ANNALS of Clinical and Translational Neurology
Open Access
ANA American Neurological Association since 1875

RESEARCH ARTICLE

Randomized, double-blind, placebo-controlled study of interferon-γ 1b in Friedreich Ataxia

David R. Lynch[1], Lauren Hauser[1], Ashley McCormick[1], McKenzie Wells[1], Yi Na Dong[1], Shana McCormack[2], Kim Schadt[1], Susan Perlman[3], Sub H. Subramony[4], Katherine D. Mathews[5], Alicia Brocht[6], Julie Ball[7], Renee Perdok[7], Amy Grahn[7], Tom Vescio[7], Jeffrey W. Sherman[7] & Jennifer M. Farmer[8]

[1]Division of Neurology, Children's Hospital of Philadelphia, 502 Abramson Research Center, 3615 Civic Center Blvd, Philadelphia, Pennsylvania, 19104-4318
[2]Division of Endocrinology & Diabetes, Children's Hospital of Philadelphia, Philadelphia 19104
[3]Department of Neurology, University of California Los Angeles, Box 956975, 1-167 RNRC, Los Angeles, California 90095
[4]Department of Neurology, University of Florida, Room L3-100, McKnight Brain Institute, 1149 Newell Drive, Gainesville, Florida 32611
[5]Department of Pediatrics and Neurology, University of Iowa Carver College of Medicine, Iowa City, Iowa
[6]Department of Neurology, University of Rochester, Rochester, New York 14620
[7]Horizon Pharma, Inc., Lake Forest, Illinois 60045
[8]Friedreich's Ataxia Research Alliance, 533 W Uwchlan Ave, Downingtown, Pennsylvania 19335

Correspondence
David R. Lynch, Division of Neurology, Children's Hospital of Philadelphia, 502 Abramson Research Center, 3615 Civic Center Blvd, Philadelphia, PA 19104-4318.
Tel: +1 215 590 2242; Fax: +1 215 590 3779;
E-mail: lynchd@pennmedicine.upenn.edu

Funding Information
This work was supported by grants from Horizon Pharma to the Children's Hospital of Philadelphia, UCLA. University of Iowa, University of Florida, and the University of Rochester.

Received: 5 December 2018; Revised: 5 January 2019; Accepted: 8 January 2019

Annals of Clinical and Translational Neurology **2019; 6(3): 546–553**

doi: 10.1002/acn3.731

Abstract

Objective: In vitro, in vivo, and open-label studies suggest that interferon gamma (IFN-γ 1b) may improve clinical features in Friedreich Ataxia through an increase in frataxin levels. The present study evaluates the efficacy and safety of IFN-γ 1b in the treatment of Friedreich Ataxia through a double-blind, multicenter, placebo-controlled trial. **Methods**: Ninety-two subjects with FRDA between 10 and 25 years of age were enrolled. Subjects received either IFN-γ 1b or placebo for 6 months. The primary outcome measure was the modified Friedreich Ataxia Rating Scale (mFARS). **Results**: No difference was noted between the groups after 6 months of treatment in the mFARS or secondary outcome measures. No change was noted in buccal cell or whole blood frataxin levels. However, during an open-label extension period, subjects had a more stable course than expected based on natural history data. **Conclusions**: This study provides no direct evidence for a beneficial effect of IFN-γ1b in FRDA. The modest stabilization compared to natural history data leaves open the possibility that longer studies may demonstrate benefit.

Introduction

Friedreich Ataxia (FRDA) is an autosomal recessive disorder associated with progressive ataxia, cardiomyopathy, scoliosis, diabetes, and loss of visual and sensorineural hearing function.[1,2] Degeneration of the dorsal root ganglion (DRG) neurons, the dorsal columns, the dentate nucleus of the cerebellum, and the dorsal spinocerebellar pathways gives rise to ataxia.[3,4] In 96% of individuals, FRDA is caused by homozygous expanded guanine – adenine – adenine (GAA) repeats in the frataxin gene (*FXN*).[5] This expanded repeat decreases ribonucleic acid (RNA) transcription in the *FXN* gene and levels of the mitochondrial protein frataxin. Frataxin is involved in the biogenesis and maintenance of mitochondrial iron-sulfur clusters; its deficiency results in mitochondrial iron accumulation and reduced ATP production, identifying mitochondrial dysfunction as a component of FRDA.[6] In FRDA, frataxin levels in peripheral tissues range from 2% to 30% of control and correlate directly with age of onset and inversely with the length of the shorter GAA repeat. In

carriers, who develop no features of FRDA, frataxin protein levels range from 30% to 80% of control,[7,8] suggesting that restoration of frataxin levels to those in carriers may improve features of FRDA.

At present, no therapy is approved for FRDA.[1] Exogenous IFN-γ 1b (ACTIMMUNE), a protein produced by the immune system in response to infections, increases both frataxin messenger RNA (mRNA) and protein levels in a variety of cell types, including cells from FRDA patients.[9] In addition, an FRDA mouse model treated with subcutaneous (SC) IFN-γ 1b for 14 weeks shows improved coordination and accumulates frataxin protein in DRG tissue.[9] In a previous study in FRDA, IFN-γ 1b was well-tolerated with no serious adverse events (SAEs) and only two severe dose-related adverse events (AEs), both of which improved with dose reduction,[10] frataxin levels changed minimally in red blood cells, peripheral blood mononuclear cells (PBMC), and buccal cells after 12 weeks of treatment. Scores on the Friedreich Ataxia Rating Scale (FARS) score, a neurologic exam-based rating scale, improved significantly after treatment to a value equivalent to a reversal of 18 months of disease progression based on natural history studies.[11] No statistically significant relationships were observed between frataxin levels, FARS scores, and in vivo IFN-γ levels.[10] On withdrawal of IFN-γ 1b during the follow-up period, FARS scores tended to worsen, suggesting a loss of therapy-related benefit. However, such encouraging results were not identified in a dose-finding study in adults.[12] In the present study we investigated further the effect of IFN-γ 1b in FRDA by performing a double-blind, randomized, placebo-controlled trial in a larger population of young persons with FRDA.

Methods

Overall study design

This was a randomized, multicenter, double-blind, placebo-controlled, dose-escalation study evaluating the efficacy, safety, and pharmacokinetic (PK) profiles of IFN-γ 1b in the treatment of FRDA in children and young adults (NCT02593773). It was performed at the Children's Hospital of Philadelphia, University of California Los Angeles School of Medicine, University of Iowa Carver College of Medicine, and University of Florida School of Medicine from May 2015 through March 2017. The study was approved by the IRB at all institutions, and informed consent was obtained from all subjects before initiating procedures. Ninety-two subjects were randomized 1:1 to receive either IFN-γ 1b or matching placebo three times weekly for 26 weeks. Study drug dose (given subcutaneously) was escalated on a weekly basis over the first 4 weeks (from 10 $\mu g/m^2$ to 25, 50, and 100 $\mu g/m^2$ or equivalent volumes of placebo) based on tolerability. By week 13, all subjects were on a stable, tolerated dose of study drug. The drug was not further increased after week 13, but could be reduced to manage drug-related adverse events. Subjects were screened within 30 days prior to the baseline visit. The first dose of study drug was administered on Day 1, with evaluations at weeks 4, 13, and 26; between visits, subjects were monitored with weekly emails/phone calls until they reached their maximum dose and monthly thereafter. Subjects who completed 26 weeks of treatment were eligible to enter a 6-month open-label extension study, followed by an open-ended extension (until IFN-γ 1b was approved for FRDA in the United States or until development of IFN-γ 1b for FRDA was discontinued). Those who did not participate in the open-label extension study returned 2 weeks after the last dose of study drug for a safety visit.

Efficacy measures

All assessments were performed prior to dosing at baseline, and 4–6 h after dosing at subsequent visits. The primary efficacy outcome was the effect of IFN-γ 1b versus placebo on the change from baseline to week 26 in neurological outcome as measured by the modified Friedreich Ataxia Rating Scale (mFARS), defined for this study as the FARS excluding the peripheral nervous system subscale and the facial and tongue evaluations from the bulbar subscale.[12] Other efficacy assessments included the total FARS, the Timed 25 Foot Walk (T25FW), and the 9-hole peg test (9-HPT) at screening, baseline, week 13, and week 26; low-contrast Sloan letter chart (LCSLC) Vision Test at baseline and week 26; frataxin protein levels in whole blood, muscle biopsies (optional), and buccal cells at baseline, week 13, and week 26; Functional Staging of Ataxia and Activity of Daily Living (ADL) at screening, baseline, week 13, and week 26; Physician and Patient Global Assessments at baseline, week 13, and week 26.[12–15] Quality of life assessments included the Modified Fatigue Impact Score (MFIS), and the Pediatric Quality of Life (PedsQL) questionnaire or 36-item short-form health survey (SF-36) at baseline, week 13, and week 26. The MFIS was completed for all subjects. For subjects <18 years of age at baseline, the PedsQL (study subject and parent/caregiver assessments) were completed throughout the study.[16,17] For subjects ≥18 years of age at baseline, the SF-36 was completed throughout the study. Frataxin levels were measured in buccal cells and blood by lateral flow assay.[8]

Inclusion criteria

Subjects were 10–25 years old (inclusive), and had genetically confirmed FRDA with two expanded GAA repeats,

an FRDA functional stage of >1 to <5, and the ability to walk 25 feet with or without an assistive device. Subjects were ineligible if they had a history of substance abuse, clinically significant cardiac disease, hypersensitivity to IFN-ɣ or *E. coli*-derived products, moderate/severe renal or hepatic disease, or significant abnormalities of white blood cell count, hemoglobin, or platelet count.

Treatment assignment

A randomization schedule was generated by the Academic Research Organization (ARO) at the University of Rochester prior to shipment of any study drug to the clinical sites. Once baseline procedures were completed, a web-based electronic data capture system randomized the subject and assigned a kit number for that subject. None of the staff at the clinical site had access to unblinded medication, and the randomization schedule with treatment identifiers was held by the ARO.

Statistical considerations

The primary efficacy endpoint was the difference between IFN-γ 1b and placebo in the observed change from baseline to week 26 in the mFARS score. The primary analysis was conducted on the mean observed change from baseline using a repeated-measures methodology with investigative site and baseline value as covariates. Secondary efficacy endpoints (the observed mean change from baseline to week 26 in ADL, T25FW, and FARS) were analyzed using the same repeated-measures methodology as the primary endpoint. The mFARS responder rate (a change of ≥3 mFARS points) was analyzed using logistic regression. Exploratory efficacy/quality of life endpoints were also analyzed using the same repeated-measures methodology as the primary endpoint. Safety endpoints were summarized by treatment group and baseline characteristics by descriptive summaries.

The primary efficacy analysis was based on an intent-to-treat approach, including all subjects randomized who received at least one dose of drug. Safety analyses were performed on all subjects randomized who received at least one dose of study drug, analyzed according to the treatment they actually received.

Sample size calculation

Approximately 90 subjects (45 per treatment group) were expected to be required for >80% power to detect a treatment difference at a two-sided 0.05 significance level, assuming an effect size of 0.6 for the repeated-measures analysis with two post-baseline measurements of the mFARS score.[12] A treatment difference of 3.0 points and a common standard deviation of 5.0 were used to predict the effect size based on 3-month data from the proof of concept study.[10]

Statistical analyses of reproducibility and baseline values

Measures were analyzed from raw data, and summary statistics generated for each variable. We examined bivariate relationships between FARS/mFARS or performance measure outcomes and clinical characteristics collected at the initial screening visit, including sex, age, BMI, and GAA repeat length of the shorter allele. The independent effects of variables on measure outcome were assessed using multivariable regression analysis. Variability in FARS score between visits was expressed as the average over all 92 subjects of absolute difference of the values at screening and baseline from mean values. Variability in performance measure outcomes between visits were expressed as the coefficient of variation (standard deviation/mean × 100), standard error (SE), and intraclass correlations (ICC). Shapiro-Wilks test for normality was used to determine distribution of performance measure outcome data. Wilcoxon rank sum tests or two-sample *t*-tests were performed, as appropriate given normality of variables, to test for differences in these measures between visit trials. Analyses were performed using STATA v.11.2 (StataCorp, LP, College Station, TX). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient features

Ninety-two subjects were screened all of whom met entry criteria (Fig. 1). Forty-seven were randomized to IFN-γ 1b, and 45 to placebo. Subjects were distributed among 4 sites: UCLA (23 subjects), Iowa (24 subjects), U Florida (14 subjects), and CHOP (31 subjects). Demographic features were balanced between the placebo and active groups (Table 1).

Safety profile

Overall IFN-γ 1b demonstrated a reasonable safety profile. No drug-related serious adverse events (SAE) were reported during the double-blind phase, and only 4 SAEs total during this phase; there was a single premature withdrawal during this phase, unrelated to study drug but related to an adverse event. Adverse events were largely limited to those previously noted with IFN-γ 1b (Table S1), and focused on injection site reactions, flu-like symptoms and neutropenia. Five subjects chose not

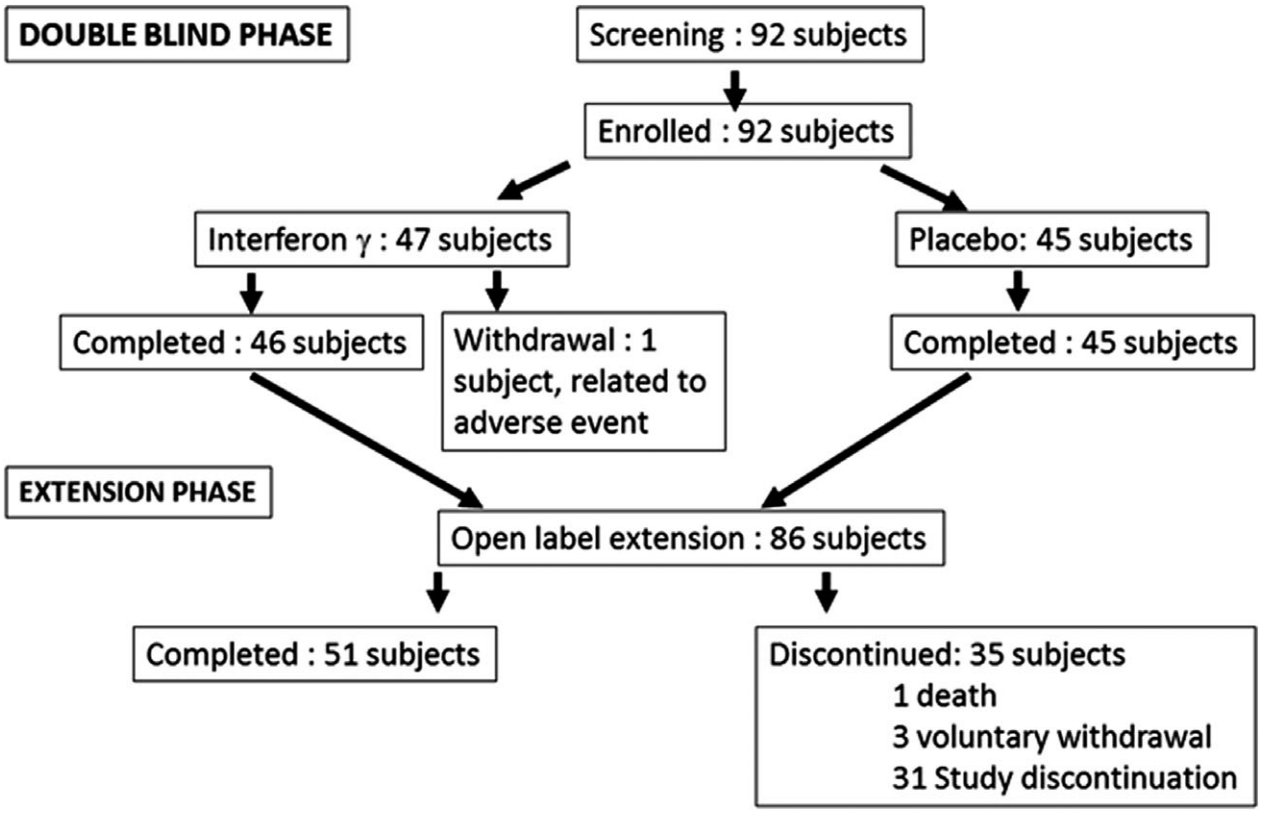

Figure 1. CONSORT diagram of subject disposition.

Table 1. Demographic and clinical features of study participants.

Parameter	IFN-γ 1b (47)	Placebo(45)
Age (years)	16.5 ± 4.4	16.1 ± 3.8
Female (%)	55.3	57.8
Ethnicity (% Hispanic)	8.5	2.2
Race (% white)	91.5	97.8
Height (cm)	161 ± 13	161 ± 11
Weight (kg)	55.8 ± 16.3	53.2 ± 13.8
BSA (m^2)	1.56 ± 0.27	1.53 ± 0.24
Disability stage (median)	3.0	3.1
Shorter GAA length (bases)	706 + 166	711 + 224
Age at onset (years)	9.5 ± 3.9	9.1 ± 3.8
Age at diagnosis (years)	11.9 ± 4.1	12.2 ± 4.1
First symptom (% balance)	83	84
mFARS	44.4 ± 11.9	44.1 ± 10.0
FARS	55.6 ± 13.8	55.7 + 10.8
ADL	11.1 ± 6.3	11.1 + 4.3
T25W^{-1} (Sec^{-1})	0.111 ± 0.074	0.118 ± 0.065
9HPT^{-1} (Sec^{-1})	0.0190 ± 0.0065	0.0200 ± 0.0055

to enter the open-label extension, and 4 subjects terminated during the extension before the study was discontinued. One subject died during the open-label phase from eosinophilic cardiomyopathy, deemed unrelated to study drug, while 3 subjects voluntarily withdrew for unnamed reasons. Over the period of open-label administration, no new safety events were defined, and none of 9 SAEs reported by 4 subjects were felt related to IFN-γ. Thirty-one subjects completed less than 6 months on open-label agents as the sponsor terminated the study after data analysis from the double-blind phase was revealed. Of the 51 subjects who completed 6 months of open-label therapy, 36 remained on active agent until study termination.

Reproducibility of measures between the baseline and screening visits

To understand the potential sensitivity of the study, we used the identical assessments at screening and baseline to assess the reproducibility of the crucial measures. For normally distributed data, there were no significant differences for the FARS ($P = 0.35$) or 9HPT^{-1} ($P = 0.34$) between screening and baseline visits (two way *t*-test).

Similarly, for non-parametric data, there were no significant differences in the T25FW^{-1} ($P = 0.96$) and FA stage ($P = 0.65$) scores from screening and baseline assessments (Wilcoxon rank sum tests). The FARS had a mean variation of 5.0 units (3.5 for the mFARS), and an ICC of 0.926 (95% CI: 0.89, 0.95) with a standard error (SE) of 0.90 points.

Ninety of 92 participants completed the T25FW at both screening and baseline visits. The T25FW test allows participants to use an assistive device. Among participants completing the test, 2 participants used unilateral assistance, 40 used bilateral assistance, and 50 (54.4%) ambulated independently without an assistive device. Three subjects changed assistive devices between the screening and baseline visits. The T25FW^{-1} was relatively reproducible; the coefficient of variation between screening and baseline visits was 8.6% while the ICC between visits was 0.96 (95% CI: 0.95, 0.98). The SE of the T25FW^{-1} was 0.0052 sec^{-1}.

Similar to T25FW^{-1} measure outcomes, 9HPT^{-1} results proved reproducible ($n = 92$), with a coefficient of variation between screening and baseline visits of 6.0% and an ICC of 0.94 (95% CI: 0.92, 0.96). The SE of the 9HPT^{-1} was 0.0044 sec^{-1}.

Efficacy analysis

There was no difference between the active agent and placebo groups for the primary outcome measure, the mFARS (Table 2). In addition, no difference was found between IFN-γ 1b and placebo for any other clinical outcome measure. Finally, frataxin levels were identical between the two groups in both whole blood and buccal cell isolates (Fig. 2). In muscle frataxin levels substantially increased (111%) in a single subject on active agent who underwent elective muscle biopsy, while the values were unchanged in 3 subjects on placebo (9% increase) who underwent muscle biopsy. Overall, the placebo response at 6 months was small (less than 1.5 points on the mFARS exam and less than 5% on the T25W^{-1} and 9HPT^{-1}).

Extension phase

After 6 months of therapy, 86 of 91 subjects who completed the double-blind portion of the study elected to enter 6 months of open-label therapy with monitoring every 13 weeks, followed by an undefined period of open-label administration with less frequent monitoring. As the studies were discontinued when preliminary statistical analysis failed to show a significant outcome, the period of open-label administration lasted from 1 to 14 months depending on a subject's time of entry, and at final visit only some of the subjects were on active agent.

Table 2. Efficacy results from double-blind phase; mean change from baseline.

Parameter	Time (weeks)	IFN-γ 1b	Placebo
mFARS	13	−2.2 ± 4	−2.2 ± 4.9
	26	−0.6 ± 4.6	−1.0 ± 4.4
ADL	13	0.55 ± 2.38	−0.24 ± 2.48
	26	0.64 ± 2.94	0.01 ± 2.60
T25W^{-1} (sec^{-1})	13	−0.001 ± 0.020	0.000 ± 0.017
	26	−0.006 ± 0.025	−0.003 ± 0.018
FARS	13	−2.0 ± 4.8	−2.3 ± 5.6
	26	−0.2 ± 5.5	−0.6 ± 5.2
MFIS	13	−0.9 ± 8.1	−1.6 ± 6.5
	26	0.8 ± 6.9	−2.5 ± 7.4

Efficacy results from the 6-month double-blind phase. No differences were noted between active and placebo groups. For all measures except the T25W^{-1}, negative numbers represent improvement over the course of the study.

Over the 52 weeks of efficacy monitoring including the double-blind and open-label periods, the change in the complete cohort was less than predicted from natural history studies[12] (Tables 3 and 4). In addition, buccal cell frataxin levels increased. This stabilization of mFARS was slightly greater in the individuals who were on IFN-γ 1b for the entire study. When results of the double-blind study were released, subjects were given the option of completing the study drug they had on hand or discontinuing study drug. Thus, at final evaluation 48 subjects were still taking study drug and 39 subjects had discontinued it between 1 and 13 weeks previously. Those who remained on active medicine had mFARS values 4 points better than those who had electively discontinued drug, suggestive of a benefit of IFN-γ 1b that was lower in magnitude than predicted.[10]

Discussion

The present study found no benefit of IFN-γ 1b on mFARS or other neurological measures in a 6-month double-blind study in FRDA despite the promising preclinical data and previous open-label study. In addition, blood and buccal frataxin levels in the double-blind phase were not different between active drug and placebo groups, thus finding no evidence for the primary mechanism of IFN-γ 1b in its proposed benefit on FRDA.

This negative result is limited by several aspects of study design. First, the mFARS exam scores between screening and baseline visits differed by a mean of 3.5 units, a difference usually seen over greater than 1 year in a natural history study of FRDA.[12] This makes it difficult to measure smaller effects of drug, and the present study becomes under-powered for 6 months duration. The

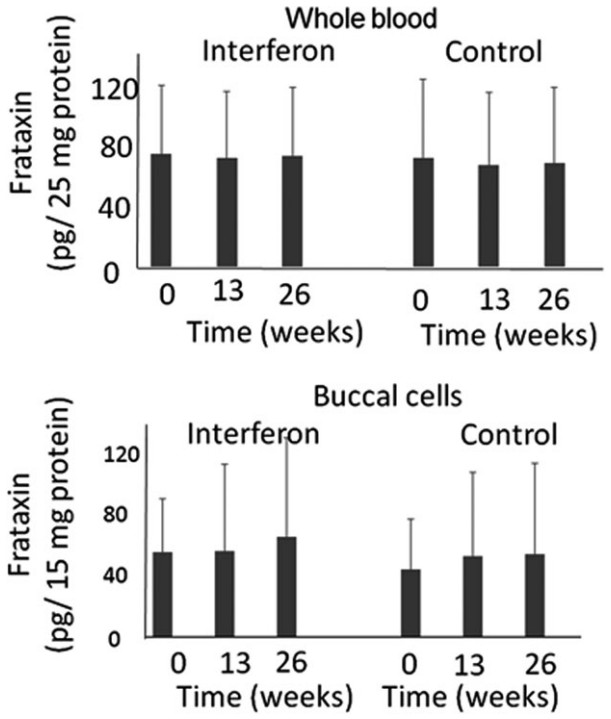

Figure 2. Frataxin levels in whole blood and buccal cells. Frataxin levels were assayed over time of drug treatment in both the placebo and active drug groups. No differences were noted.

variability of the mFARS assessment was higher than that in a similar trial IONIA (which used a slightly different scale), though similar variability was obtained between the two studies for the performance measures.[18,19] The high variability in mFARS could reflect either the larger number of sites used in the present study (4 vs. 2 in IONIA) or an increased level of day-to-day variability in subjects from the present cohort. Natural history cohorts predict that most intervention studies in FRDA should use larger cohorts or longer durations than the present study, unless the therapeutic effect is sizable. The reproducibility assessments in the present study support this assertion. These results are particularly useful for future trials that integrate similar visit structures and exam-based metrics.

Interpretation of results in the current study was further complicated by the co-occurrence of study exam and side effects. The mFARS exam was timed to occur at the time of maximal biochemical increase in IFN-γ 1b related mRNAs, 4–6 h after dosing. Unfortunately, several subjects reported this as the time of maximal side effects such as fatigue, perhaps making it more difficult to measure a clinical benefit, even if the pharmacodynamics of the induction of frataxin are maximal at this point.

Finally, the frataxin measurement is an incompletely developed outcome measure. Buccal cell frataxin levels correlate with disease severity, but they are present in very low levels, and their changes may not match neurological function.[20,21] Whole blood frataxin levels largely represent levels in erythrocytes, where frataxin has a slightly different amino acid sequence and is made from a different splice variant.[8,9,22–24] These levels are unlikely to correlate with neurological function. Overall, some of the difficulties in frataxin measurement could be resolved using novel frataxin assays based on mass spectrometry, which markedly improves reproducibility (Fig. 2; 24).

Interestingly, subjects in the present study appear to show a differentiation from natural history data over the open-label period of the study. Absolute values of mFARS are better than those from parallel natural history studies, and the rate of progression slowed slightly over this short period. Similar results have been noted in other FRDA studies, including those of idebenone and EPI743.[18–21] The final mFARS results from the study suggest a potential benefit smaller than that utilized in sample size calculations. Subjects had diverging opinions of their own response (data not shown), with some reporting clear benefit and others seeing no effect. This suggests the possibility of responsive and non-responsive subgroups that

Table 3. Clinical changes in combined open-label and double-blind phases: mFARS exams, synchronized to initiation of active drug.

Time in weeks	−28	−15	0	13	26	39	52	Last eval	On drug	Off drug
mFARS	44.6 ± 10.0 (45)	41.9 ± 8.7 (45)	43.9 ± 11.2 (92)	42.2 ± 10.8 (86)	44.9 ± 11.7 (79)	42.4 ± 12.1 (39)	44.3 ± 12.8 (29)	44.9 ± 11 (87)	43.0 + 10.2 (48)	47.2 ± 12.7 (39)
Fxn buccal cells	39.1 ± 30 (22)	34.0 ± 23.2 (17)	46.1 ± 43 (46)	53.6 ± 60 (35)	51 ± 52 (21)	93 ± 81 (15)	69 ± 53 (5)	69 ± 72 (37)	71 ± 77 (31)	57 ± 44 (6)

Results were tabulated based on initiation of active agent at time zero. By convention, negative days are prior to first dose and 0 means baseline. The number of subjects (*n*) at each time is given in parentheses. Lower mFARS scores mean better function. Overall subjects receiving active drug showed no change over the study comparing first and last visit. At the time of final visit, some subjects had electively discontinued drug (Off Drug column) while others continued it (On Drug column). Frataxin levels are given in pg/15 micrograms of protein.

Table 4. Change in mFARS exams, synchronized to initiation of study.

Time in weeks	13	26	39	52
Interferon gamma	−2.08	−0.47	−1.25	0.22
Placebo	−2.11	−0.79	−1.14	0.35

Data is displayed comparing the difference from baseline in exam results over the 52 weeks of double-blind and open-label extension.

could not be discerned in a brief, moderate size study. Thus, while the 6-month placebo-controlled trial failed to show benefit, several observations raise a question of whether a longer study might show a modest benefit of IFN-γ 1b in FRDA.[25]

Conflicts of Interest

Julie Ball, Renee Perdok, Amy Grahn, Tom Vescio, and Jeffrey W. Sherman are employees of Horizon Pharmaceutical. David Lynch also receives grants from the MDA, FDA, NIH, FARA, and Reata Pharmaceutical.

References

1. Strawser C, Schadt K, Hauser L, et al. Pharmacological therapeutics in Friedreich ataxia: the present state. Expert Rev Neurother 2017;17:895–907.
2. Pandolfo M. Friedreich ataxia: the clinical picture. J Neurol 2009;256(Suppl 1):3–8.
3. Koeppen AH, Morral JA, McComb RD, Feustel PJ. The neuropathology of late-onset Friedreich's ataxia. Cerebellum 2011;10:96–103.
4. Koeppen AH, Davis AN, Morral JA. The cerebellar component of Friedreich's ataxia. Acta Neuropathol 2011;122:323–330.
5. Campuzano V, Montermini L, Moltò MD, et al. Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion. Science 1996;271:1423–1427.
6. Martelli A, Puccio H. Dysregulation of cellular iron metabolism in Friedreich ataxia: from primary iron-sulfur cluster deficit to mitochondrial iron accumulation. Front Pharmacol 2014;5:130.
7. Deutsch EC, Santani AB, Perlman SL, et al. A rapid, noninvasive immunoassay for frataxin: utility in assessment of Friedreich ataxia. Mol Genet Metab 2010;101:238–245.
8. Deutsch EC, Oglesbee D, Greeley NR, Lynch DR. Usefulness of frataxin immunoassays for the diagnosis of Friedreich ataxia. J Neurol Neurosurg Psychiatry 2014;85:994–1002.
9. Tomassini B, Arcuri G, Fortuni S, et al. Interferon gamma upregulates frataxin and corrects the functional deficits in a Friedreich ataxia model. Hum Mol Genet 2012;21:2855–2861.
10. Seyer L, Greeley N, Foerster D, et al. Open-label pilot study of interferon gamma-1b in Friedreich ataxia. Acta Neurol Scand 2015;132:7–15.
11. Marcotulli C, Fortuni S, Arcuri G, et al. GIFT-1, a phase IIa clinical trial to test the safety and efficacy of IFNγ administration in FRDA patients. Neurol Sci. 2016;37:361–364.
12. Patel M, Isaacs C, Seyer L, et al. Progression of Friedrich ataxia: quantitative characterization over five years. Ann Clin Transl Neurol. 2016;3:684–694.
13. Friedman LS, Farmer JM, Perlman S, et al. Measuring the rate of progression in Friedreich ataxia: implications for clinical trial design. Mov Disord 2010;25:426–432.
14. Lynch DR, Farmer JM, Tsou AY, et al. Measuring Friedreich ataxia: complementary features of examination and performance measures. Neurology 2006;66:1711–1716.
15. Regner SR, Wilcox NS, Friedman LS, et al. Friedreich ataxia clinical outcome measures: natural history evaluation in 410 participants. J Child Neurol 2012;27:1152–1158.
16. Paulsen EK, Friedman LS, Myers LM, Lynch DR. Health-related quality of life in children with Friedreich ataxia. Pediatr Neurol 2010;42:335–337.
17. Epstein E, Farmer JM, Tsou A, et al. Health related quality of life measures in Friedreich Ataxia. J Neurol Sci 2008;272:123–128.
18. Meier T, Perlman SL, Rummey C, et al. Assessment of neurological efficacy of idebenone in pediatric patients with Friedreich's ataxia: data from a 6-month controlled study followed by a 12-month open-label extension study. J Neurol 2012;259:284–291.
19. Lynch DR, Perlman SL, Meier T. A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia. Arch Neurol 2010;67:941–947.
20. Lynch DR, Willi SM, Wilson RB, et al. A0001 in Friedreich ataxia: biochemical characterization and effects in a clinical trial. Mov Disord 2012;27:1026–1033.
21. Zesiewicz T, Salemi JL, Perlman S, et al. Double-blind, randomized and controlled trial of EPI-743 in Friedreich's ataxia. Neurodegener Dis Manag. 2018;8:233–242.
22. Lazaropolous M, Dong Y, Clark E, et al. Measurement of frataxin levels in peripheral tissue in Friedreich ataxia: analysis using repeated measures. Ann Clin Transl Neurol. 2015;2:831–842.
23. Oglesbee D, Kroll C, Gakh O, et al. High-throughput immunoassay for the biochemical diagnosis of Friedreich ataxia in dried blood spots and whole blood. Clin Chem 2013;59:1461–1469.

24. Guo L, Wang Q, Weng L, et al. Liquid chromatography-high resolution mass spectrometry analysis of platelet Frataxin as a protein biomarker for the rare disease Friedreich's Ataxia. Anal Chem 2018;90:2216–2223.
25. Rummey C, Kichula E, Lynch DR. Clinical trial design for Friedreich ataxia - where are we now and what do we need? Exp Opin Orphan Drugs 2018;6:219–230.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Adverse events seen in >10% of subjects in either treatment group.

