ACTIMMUNE in Friedreich’s Ataxia (FA)

Why interferon gamma for FA?

FA is a hereditary disease caused by a genetic mutation in the frataxin (FXN) gene

In healthy people, the GAA triplet in the FXN gene is repeated 5 – 33 times. In FA patients, the GAA triplet is repeated 66 – 1000+ times

The abnormal GAA triplet repeat disrupts production of FXN

FXN levels of 30 – 80% in a control group of FA carriers who do not exhibit any symptoms vs. 2 – 30% in FA patients who experience multisystem damage

Decreased FXN expression is implicated in the assembly and repair of mitochondrial iron-sulfur-cluster containing enzymes and the ability to produce adenosine triphosphate, leading to mitochondrial iron accumulation. This may initiate or propagate free radical reactions leading to cell death

Preclinical studies indicate that interferon gamma increases FXN levels in both cell and animal models of FA

Phase 2 clinical study data showed that interferon gamma significantly improved neurological function measured by the Friedreich’s Ataxia Rating Scale (FARS) score

Mechanism of Action:
Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich’s Ataxia model

Sources: NIH, Friedreich’s Ataxia Research Alliance (FARA). Muscular Dystrophy Association (MDA)
Why Interferon gamma for FA?

- FRDA mouse model; half treated with interferon gamma (40 mcg/kg TIW) and half with vehicle (placebo) for 10 weeks

- Results:
  - IFNγ treated mice significantly improved both locomotor activity and motor coordination
  - IFNγ mechanism of action postulated to be upregulation of frataxin gene expression and neuronal preservation in dorsal root ganglion

Tomassini et al. 2012
Pilot Study of IFNγ in Children with FA

- Investigator-initiated study at CHOP
  - Goals
    - Safety and tolerability of IFNγ
    - Effect on frataxin protein levels
    - Effect on neurologic function
- Design: Small, open-label pilot study
  - 12 Individuals with genetic confirmation of FA, ages 5-17 enrolled September – December 2013
  - Dose-escalation every two weeks based on tolerability
    - 10mcg/m², 25mcg/m², 50mcg/m² TIW– 3xwk
  - Overall treatment phase was 12 weeks
  - Reevaluation 1 month post treatment; last study visit March 2014

Seyer et al. 2014
Results: Demographics

- 8-17 years old, mean age of 12
- Mean GAA repeat length 835
- Mean age of onset was 6
- 12 of 12 subjects screened met criteria
- Two subjects did not follow dose escalation protocol due to adverse events
- Two subjects withdrawn from the study for inability to complete study procedures

Seyer et al. 2014
Results: Safety and tolerability

- No drug-related serious adverse events (SAE) occurred
- 11 of 12 subjects experienced at least 1 AE
- Low grade, not dose related
- Largely known side-effects of IFN\(\gamma\)
- Two subjects were unable to continue with dose-escalation of IFN-\(\gamma\) due to moderate to severe flu-like symptoms

Seyer et al. 2014
Conclusions

• IFNγ was considered safe and well-tolerated
• No overt significant increase in frataxin levels
  – Presence of increased levels through treatment
  – Sampling limited to unaffected tissue
  – Timing of sampling - short half life of IFNγ
  – Limited to FDA approved dose for other diseases
• Clinically significant neurologic improvement

Limitations:
  – The small size of the study
  – Absence of a placebo group
  – Single center

Seyer et al. 2014
Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy, Safety, and Pharmacokinetic Study of ACTIMMUNE® (interferon γ-1b) in Children and Young Adults with Friedreich’s Ataxia

Short title:

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

Clinicaltrials.gov: NCT02415127
• **Four Study Centers**
  
  – *Children’s Hospital of Philadelphia (CHOP)*
    • Dr. David Lynch, Coordinating Principal Investigator (PI)
  
  – *University of California, Los Angeles (UCLA)*
    • Dr. Susan Perlman
  
  – *University of Florida*
    • Dr. Subramony
  
  – *University of Iowa*
    • Dr. Kathy Mathews
Randomized, double-blind, multicenter, placebo-controlled, 26-week study in children and young adults (10-25 years of age) with FA functional stage of >1 (minimal disability) to <5 (severe disability)

It is anticipated that up to 110 subjects will be screened at four U.S. centers for eligibility to randomize approximately 90 subjects 1:1 to receive either ACTIMMUNE or placebo

Primary endpoint is change in Friedreich’s Ataxia Rating Scale-modified neurological exam score (FARS-mNeuro)

Subjects completing 6 months of treatment may enter 6-month open-label safety study
Objectives

• Primary Efficacy Objective
  - Evaluate the effect of ACTIMMUNE vs. placebo on the change from Baseline to Week 26 in Neurological Outcome
  - Measure is FARS-mNeuro score
    • FDA agreed primary endpoint measure

• Secondary Efficacy Objectives
  - ACTIMMUNE vs. Placebo on change from Baseline to Week 26:
    • Key secondary endpoint: Activities of Daily Living (ADL);
    • Timed 25-foot-walk test (T25FW);
    • Responder rate (≥3 point improvement in the FARS-mNeuro score from Baseline to Week 26)
    • Neurological outcome as measured by the total FARS score (FARStot)

• Safety Objective: To evaluate the safety and tolerability of ACTIMMUNE in FA
Subject Eligibility Criteria

90 male and female FA patients randomized 1:1/ACT vs Placebo

- **Key Inclusion Criteria**
  - Male or female subject between the ages of 10 and 25 years, inclusive
  - FA confirmed by genetic testing with two expanded guanine-adenine-adenine (GAA) repeats
  - FA functional stage of >1 (minimal disability) to <5 (severe disability) and ability to walk 25 feet with or without an assistive device

- **Key Exclusion Criteria**
  - Presence of clinically significant cardiac disease (Baseline ECG & ECHO): ejection fraction of <40% or a prolonged QT interval (>50% of cycle duration)
  - Presence of moderate or severe renal disease or hepatic disease
  - Clinically significant abnormal white blood cell count, hemoglobin, or platelet count
  - History of hypersensitivity to IFNγ or E. coli-derived products
The Schematic of Study Design illustrates the study protocol for screening and baseline assessments, followed by a treatment period (26 weeks) with visits at Week 4, Week 13, Week 26, and Week 28. The study includes a follow-up period with a safety visit.

- **Screening Days -30 to -7 with Baseline Day 1**
  - N = 90

- **Treatment Period**
  - Visit 1
  - Visit 2
  - Visit 3
  - Safety Visit

- **ACTIMMUNE (10 µg/m² to 100 µg/m²) TIW SC**

- **Placebo TIW SC**

- **Dose Escalation**
  - Stable dose
  - Weekly contact

1. The follow-up safety visit will not occur for subjects who elect to enroll in the open-label extension study.
2. Randomization will occur on Day 1 after completion of all baseline assessments.
3. Study drug will be initiated on Day 1 at 10 µg/m² (or matching volume of placebo), with a planned weekly dose escalation to 25, 50, and 100 µg/m² (or matching volume of placebo) on Days 7, 14, and 21, respectively; however, the dose may be reduced, interrupted, or held based on tolerability. All subjects are to be on a stable tolerated dose of study drug by Week 13 in order to continue study participation.
4. Subjects and/or caregivers will be contacted by email or phone to monitor safety and dosing logistics on a weekly basis from Day 1 through Week 4 (or until stable tolerated dose is achieved) and on a monthly basis after Week 4 (or after dose stabilization) through Week 26.
This is a double-blind study

Participants will be randomized to either ACTIMMUNE or placebo (1:1)
  - Participants stay in their assigned group for the duration of the trial

Study drug will be administered at home 3 times per week for 26 weeks via injections under the skin (subcutaneous)

To reduce flu-like symptoms, dose escalation weekly:

<table>
<thead>
<tr>
<th>When</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>10 mcg/m²</td>
<td>Three times per week</td>
</tr>
<tr>
<td>Week 2</td>
<td>25 mcg/m²</td>
<td>Three times per week</td>
</tr>
<tr>
<td>Week 3</td>
<td>50 mcg/m²</td>
<td>Three times per week</td>
</tr>
<tr>
<td>Week 4</td>
<td>100 mcg/m²</td>
<td>Three times per week</td>
</tr>
</tbody>
</table>

Study doctors can adjust dose to ensure tolerability
<table>
<thead>
<tr>
<th>Subject Enrollment Currently &gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More than 50 percent enrolled to-date</td>
</tr>
<tr>
<td>• Target date for full enrollment of 90 patients is mid-year 2016</td>
</tr>
<tr>
<td>• Identifying and enrolling subjects via FARA patient registry</td>
</tr>
<tr>
<td>• Data projected December 2016</td>
</tr>
</tbody>
</table>
Road map for study

1. IND accepted, Protocol finalized, Sites IRB submissions
   ✔ First subject randomized June 2015

2. Last subject enrolled mid 2016, last subject to complete study participation 4th quarter 2016

3. Subject enrollment: 10 months Complete mid 2016
   Study intensive assessments limit enrollment to approximately 3 subjects per month per site.

4. Complete all subject treatment 6 months

Study conduct on track
Open label extension study initiated in December,
http://www.curefa.org/active-clinical-trials/horizon-s-actimmune-phase-3-trial
FARA/UCLA Friedreich’s Ataxia Patient Symposium
January 21, 2016

STEADFAST Trial (ACTIMMUNE)