indicate why: D.

4 = Subject refused to complete trial.

5 = Other, specify _____

C. Respondent: C.

(1 = Subject, 2 = Family/Spouse/Caregiver, 3 = Subject and Family)

1 5 6 STEADFAST
SUBJECT ID 6 8
INITIALS SITE NO VISIT DATE MM DD YYYY

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

136	STEADFAST	68
HEALTH STATUS QUESTIONNAIRE (SF-36)		
SUBJECT ID	VISIT NO	VISIT DATE
		MM DD YYYY

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Yes, limited a lot	Yes, limited a little	No, not limited at all
▼	▼	▼

- a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports 1 2 3
- b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf 1 2 3
- c. Lifting or carrying groceries 1 2 3
- d. Climbing several flights of stairs 1 2 3
- e. Climbing one flight of stairs 1 2 3
- f. Bending, kneeling, or stooping 1 2 3
- g. Walking more than a mile 1 2 3
- h. Walking several hundred yards 1 2 3
- i. Walking one hundred yards 1 2 3
- j. Bathing or dressing yourself 1 2 3

STEADFAST
HEALTH STATUS QUESTIONNAIRE (SF-36)

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....
b. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....
c. Were limited in the <u>kind of</u> work or other activities	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....
b. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....
c. Did work or other activities less carefully than usual	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....

150	STEADFAST	68
HEALTH STATUS QUESTIONNAIRE (SF-36)		
SUBJECT ID	VISIT NO	VISIT DATE

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much body pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

1	3	0	STEADFAST			6	8
HEALTH STATUS QUESTIONNAIRE (SF-36)							
SUBJECT ID			VISIT NO		VISIT DATE		
					MM	DD	YYYY

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
1	2	3	4	5

a. Did you feel full of life? 1 2 3 4 5

b. Have you been very nervous? 1 2 3 4 5

c. Have you felt so down in the dumps that nothing could cheer you up? 1 2 3 4 5

d. Have you felt calm and peaceful? 1 2 3 4 5

e. Did you have a lot of energy? 1 2 3 4 5

f. Have you felt downhearted and depressed? 1 2 3 4 5

g. Did you feel worn out? 1 2 3 4 5

h. Have you been happy? 1 2 3 4 5

i. Did you feel tired? 1 2 3 4 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

STEADFAST
1 3 6 HEALTH STATUS QUESTIONNAIRE (SF-36) 6 8
SUBJECT ID VISIT NO
VISIT DATE MM DD YYYY

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

17.7 MFIS Assessment

Because of my fatigue during the past 4 weeks...

	Never	Rarely	Sometimes	Often	Almost Always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been limited in my ability to do things away from home.	0	1	2	3	4
10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. My muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. My thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Physical Subscale	This scale can range from 0-36. It is computed by adding raw scores on the following items: 4+6+7+10+13+14+17+20+21.
Cognitive Subscale	This scale can range from 0-40. It is computed by adding raw scores on the following items: 1+2+3+5+11+12+15+16+18+19.
Psychosocial Subscale	This scale can range from 0-8. It is computed by adding raw scores on the following items: 8+9
Total MFIS Score	The total MFIS score can range from 0-84. It is computed by adding scores on the physical + cognitive + psychosocial subscales.