CLINICAL STUDY PROTOCOL FOR ACTIMMUNE®

IND: 123947

Protocol Number: HZNP-ACT-303
Version 1.0

Long-Term Safety Extension Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia

Short title: STEADFAST Long-Term Safety Extension

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

Date: 05 April 2016

Collaborator:
Friedreich's Ataxia Research Alliance (FARA)

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

PROTOCOL

1. TITLE PAGE

Study Title:	Long-Term Safety Extension Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia
Protocol Number:	HZNP-ACT-303
Version:	1.0
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 S. Saunders Rd. Lake Forest, IL 60045
Sponsor Signatory:	[redacted] Chief Medical Officer Horizon Pharma Ireland Ltd.
Approval Date:	05 April 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

Protocol Number: HZNP-ACT-303

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Protocol Title: Long-Term Safety Extension Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia

Version Date: 05 April 2016

Approved by:

[redacted]

06 April 2016
Date

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

[redacted]

5 APR-2016
Date

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

[redacted]

4/6/2016
Date

Executive Director
Friedreich's Ataxia Research Alliance

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-ACT-303

Version: 1.0

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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

2. SYNOPSIS

Protocol Title: Long-Term Safety Extension Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia	
Protocol Number: HZNP-ACT-303	**Phase**: 3
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.	
Objective: Evaluate the long-term safety of ACTIMMUNE in subjects with FA.	
Study Design: This is a multi-center, open-label, long-term safety extension study of ACTIMMUNE in the treatment of FA in children and young adults. Subjects who complete 26 weeks of treatment and the Week 28 Follow-Up Visit in HZNP-ACT-302 (Multicenter, Safety and Efficacy, Open-Label Extension Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich's Ataxia) will be eligible to enter this long-term safety extension protocol. The Day 1 Visit of this study (HZNP-ACT-303) occurs on the same day as the Week 28 Follow-Up Visit for HZNP-ACT-302. The treatment duration is open-ended, and treatment will continue until ACTIMMUNE is commercially available for the treatment of FA in the United States (US) or until the Sponsor decides not to continue development for the treatment of FA. The initial dose of ACTIMMUNE will be individualized for each subject and will be determined by the investigator, provided that the initial dose does not exceed the maximum tolerated dose in HZNP-ACT-302. The investigator may subsequently adjust the dose for any subject if deemed clinically appropriate, provided that the dose does not exceed 100 $\mu g/m^2$. Dose adjustments, including the reason for the change, will be recorded on the appropriate electronic case report form. All doses of ACTIMMUNE will be administered by subcutaneous injection three times a week (TIW) at home. Subjects will be required to return for clinic visits at least every six months. At each 6-month assessment clinic visit, subjects will be dispensed a 3-month supply of study drug, and an additional 3-month supply will be directly shipped to the subjects' home in between the required 6-month clinic visits. Subjects who are not able to receive study drug shipments at their home will return to the clinic for interim clinic visits three months after the Baseline and 6-month assessment visits to obtain study drug; however, assessments (other than enquiries regarding adverse events and concomitant medications) will only be performed every six months. Subjects who are able to receive direct-to-home shipments will be contacted by telephone at the 3-month interim visits and queried regarding adverse events and concomitant medication use. At each 6-month assessment visit, subjects will be queried about any adverse events that occurred since the last visit, concomitant medication use, and undergo brief physical examinations (including vital sign monitoring) and blood sample collection for routine clinical laboratory safety tests. If applicable, urine samples will be collected for pregnancy testing. At the time ACTIMMUNE becomes commercially available or if development is ceased for the treatment of FA, subjects who are active on study will return to the clinic while still on study drug and undergo electrocardiogram (ECG) and Friedreich's Ataxia Rating Scale (FARS) assessments in addition to the above 6-month safety assessments at an End-of-Study (EOS) Visit prior to transitioning to the commercial product or discontinuing study drug. Subjects who prematurely withdraw from the study will have EOS assessments completed within two weeks of study drug discontinuation. Details of study activities are provided in Section 2.1, *Schedule of Assessments*.	
Subject Population: Male and non-pregnant female subjects who completed 26 weeks of treatment and the Week 28 Follow-Up Visit in Study HZNP-ACT-302 will be eligible for enrollment.	

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 treatment and the Week 28 Follow-Up Visit in Study HZNP-ACT-302.
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 Week 26 of Study HZNP-ACT-302, 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 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:

ACTIMMUNE will be administered TIW by subcutaneous injection. The initial dose will be individualized for each subject and will be determined by the investigator, provided that the initial dose does not exceed the maximum tolerated dose in HZNP-ACT-302. The investigator may subsequently adjust the dose for any subject if deemed clinically appropriate, provided that the dose does not exceed 100 $\mu g/m^2$.

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 open-ended, and treatment will continue until ACTIMMUNE is commercially available for the treatment of FA in the US or until the Sponsor decides not to continue development for this indication.

Criteria for Evaluation:

Efficacy will be assessed using the FARS.

Safety assessments will include adverse event monitoring, concomitant medication monitoring, physical examinations, vital signs, ECGs, clinical safety laboratory evaluations (complete blood count, chemistry, and urinalysis), and pregnancy testing (if applicable).

Statistical Analyses:

No formal statistical hypothesis testing will be performed.

FARS results (FARS total score [FARStot] and the FARS score excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score [FARS-mNeuro score]) will be summarized with descriptive statistics for the EOS Visit. For statistical purposes, the FARS results for the last on-treatment visit in HZNP-ACT-302 (Week 26) and the change from the Week 26 HZNP-ACT-302 Visit to the EOS Visit in this study will also be summarized.

Adverse event and concomitant medication data will be summarized. Vital sign and clinical safety laboratory data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values, and shift tables will be presented for clinical laboratory values from Baseline to each post-dose visit. The ECG analysis will use the same approach as described above for the FARS analysis.

Physical examination findings will be listed by subject.

Sample Size Estimate:

Subjects who complete 26 weeks of treatment and the Week 28 Safety Follow-Up Visit in Study HZNP-ACT-302 will be eligible for enrollment. The sample size is not based on statistical considerations.

2.1 Schedule of Assessments

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

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

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

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

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

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

[5] Only for female subjects of childbearing potential.

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

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

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

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

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

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

3. TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ATP	adenosine triphosphate
BLA	Biologics License Application
BSA	body surface area
CFR	Code of Federal Regulations
CGD	chronic granulomatous disease
CPI	coordinating principal investigator
CSM	Clinical Supplies Management, Inc.
DNA	deoxyribonucleic acid
DRG	dorsal root ganglion
eCRF	electronic case report form
EOS	end-of-study
FA	Friedreich's Ataxia
FDA	Food and Drug Administration
FXN	frataxin gene
GAA	guanine-adenine-adenine
GCP	Good Clinical Practice
HDAC	histone deacetylase
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IIS	Investigator-Initiated Study
IFN-ɣ	interferon gamma
IFN- ɣ 1b	ACTIMMUNE
IND	Investigational New Drug
IRB	Institutional Review Board
IU	international units
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
PBMC	peripheral blood mononuclear cells
PW	premature withdrawal
RNA	ribonucleic acid
SAE	serious adverse event
SC	subcutaneous
SMO	severe, malignant osteopetrosis
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIW	three times per week
URMC	University of Rochester Medical Center
US	United States
WHODrug	World Health Organization Drug Dictionary

4. ETHICS

4.1 Institutional Review Board

The Principal Investigator (Investigator) will submit this protocol, any protocol modifications, and the subject Consent/Assent 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/Assent 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/Assent 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.

4.2 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 for the treatment of FA; 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.

4.3 Subject Information and Consent/Assent

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.

5. 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 16.1 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 5.1). 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.

The Sponsor will perform the responsibilities of project management and study monitoring. Data management and safety summaries will be performed by Premier Research International, LLC (Durham, NC). 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. SAE intake will be performed by Med Communications, Inc. (Memphis, TN). A central laboratory will be used for clinical safety laboratory tests (Table 5.1).

Table 5.1 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 management and statistical analyses	Premier Research International, LLC One Park Drive, Suite 150 Durham, NC 27709
Clinical drug supply	Clinical Supplies Management, Inc. (CSM) 342 42nd Street South Fargo, ND 58103
Central safety laboratory	University of Rochester Medical Center (URMC) 77 Ridgeland Road Rochester, NY 14623 USA

6. INTRODUCTION

6.1 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 Friedreich's Ataxia (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, ACTIMMUNE is approved for use in the US in patients with CGD and SMO (see prescribing information in Section 16.2), and has been investigated in other conditions, including oncology, infectious diseases, and inflammatory disorders.

6.2 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 $\mu g/m^2$ for the first two weeks of the study, then escalated to 25 $\mu g/m^2$ for weeks three and four, and then escalated to 50 $\mu g/m^2$ 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. Ten of the subjects completed 12 weeks of treatment, with the remaining two 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 adverse events 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 adverse events 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. Subjects were able to continue in the study following dose reduction.

Based on the results of the IIS, Horizon is currently conducting two studies with ACTIMMUNE. The first study (HZNP-ACT-301) is a randomized, multicenter, double-blind, placebo-controlled

26-week study evaluating the efficacy and safety of ACTIMMUNE administered to children and young adults with FA, and the second study (HZNP-ACT-302) is an open-label 26-week efficacy and safety extension of HZNP-ACT-301, in which all subjects who complete blinded treatment in HZNP-ACT-301 will be offered the opportunity to receive ACTIMMUNE for an additional 26 weeks. As of 10 March 2016, 14 subjects had completed HZNP-ACT-301 and enrolled in HZNP-ACT-302, and it is projected that the first subject will complete HZNP-ACT-302 in June of 2016. Therefore, the Sponsor has designed this protocol to collect long-term safety data and to offer subjects who complete HZNP-ACT-302 the opportunity to continue receiving ACTIMMUNE until it is commercially available for the treatment of FA in the US or until the Sponsor decides to discontinue development for this indication.

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 ACTIMMUNE 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. STUDY OBJECTIVES

7.1 Study Objective

The objective is to evaluate the long-term safety of ACTIMMUNE in subjects with FA.

8. INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

This is a multi-center, open-label, long-term safety extension study of ACTIMMUNE in the treatment of FA in children and young adults. Subjects who complete 26 weeks of treatment and the Week 28 Follow-Up Visit in HZNP-ACT-302 (Multicenter, Safety and Efficacy, Open-Label Extension Study of ACTIMMUNE® [interferon γ-1b] in Children and Young Adults with Friedreich's Ataxia) will be eligible to enter this long-term safety extension protocol. The Day 1 Visit of this study (HZNP-ACT-303) occurs on the same day as the Week 28 Follow-Up Visit for HZNP-ACT-302.

The treatment duration is open-ended, and treatment will continue until ACTIMMUNE is commercially available for the treatment of FA in the US or until the Sponsor decides to discontinue development for this indication. The initial dose of ACTIMMUNE will be individualized for each subject and will be determined by the investigator, provided that the initial dose does not exceed the maximum tolerated dose in HZNP-ACT-302. The investigator may subsequently adjust the dose for any subject if deemed clinically appropriate, provided that the dose does not exceed 100 $\mu g/m^2$. Dose adjustments, including the reason for the change, will be recorded on the appropriate electronic case report form (eCRF). All doses of ACTIMMUNE will be administered by subcutaneous injection three times a week (TIW) at home.

Subjects will be required to return for clinic visits at least every six months. At each 6-month assessment clinic visit, subjects will be dispensed a 3-month supply of study drug, and an additional 3-month supply will be directly shipped to the subjects' home in between the required 6-month clinic visits. Subjects who are not able to receive study drug shipments at their home will return to the clinic for interim clinic visits three months after the Baseline and 6-month assessment visits to obtain study drug; however, assessments (other than queries regarding adverse events and concomitant medications) will only be performed every six months. Subjects who are able to receive direct-to-home shipments will be contacted by telephone at the 3-month interim visits and queried regarding adverse events and concomitant medication use.

At each 6-month assessment visit, subjects will be queried about any adverse events that occurred since the last visit, concomitant medication use, and undergo brief physical examinations (including vital sign monitoring) and blood sample collection for routine clinical laboratory safety tests. If applicable, urine samples will be collected for pregnancy testing.

At the time ACTIMMUNE becomes commercially available or if development is ceased for the treatment of FA, subjects will return to the clinic while still on active study drug and undergo electrocardiogram (ECG) and Friedreich's Ataxia Rating Scale (FARS) assessments in addition to the above 6-month safety assessments at an End-of-Study (EOS) Visit prior to transitioning to the commercial product or discontinuing study drug. Subjects who prematurely withdraw from the study will have EOS assessments completed within two weeks of study drug discontinuation.

8.2 Discussion of Study Design

The study population consists of subjects who completed Study HZNP-ACT-302; 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).

8.3 Selection of Study Population

8.3.1 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 treatment and the Week 28 Follow-Up Visit in Study HZNP-ACT-302.

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 Week 26 of Study HZNP-ACT-302 and agree to use a reliable method of contraception throughout the study and for 30 days after the last dose of study drug.

8.3.2 Exclusion Criteria

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

8.3.3 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 eCRF using one of the following categories:

- Adverse event. The subject experiences an adverse event that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of an adverse event.
- 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.
- 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 adverse event or lack of efficacy, the category of withdrawal should be marked in the corresponding category and not as voluntary withdrawal.
- Study termination. The Sponsor, IRB, or regulatory agency terminates the study.
- Pregnancy.

Following premature withdrawal from the study, the subject or his/her legally acceptable representative will be contacted by telephone to enquire about any adverse events and concomitant medication use.

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

8.4 Treatments

8.4.1 Treatments Administered

All subjects will receive ACTIMMUNE. The planned treatment duration is open-ended, and treatment will continue until ACTIMMUNE is commercially available for the treatment of FA in the US or until the Sponsor discontinues development for this indication.

8.4.1.1 Dose Adjustment Guidelines

Subjects will receive SC doses of ACTIMMUNE TIW at home. The initial dose of ACTIMMUNE will be determined by the investigator for each subject, provided that the initial dose does not exceed the maximum tolerated dose in HZNP-ACT-302. The investigator may subsequently adjust the dose for any subject if deemed clinically appropriate, provided that the dose does not exceed 100 µg/m^2.

8.4.2 Identity of Investigational Products

8.4.2.1 ACTIMMUNE

ACTIMMUNE is a single-chain polypeptide containing 140 amino acids with a molecular weight of approximately 16,465 Daltons. ACTIMMUNE 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 µg (2 million international units [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. The commercial formulation will be utilized, with each unlabeled vial containing ACTIMMUNE in a concentration of 200 µg/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 8.4.3) and assembling vials into kits. If a subject requires two vials per dose, 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.

8.4.3 Labeling

CSM will label the ACTIMMUNE vials, assemble the study drug into kits, and ship kits to the study sites as well as provide direct-to-subject shipments.

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. Kit labels will also include the unique subject ID. Dosing instructions will be provided separately to the subject/caregiver.

8.4.4 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; significant 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.

8.4.5 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. The clinic will notify the Sponsor and Med Communications, Inc. of any product complaints.

8.4.6 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 the Sponsor or the Sponsor's representative. Once accountability is completed, the Sponsor or it'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.

8.4.7 Study Drug Administration and Timing of Dose for each Subject

8.4.7.1 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 as well as the direct-to-subject shipments.

8.4.7.2 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 body surface area (BSA). The BSA will be calculated 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.

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

For example, a subject who is 62 inches tall and weighs 100 pounds will have a BSA of 1.41 m^2. If the dose is 100 µg/m^2, the subject will receive **0.71 mL** of study drug.

$$100\ \mu g/m^2 \times 1.41\ m^2 \times 0.005\ mL/\mu g = 0.705\ mL, \text{ rounded to } \mathbf{0.71\ mL} \text{ of study drug}$$

8.4.7.3 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. If 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.

Subjects and their caregivers will be instructed to administer study drug on an outpatient basis TIW (e.g., a dosing schedule of Monday, Wednesday and Friday or Tuesday, Thursday, and Saturday) for the duration of the study.

At each clinic visit, subjects and/or their caregivers will be dispensed a 3-month supply of study drug, and an additional 3-month supply will be directly shipped to the subjects' home in between the required 6-month clinic visits. If direct shipments are not feasible, subjects will return to the clinic every three months to obtain study drug. At all post-Baseline clinic visits, subjects and/or their caregivers will return all unused kits and study drug vials.

8.4.8 Method of Assigning Subjects to Treatment

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

Subjects will maintain the unique 6-digit subject ID number assigned in Study HZNP-ACT-301 and carried through to Study HZNP-ACT-302; 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.

8.4.9 Blinding

This is an open-label safety extension study.

8.4.10 Concomitant Therapy and Restricted Medications

Concomitant medication use will be monitored throughout the study. No specific concomitant medications are restricted.

8.4.11 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.

8.5 Efficacy and Safety Variables

The Schedule of Assessments was previously provided in Section 2.1.

8.5.1 Efficacy Variables

Efficacy will be assessed using the Friedreich's Ataxia Rating Scale (FARS) (total score [FARStot] and score excluding the peripheral nervous system subscale score and the facial and tongue atrophy and fasciculations from the bulbar subscale score [FARS-mNeuro score]).

8.5.1.1 Friedreich's Ataxia Rating Scale (FARS)

The FARS will be performed at the EOS (or PW) Visit. 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 Section16.3), and the FARS-mNeuro score has a maximum of 93 points.

8.5.2 Safety Variables

Safety assessments will include adverse event monitoring, concomitant medication monitoring, physical examinations, vital signs, ECGs, clinical safety laboratory evaluations (complete blood count, chemistry, and urinalysis), and pregnancy testing (if applicable).

8.5.2.1 Adverse Events

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

Adverse event 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?" Adverse event 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 adverse event based on the following definitions and documentation requirements.

8.5.2.1.1 Definitions

Adverse Event: As defined by the ICH, an adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product, whether or not the event is considered related to the investigational product. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product.

NOTE: The term "adverse event" includes both non-serious and serious adverse events unless otherwise specified

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 adverse event is considered related to the treatment or not. Adverse events include the following types of occurrences:

- Adverse reaction: an adverse reaction means any adverse event 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 adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug. Suspected adverse reactions are the subset of all adverse events 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 adverse event 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 adverse event 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 adverse event 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 adverse event includes any adverse event that is not described in the previous SAE category.

Unexpected: An adverse event 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 adverse events 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.

8.5.2.1.2 Documentation of Adverse Events

Adverse events that are ongoing from Study HZNP-ACT-302 will be considered baseline signs/symptoms. The TEAE reporting period begins with the date of the first dose of study drug in Study HZNP-ACT-303 and continues until completion of study participation (i.e., the patient is transitioned to the commercially available product, the Sponsor decides not to continue development for the treatment of FA, or the subject prematurely withdraws from the study). 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 8.5.2.1.5.

Unchanged, chronic conditions are **NOT** considered adverse events and should not be recorded on the adverse event 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 adverse event. Events, which are unequivocally due to disease progression, should only be reported as adverse events 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 adverse event 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.

8.5.2.1.3 Grading of Adverse Events

The severity of all adverse events, 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 adverse event.

8.5.2.1.4 Relationship to Study Drug

The relationship of the study drug to each adverse event 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.

8.5.2.1.5 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 16.1 for contact information).

2) Record the SAE accurately in the source documents and on the adverse event page of the subject's eCRF, as described in Section 8.5.2.1.2. 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 adverse events or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB.

8.5.2.1.6 Follow-Up of Adverse Events

Once the study-defined non-serious adverse event and SAE reporting periods have passed, reporting is required only if an Investigator becomes aware of an SAE that he or she considers related to the study treatment.

After the initial recording of an adverse event, the Investigator should proactively follow the subject. Any ongoing study drug-related adverse event 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.

The Investigator will document on the adverse event eCRF any/all ongoing non-serious adverse events that will not be followed further after the subject exits the study. If in doubt, the Investigator should consult the sponsor's medical monitor.

All SAEs should be followed until resolution, until the condition stabilizes, or until the subject is lost to follow-up. Once the SAE is resolved, the corresponding adverse event eCRF page should be updated.

8.5.2.1.7 Medication Error and Overdose

A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm.

An overdose is defined as a known deliberate or accidental administration of investigational drug, to, or by a study subject, at a dose above the target dose of 100 $\mu g/m^2$ or above the stable tolerated dose for an individual subject.

If the subjects/caregivers accidently 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 adverse events) will be documented on the eCRF in order to capture this important safety

information consistently in the database. Adverse events associated with an overdose or medication error and SAEs of overdose or medication error are to be reported according to the procedures outlined in Sections 8.5.2.1.2 and 8.5.2.1.5, respectively.

In the event of drug overdose, the subject is to be treated symptomatically with supportive measures instituted as required.

8.5.2.1.8 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 adverse events and all other emerging new information relevant to the safety of the drug.

8.5.2.1.9 Reporting of Investigational New Drug (IND) Safety Reports

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

8.5.2.2 Pregnancy Reporting

All female subjects of childbearing potential will undergo urine pregnancy tests at Baseline/Day 1, each 6-month assessment clinic visit, and the EOS (or PW) Visit. Subjects 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 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 adverse event 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 adverse event; however, the outcome of all pregnancies should (if possible) be followed up and documented.

8.5.2.3 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, each subsequent 6-month assessment clinic visit, and the EOS (or PW) Visit. 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.

8.5.2.4 Brief Physical Examinations

Brief physical examinations will be performed at Baseline/Day 1, each subsequent 6-month assessment clinic visit, and the EOS (or PW) Visit; these exams will include evaluation of general appearance and the following body systems: skin, lungs, cardiovascular (including peripheral vascular), abdomen, and other.

8.5.2.5 Clinical Laboratory Tests

Samples of blood (4.5 mL) and urine are scheduled for collection at Baseline/Day 1, each 6-month assessment clinic visit, and the EOS (or PW) Visit. 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
- Chemistry panel
- Urinalysis

8.5.2.6 Electrocardiograms

ECGs are scheduled for the EOS (or PW) Visit.

8.5.3 Appropriateness of Measurements

The efficacy and safety measurements in this study are widely used and generally recognized as reliable, accurate, and relevant.

The study population consists of subjects who completed Studies HZNP-ACT-301 and HZNP-ACT-302; 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).

8.5.4 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 long-term safety extension study. The treatment duration is open-ended, and subjects will be seen at the clinic at least every six months.

8.5.4.1 Baseline/Day 1 (Week 28 of Study HZNP-ACT-302)

The Baseline/Day 1 Visit of this study (HZNP-ACT-303) occurs on the same day as the EOS Visit (Week 28 Follow-Up Visit) for HZNP-ACT-302. At the Baseline Visit, study drug will be

distributed for administration at home according to the planned TIW dosing schedule. Clinic staff will perform the following procedures:

- 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-303. 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.

- Record any changes in medical history since Baseline of HZNP-ACT-301.

- Perform brief physical examination[1], including vital signs.

- Enquire about adverse events[1] and concomitant medications[1].

- Collect blood (4.5 mL) and urine samples for safety clinical laboratory values (including urine pregnancy test [if applicable]).

- Dispense a 3-month supply of study drug.

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

Subjects will be discharged from the study center after all of the Study Day 1 procedures have been completed. Subjects who are able to receive study drug shipped directly to their home will be instructed to return to the clinic in six months, and those who are not able to receive study drug shipments at home will be instructed to return in three months.

8.5.4.2 3-Month Visits

Subjects who are able to receive direct-to-home shipments of study drug will be contacted by phone three months after the Baseline and 6-month assessment visits and queried regarding adverse events and concomitant medication use.

Subjects who are not able to receive study drug shipments at their home will return to the clinic for interim clinic visits three months after the Baseline and 6-month assessment visits, and clinic staff will perform for the following assessments:

- Collect all used, partially used, and unused study medication kits and vials from the previous clinic visit.

- Enquire about adverse events and concomitant medication use

- Dispense a 3-month supply of study drug.

8.5.4.3 6-Month Assessment Clinic Visits

- Collect all used, partially used, and unused study medication kits and vials from previous clinic visit.
- Perform brief physical examination, including vital signs.
- Collect blood (4.5 mL) and urine samples for safety clinical laboratory values (including urine pregnancy test [if applicable]).
- Enquire about adverse events and concomitant medication use.
- Dispense a 3-month supply of study drug.

Subjects will be released from the study center after all of the visit procedures have been completed and instructed to return to the clinic in three or six months, as applicable.

8.5.4.4 End-of-Study or Premature Withdrawal Visit

At the time ACTIMMUNE becomes commercially available or if development is ceased for the treatment of FA, subjects will return to the clinic while still on active study drug for an EOS Visit prior to transitioning to the commercial product or discontinuing study drug. Subjects who prematurely withdraw from the study will have EOS assessments completed within two weeks of study drug discontinuation. Clinic staff will perform the following procedures at the Final/EOS visit:

- Collect all used, partially used, and unused study medication kits and vials from previous clinic visit.
- Perform brief physical examination, including vital signs.
- Collect blood (4.5 mL) and urine samples for safety clinical laboratory values (including urine pregnancy test [if applicable]).
- Enquire about adverse events and concomitant medication use.
- Perform FARS.
- Perform ECG.

8.6 Statistical Methods and Determination of Sample Size

No formal statistical hypothesis testing will be performed. Detailed statistical analyses will be presented in a separate statistical analysis plan. Some key points identified for statistical analyses are outlined below.

8.6.1 Efficacy Variables

FARS results (FARStot and FARS-mNeuro) will be summarized with descriptive statistics for the EOS Visit. For statistical purposes, the FARS results for the last on-treatment visit in HZNP-ACT-302 (Week 26) and the change from the Week 26 HZNP-ACT-302 Visit to the EOS Visit in this study will also be summarized.

8.6.2 Safety Variables

Adverse event and concomitant medication data will be summarized. Vital sign and clinical safety laboratory data will be summarized with descriptive statistics for Baseline, post-dose, and change from Baseline to post-dose values, and shift tables will be presented for clinical laboratory values from Baseline to each post-dose visit. The ECG statistical analysis will use the same approach as described above for the FARS analysis.

Physical examination findings will be listed by subject.

8.6.3 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 study drug on or after the Baseline/Day 1 Visit.

8.6.4 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).

8.6.5 Sample Size and Power Considerations

Subjects who complete 26 weeks of treatment and the Week 28 Follow-Up Visit in Study HZNP-ACT-302 will be eligible for enrollment. The sample size is not based on statistical considerations.

8.7 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 the Sponsor as soon as possible to discuss the associated circumstances. All protocol deviations and the reasons for such deviations **must** be documented. 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.

9. 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:

- 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 adverse event.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or PW from, the study.

10. CASE REPORT FORMS

An 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 Premier Research. Final eCRFs will be provided to the Investigator and Sponsor by Premier Research.

11. 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 and/or it'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 Sponsor 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.

12. DATA MANAGEMENT

Data will be entered into a clinical database as specified in Premier Research'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 Premier Research 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).

13. 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.

14. 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.

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16. APPENDICES

16.1 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 S. Saunders Rd. Lake Forest, IL 60045 Mobile telephone number: [redacted] Fax number: Email: [redacted]
Sponsor Representative	[redacted] Executive Director, Clinical Development & Operations Horizon Pharma, Inc. 150 S. Saunders Rd. Lake Forest, IL 60045 Mobile telephone number: [redacted] Business telephone number: [redacted] Fax number: 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]

16.2 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/m^2 for patients whose body surface area is greater than 0.5 m^2 and 1.5 mcg/kg/dose for patients whose body surface area is equal to or less than 0.5 m^2 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*

*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/m^2. Higher doses (i.e., greater than 50 mcg/m^2) 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/m^2/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/m^2/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/m^2, 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/mm^3) 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, Hematoxic 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/m^2/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 ($2x10^6$ 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/m^2 (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/m^2 in healthy male subjects was 38 minutes. The mean elimination half-lives for intramuscular and subcutaneous dosing with 100 mcg/m^2 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/m^2.

Interferon gamma was not detected in the urine of healthy human volunteers following administration of 100 mcg/m^2 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.

NDC Number	Size
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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16.3 FARS Neurological Assessment

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Time exam was conducted: (24 hr clock) 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. 2008; 66(11):1711-6. 5/28/15 Page 1 of 7

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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. 2006. 66(11):1711-6.　5/28/15　Page 2 of 7

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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 . 5b. Left .
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.

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):** 1a. Right . 1b. Left .
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.

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):** 2a. Right . 2b. Left .
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.

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.

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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 hypo/areflexia 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

   1a. Right ☐
   1b. Left ☐

   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).

   2a. Right ☐
   2b. Left ☐

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 *toes* (Right) — 3a. Right | | | |
   3b. Time felt for *toes* (Left) — 3b. Left | | | |
   3c. Time felt for *fingers* (Right) — 3c. Right | | | |
   3d. Time felt for *fingers* (Left) — 3d. Left | | | |

   3e. 0 = Normal.
   1 = Impaired at toes or fingers.
   2 = Impaired at toes and fingers.

   3e.1 Right ☐
   3e.2 Left ☐

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 ☐
   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. 2006. 66(11):1711-6. 5/28/15 Page 4 of 7

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5. **DTR** (0 = absent, 1 = hyporeflexia, 2 = normal, 3 = hyperreflexia, 4 = pathologic hyperreflexia)

5a. Right	5a.1 BJ ☐	5a.2 BrJ ☐	5a.3 KJ ☐	5a.4 AJ ☐
5b. Left	5b.1 BJ ☐	5b.2 BrJ ☐	5b.3 KJ ☐	5b.4 AJ ☐

5c. **DTR**
0 = No areflexia.
1 = Areflexia or mild hyperreflexia in either upper or lower limbs.
2 = Generalized areflexia or pathologic hyperreflexia.

5c.1 Right ☐

5c.2 Left ☐

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. 2006. 66(11):1711-6. 5/28/15 Page 5 of 7

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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 ☐

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.

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STEADFAST

1 5 9 **NEUROLOGICAL EXAMINATION** 3 2

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4. Tandem Stance (dominant foot in front; front foot lined up with great toe of the back foot)
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

4.1 Trial One ☐
4.2 Trial Two ☐
4.2.1 Trial Three ☐

5. Stance on Dominant Foot (Elevate leg straight out in front, 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 seconds or needs hands held by assistant/device

5.1 Trial One ☐
5.2 Trial Two ☐
5.3 Trial Three ☐

6. Tandem Walk (tandem walk 10 steps in straight line; performed in hallway with no furniture within reach of 1 m / 3 ft. and no loose carpet): 6. ☐
0 = Normal (able to tandem walk greater than 8 sequential steps).
1 = Able to tandem walk in less than perfect manner/can tandem walk greater than 4 sequential steps, but less than 8.
2 = Can tandem walk, but fewer than 4 steps before losing balance.
3 = Too poorly coordinated to attempt task.

7. Gait (Observe subject walk at normal pace with assistive device in one direction, turn around and return to start; performed in hallway with no furniture within reach of 1 m / 3 ft. and no loose carpet): 7. ☐

0 = Normal.
1 = Mild ataxia/veering/difficulty in turning; no cane/other support needed to be safe.
2 = Walks with definite ataxia; may need intermittent support/or examiner needs to walk with subject for safety sake.
3 = Moderate ataxia/veering/difficulty in turning; walking requires cane/holding onto examiner with one hand to be safe.
4 = Severe ataxia/veering; walker or both hands of examiner needed.
5 = Cannot walk even with assistance (wheelchair bound).

Signature: _____ Date: _____ Staff Code | | | | |

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.

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