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A Phase 3, Double-blind, Placebo-Controlled Trial of Idebenone in Friedreich Ataxia

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Objective: To assess the efficacy of idebenone on neurological function in patients with Friedreich ataxia.

Design: Randomized, double-blind, placebo-controlled intervention trial.

Setting: Children's Hospital of Philadelphia and the University of California at Los Angeles.

Participants: Seventy ambulatory pediatric patients (age, 8-18 years) with a baseline International Cooperative Ataxia Rating Scale (ICARS) score of 10 to 54.

Interventions: Participants were randomized into 1 of 3 treatment arms: 450 or 900 mg of idebenone per day (in those with a body weight ≤ or >45 kg, respectively; n=22); 1350 or 2250 mg of idebenone per day (n=24); or placebo (n=24).

Main Outcome Measures: Mean change from baseline to week 24 in ICARS score was the primary efficacy variable. Mean change in Friedreich Ataxia Rating Scale (FARS) score, performance measures, and activities of daily living were the secondary efficacy variables.

Results: Patients who received idebenone improved by 2.5 points on mean ICARS score compared with baseline, while patients in the placebo group improved by 1.3 points. Patients who took idebenone also improved by 1.6 points on the FARS, while patients taking placebo declined by 0.6 points. For both end points, the difference between the idebenone and placebo groups was not statistically different.

Conclusions: Idebenone did not significantly alter neurological function in Friedreich ataxia during the 6-month study. Larger studies of longer duration may be needed to assess the therapeutic potential of drug candidates on neurological function in Friedreich ataxia.

Trial Registration: clinicaltrials.gov Identifier: NCT00537680

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FRIEDREICH ATAXIA IS AN AUTOSOMAL recessive degenerative disorder characterized by ataxia, areflexia, sensory loss, weakness, scoliosis, and cardiomyopathy. Diabetes mellitus, optic neuropathy, and hearing loss are also seen.[1,2] Most patients with Friedreich ataxia (97%) have expansions of a GAA repeat in the first intron on both alleles of the gene encoding the mitochondrial protein frataxin,[2,3] whose expression is reduced in Friedreich ataxia.[4] The size of the GAA-repeat expansion inversely correlates with frataxin expression and age at disease onset.[3] Deficiency of frataxin in cells leads to decreased activities of iron-sulfur cluster–containing enzymes, accumulation of iron in the mitochondrial matrix, increased sensitivity to oxidative stress, and impaired adenosine triphosphate production.[5-7]

Idebenone, a synthetic analogue of coenzyme Q10, has potent antioxidant activity and facilitates the flux of electrons along the mitochondrial electron transport chain, increasing the production of adenosine triphosphate.[8] In Friedreich ataxia, idebenone may decrease cardiac hypertrophy and improve cardiac function, with beneficial effects observed at dose levels of 5 mg/kg per day.[9-13] Data on neurological effects at this dose level are inconsistent.[9-13] A 6-month, double-blind, placebo-controlled phase 2 clinical trial (National Institutes of Health [NIH] Collaboration With Santhera in Ataxia [NICOSIA]) using higher doses of idebenone showed evidence of dose-dependent improvement in secondary neurological end points compared with placebo.[14] This was best noted on the International Cooperative Ataxia Rating Scale (ICARS), with a similar pattern observed for the Activities of Daily Living and neurological scales of the Friedreich's Ataxia Rating Scale (FARS). Neurological improvement was especially evident in ambulatory patients with ICARS scores of 10 to 54 at baseline. The trend to improvement was

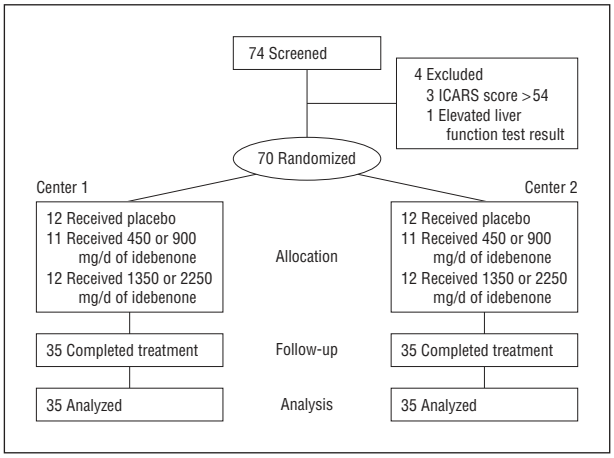

Figure 1. Participant flow diagram. ICARS indicates International Cooperative Ataxia Rating Scale.

only evident at idebenone doses approximately 3- to 10-fold higher than the previously used daily 5-mg/kg dose. The present study, Idebenone Effects on Neurological ICARS Assessments (IONIA), is a double-blind, randomized, placebo-controlled intervention trial of 6 months' duration evaluating the safety and efficacy on neurological function of idebenone in ambulatory pediatric patients with Friedreich ataxia.

METHODS

STUDY DESIGN

The study was a double-blind, randomized, placebo-controlled, parallel-group study investigating the safety, tolerability, and efficacy of idebenone in the treatment of patients with Friedreich ataxia conducted at 2 centers: Children's Hospital of Philadelphia and the University of California at Los Angeles. Inclusion criteria included a diagnosis of Friedreich ataxia with confirmed GAA-expansion mutations (patients having point mutations were not eligible); age older than 7 and younger than 18 years at baseline evaluation; body weight above 25 kg; and ability to walk at least 10 m without an accompanying person (ICARS Walking Capacities score ≤6). Patients were excluded if they had an ICARS score greater than 54 or less than 10 at screening; were pregnant or breastfeeding; had clinically significant abnormalities of hematology or biochemistry; or had participated in the previous phase 2 trial of idebenone.[14] Patients being treated at screening with antioxidants (vitamin E, coenzyme Q, and idebenone purchased from noncontrolled sources) were required to have a 1-month washout of these agents before the baseline visit.

RANDOMIZATION

Of 74 patients who were screened, 4 did not qualify for enrollment (3 patients had ICARS scores >54 and 1 patient had an abnormal liver function test result) (**Figure 1**). Seventy patients were randomized 1:1:1 to 1 of 3 treatment arms using a central block randomization scheme. A list of randomization numbers and corresponding treatment numbers was computer generated by a third party (Fischer Services, Allschwil, Switzerland). Patients and investigators were blinded to the allocated study group. Treatment assignments were maintained by the third party and only made available after the trial was complete and the database locked. Study medication was provided as prepackaged kits marked with the appropriate treatment number. Group A received idebenone (150-mg idebenone tablets, Catena, Santhera Pharmaceuticals) at 450 mg per day (if ≤45-kg body weight at baseline) or 900 mg per day (if >45-kg body weight at baseline); group B received idebenone at 1350 mg per day (if ≤45 kg) or 2250 mg per day (if >45 kg); and group C received placebo. These dosages correspond to doses in the range of approximately 10 to 20 mg/kg per day (group A) and approximately 30 to 54 mg/kg per day (group B) for patients weighing 25 to 80 kg within each dose group. The drug was administered in 3 divided doses with meals.

STUDY CONDUCT

Within 8 weeks prior to randomization (at the baseline visit), patients attended a screening visit where informed consent/assent was obtained and inclusion/exclusion criteria were assessed. They underwent a physical and neurological examination, including an assessment of vital signs and electrocardiography, and a pregnancy test for female patients of childbearing potential. Thereafter, neurological efficacy assessments were undertaken at baseline (day 1) and weeks 12 and 24 (end of therapy). Safety assessments were performed at weeks 4, 12, 24, and 28 (follow-up); no follow-up visit was undertaken in patients who enrolled into the open-label extension. Patients maintained a diary, with daily documentation of study medication intake and recording of adverse events and concomitant medications.

OUTCOME MEASURES AND OBJECTIVES

The primary objective was to compare the efficacy of 24 weeks' treatment with 2 different doses of idebenone with that of placebo on neurological impairment as assessed by the ICARS. Secondary measures included the neurological examination of the FARS; the Friedreich's Ataxia Composite Test (FACT-Z_3), derived from the Timed 25-Foot Walk test, the 9-hole peg test, and the low-contrast letter acuity test; and the activities of daily living scale.[15-18]

STATISTICAL ANALYSIS

The primary and secondary efficacy analyses were conducted in the intent-to-treat population, including all randomized patients. The patients were analyzed as randomized regardless of protocol deviations. The last observation carried forward method was applied to impute missing data. Safety analysis included all randomized patients who received at least 1 dose of the trial medication and for whom safety assessments were available.

Unless specified, efficacy analyses for each group receiving idebenone were compared against the placebo group using pairwise comparison based on an analysis of covariance model, with treatment as a factor and baseline value as a covariate testing a 2-sided alternative at a Bonferroni-adjusted α level of 2.5%. With a minimum of 15 evaluable patients in each of the groups, an anticipated effect size (difference between placebo and idebenone) of more than 6.2 ICARS points, and a common SD of 5.0 points, the study would provide 85% power to reject the null hypothesis of no difference between any idebenone dose and placebo with regard to the change from baseline to week 24 in ICARS using a pairwise comparison test. This effect size is based on results from subgroup analysis of NICOSIA[14] and is greater than the expected yearly decline in ICARS score for patients with Friedrich ataxia.

A prespecified responder analysis derived from ICARS scores was also conducted. Herein, each active treatment dose was compared with placebo using a 2-sided χ^2 test on the intent-to-treat population. The responder analysis compared the num-

Table 1. Characteristics of Patients With Friedreich Ataxia

Characteristic	Mean (SD), Range by Group			
		Idebenone		
	Placebo (n=24)	450 or 900 mg (n=22)	1350 or 2250 mg (n=24)	Total (N=70)
Age, mean (SD), median (range), y	13.7 (2.8), 13.15 (8.7-18.1)	13.9 (2.5), 14.5 (9.7-17.3)	13.4 (3.0), 12.9 (8.0-18.0)	13.7 (2.8), 13.9 (8.0-18.1)
Sex, No. (%)				
M	8 (33.3)	15 (68.2)	10 (41.7)	33 (47.1)
F	16 (66.7)	7 (31.8)	14 (58.3)	37 (52.9)
GAA-repeat length,[a] mean (SD), median (range)	738 (130), 717 (520-1000)	725 (109), 741 (521-900)	735 (128), 718 (486-970)	733 (121), 727 (486-1000)
Disease duration,[b] mean (SD), median (range), mo	71.4 (47.4), 74.5 (1.1-196.9)	64.9 (32.3), 63.2 (0.8-124.7)	63.1 (33.6), 55.4 (6.4-134.7)	66.6 (38.3), 68.7 (0.8-196.9)
Patients with previous use of idebenone, No. (%)	3 (12.5)	3 (13.6)	6 (25.0)	12 (17.1)
Baseline ICARS score[c]	35.6 (7.0), 24-48	36.0 (7.1), 23-49	34.0 (8.9), 16-52	35.2 (7.7), 16-52
Baseline FARS score[c]	55.9 (10.4), 36-78	59.0 (8.2), 41-73	56.5 (11.6), 34-81	57.1 (10.1), 34-81
Baseline FACT-Z_2 score[c]	0.03 (0.81), −1.4 to 2.2	−0.2 (0.91), −2.3 to 1.2	0.16 (0.99), −2.2 to 2.2	0.00 (0.91), −2.3 to 2.2
Baseline FACT-Z_3 score[c]	−0.08 (0.79), −1.4 to 1.8	−0.09 (0.79), −1.8 to 1.3	0.16 (0.85), −1.6 to 1.8	0.00 (0.81), −1.8 to 1.8
Baseline ADL score[c]	9.7 (3.9), 3-16	10.5 (2.9), 3-14	9.5 (5.1), 0-19	9.9 (4.1), 0-19

Abbreviations: ADL, activities of daily living; FACT-Z_2, Friedreich's Ataxia Composite Test (contains only the Timed 25-Foot Walk and the 9-hole pegboard test)[16]; FACT-Z_3, Friedreich's Ataxia Composite Test; FARS, Friedreich Ataxia Rating Scale; ICARS, International Cooperative Ataxia Rating Scale.

[a] Repeat length of the shorter GAA allele.

[b] The time since diagnosis is based on the medical history case report form pages. Missing day of onset is imputed to 15, missing day and month of onset are imputed to June 30, and missing year of onset is considered missing. Twenty-four participants in the placebo group; 22 in the 450- or 900-mg idebenone group; and 22 in the 1350- or 2250-mg group.

[c] For intent-to-treat population.

ber and percentage of patients in each treatment arm showing (1) a 2.5-point or greater improvement on ICARS and (2) a 5-point or greater improvement on ICARS, the latter corresponding to the annual rate of decline in untreated patients with Friedreich ataxia.[19] Additional subgroup analyses were performed on the primary efficacy end point for the study population split by the median ICARS score at baseline, disease duration of shorter or longer than 5 years prior to study start, sex, previous use of idebenone, GAA value reported at screening (≤800 vs >800), and study site.

RESULTS

RESULTS OF RANDOMIZATION

Seventy patients (35 patients/center) were randomized to 1 of 3 treatments (Figure 1), and the characteristics of each group were compared (**Table 1**). Disease severity was similar in the groups based on GAA-repeat length, disease duration, and baseline neurological scores. The groups differed by sex ($P=.049$, χ^2 test for between-treatment comparison), as group A contained more men. The demographic characteristics of the cohort were similar to those of the NICOSIA study in age, GAA-repeat length, and sex. As efficacy parameters were available from all patients for analysis, no data imputation was required.

SAFETY AND TOLERABILITY

As seen previously, idebenone was safe and well tolerated, and all subjects completed the treatment period. Two patients in group B experienced serious adverse events: 1 patient experienced chest pain not related to cardiac involvement and another had an episode of idiopathic thrombocytopenic purpura. Both patients had a history of the respective condition. The events were classified as unrelated and resolved spontaneously while they continued taking the study medication. Most adverse events occurred equally between patients taking idebenone and those taking placebo (eTable, available at http://www.archneurol.com), except for gastrointestinal tract irritations (defined as nausea, upper abdominal pain, diarrhea, abdominal pain, vomiting, and dyspepsia). These were more frequent in patients in the high-dose (n=14) compared with the low-dose (n=7) and placebo (n=10) groups, but this difference was not statistically significant. No safety effects were identified following the withdrawal of antioxidants at trial initiation.

CHARACTERIZATION OF EFFICACY VARIABLES AT SCREENING AND BASELINE

Although many measures have been developed and used to assess ataxia, few have been tested under clinical trial conditions. We examined the difference between the screening and baseline values for the primary outcome measure (ICARS score) and 2 other neurological measures, the FARS and the FACT-Z_3 (**Figure 2**). The correlation between scores at these 2 visits was very high for all 3 parameters, with Pearson correlation coefficients of 0.88 (ICARS), 0.89 (FARS), and 0.95 (FACT-Z_3) ($P<.001$ for all 3 comparisons). This indicates the high reliability of these assessments at screening and baseline visits, which were up to 8 weeks apart, and shows that these outcome measures are reproducible enough

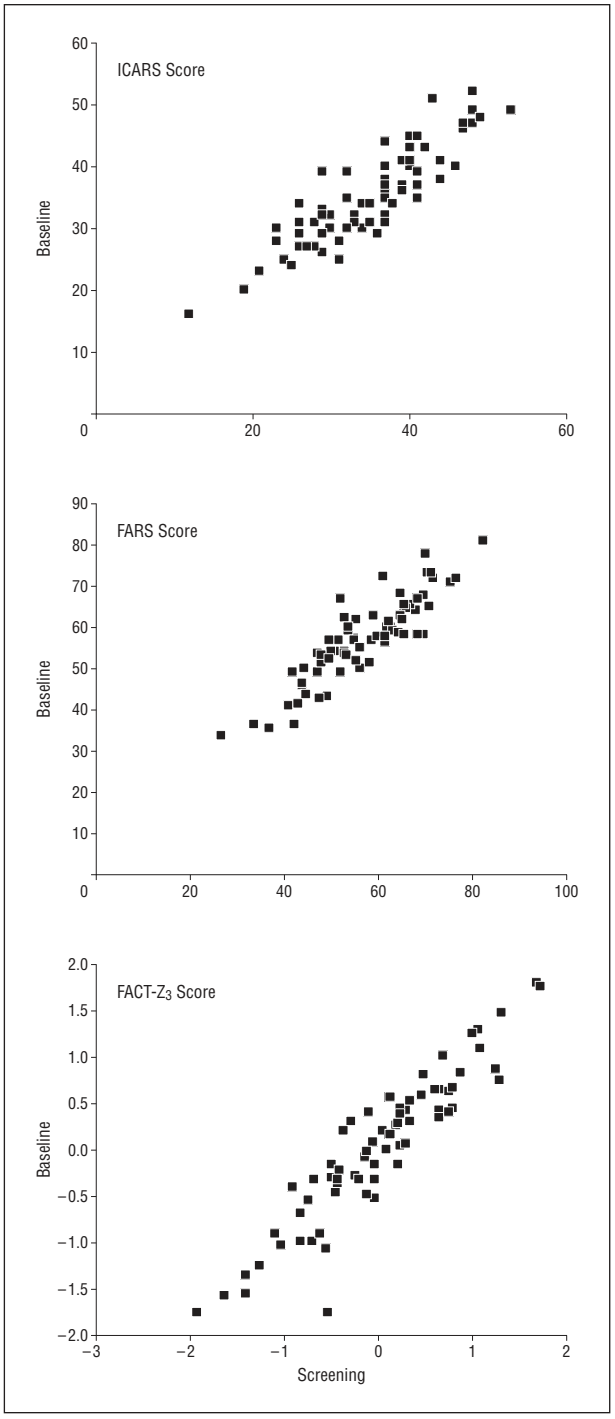

Figure 2. Scatterplots comparing screening and baseline ataxia scale scores in all patients (N=70). FACT-Z_3 indicates Friedreich's Ataxia Composite Test; FARS, Friedreich Ataxia Rating Scale; and ICARS, International Cooperative Ataxia Rating Scale.

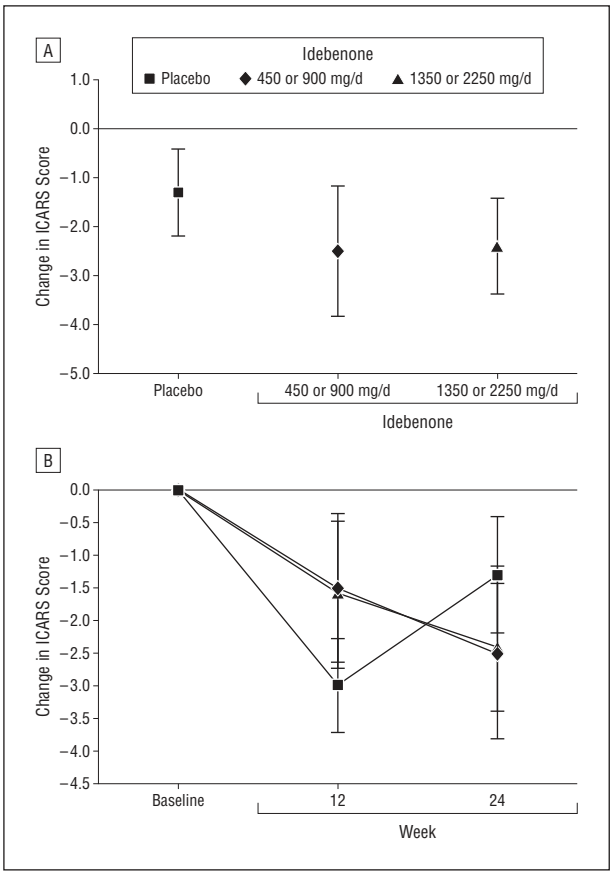

Figure 3. Analysis of the primary efficacy parameter (International Cooperative Ataxia Rating Scale score [ICARS] score). Mean change between week 24 and baseline (A) and mean change between week 12 and baseline and week 24 and baseline (B). Error bars represent the standard error of the mean.

to be useful in assessing neurological progression in Friedreich ataxia.

EFFECT OF IDEBENONE ON NEUROLOGICAL STATUS OF FRIEDREICH ATAXIA

When the 3 study groups were compared for the change between baseline and week 24, subjects taking idebenone showed a mean improvement (ie, reduction on ICARS) of 2.5 (group A) and 2.4 (group B) points, not significantly different compared with placebo (which improved by 1.3 points) (**Figure 3**A). Moreover, the mean difference between the idebenone groups and placebo was driven by one investigation site (based on a site-specific improvement in the idebenone groups), and no dose correlation was seen between the idebenone groups. The improvement in the placebo group was particularly prominent between baseline and week 12 and reduced during the second 12-week study period (Figure 3B). In contrast to ICARS, a slight worsening on the FARS, a secondary neurological outcome measure, was observed for patients taking placebo. Although patients receiving idebenone improved on the FARS (ie, reduced mean FARS score), the difference between the idebenone and placebo groups was not significant (**Figure 4**A). Likewise, no clear differences were seen in the FACT-Z_3 or activities of daily living scales between the study groups (Figure 4B and C).

The change in ICARS score between baseline and week 24 for patients correlated with the change in FARS score (Pearson correlation coefficient $r=0.62$, $P<.001$) and FACT-Z_3 ($r=-0.26$, $P=.033$). No differences were seen in these correlations between the different treatment groups (**Figure 5**).

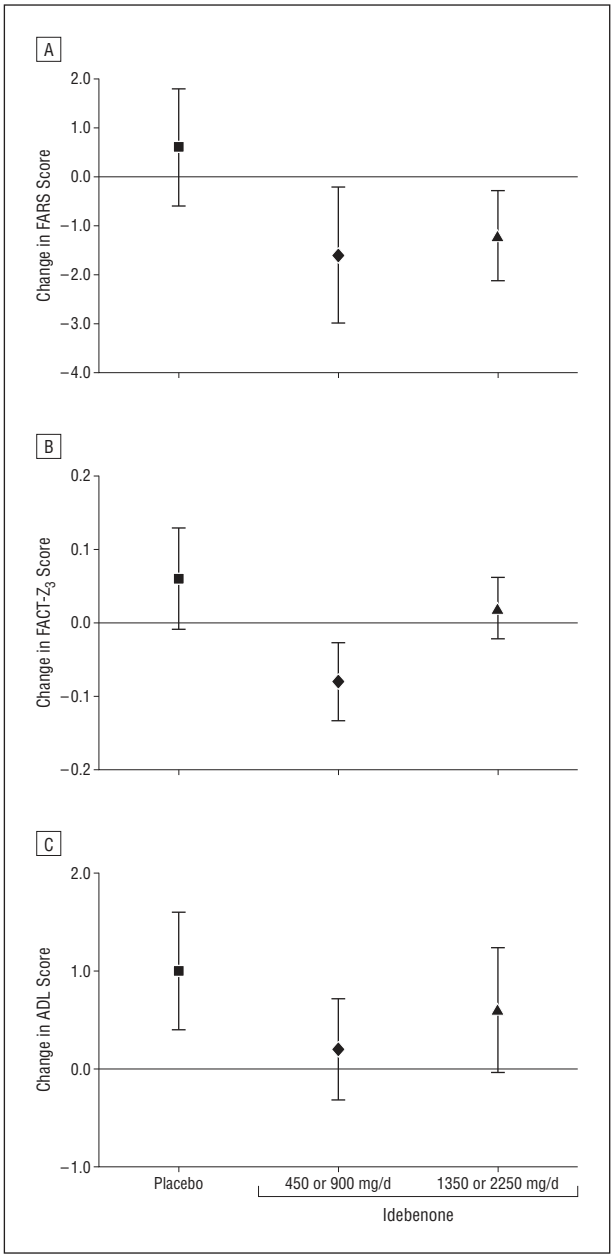

Figure 4. Mean changes between week 24 and baseline for the secondary efficacy parameters. ADL indicates activities of daily living; FACT-Z_3, Friedreich's Ataxia Composite Test; and FARS, Friedreich Ataxia Rating Scale. Error bars represent the standard error of the mean.

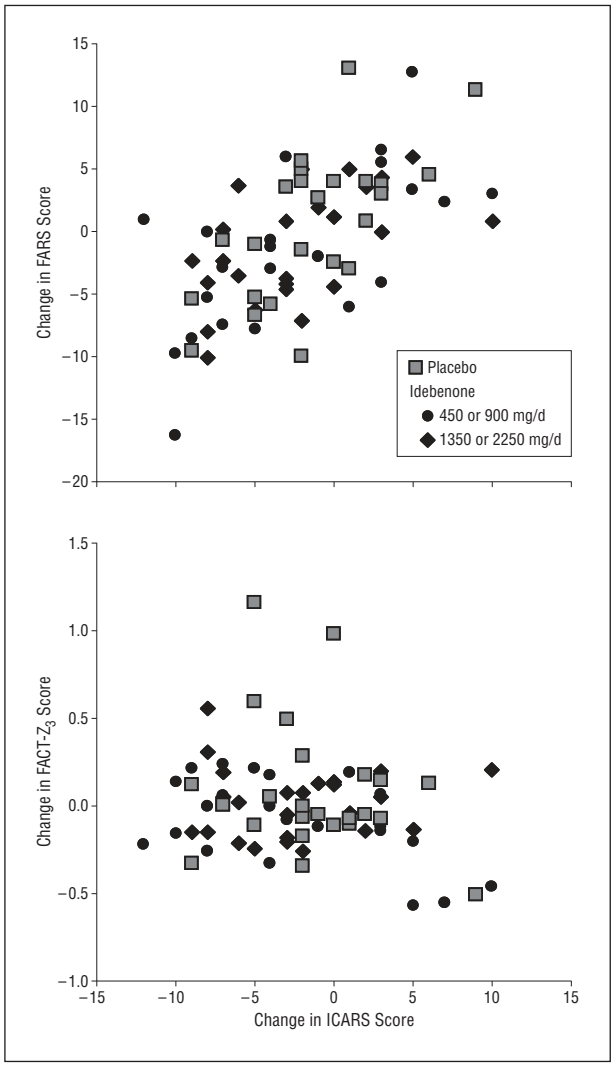

Figure 5. Scatterplot for changes between week 24 and baseline for ataxia scale scores in all patients (N=70). FACT-Z_3 indicates Friedreich's Ataxia Composite Test; FARS, Friedreich Ataxia Rating Scale; and ICARS, International Cooperative Ataxia Rating Scale.

RESPONDER ANALYSIS

We also analyzed the data for the number and percentage of patients who improved by 2.5 or 5 points on ICARS over the course of the study (**Figure 6**). These levels were selected as being roughly the amount of progression expected to occur during 6 or 12 months, respectively, in untreated patients with Friedreich ataxia,[19] and therefore improvement of this magnitude would be considered clinically meaningful. At 24 weeks of therapy, more than 50% of subjects taking idebenone improved by 2.5 points and almost 40% by 5 points, but there was also a high number of responders in the placebo group (58% improved by 2.5 points and 41% by 5 points at week 12; 33% by 2.5 points and 25% by 5 points at week 24). Thus, no statistically significant differences were noted between placebo and idebenone therapy.

The present results seem paradoxical based on the encouraging results of a previous phase 2 study[14] that suggested that idebenone might be most effective in less affected patients. Thus, we examined the change in ICARS scores in 2 subgroups split by the median ICARS at baseline (**Table 2**). The improvement on ICARS in the idebenone and placebo groups was generally larger in patients with lower ICARS scores at baseline (ie, milder affected patients) compared with the subgroup with a higher range of ICARS scores at baseline. Similar analysis separating subgroups by disease duration ($>$ or $\leq$ 5 years) or age showed a congruent picture with greater improvement with both placebo and idebenone seen in the subgroup with shorter disease duration or younger age (data not shown). These analyses indicate that improvements in mean ICARS scores, whether with idebenone or placebo, were greater in patients with shorter disease duration, younger age, or lower ICARS scores prior to the study.

COMMENT

The major finding of the present 6-month study is that idebenone did not significantly improve the neurological status of pediatric patients with Friedreich ataxia compared with placebo. Thus, the present short-term study does not provide evidence for efficacy of idebenone in the treatment of ataxia in this disorder.

The present design is derived from a prespecified subgroup analysis of the data of a previous study (NICOSIA)[14] in which ambulatory patients (33 of 48) undergoing treatment with higher doses of idebenone had improved neurological function as measured by the ICARS, while patients taking placebo worsened (in NICOSIA the 95% confidence intervals for change from baseline in the idebenone groups were –10.8 to –1.7 points [dose A] and –12.5 to –3.1 points [dose B]). The inclusion criteria for this study (IONIA) were directed to match this population, and the baseline ICARS score matched that of the ambulatory NICOSIA subgroup, but the effect size was smaller than that noted in NICOSIA and not different from placebo. A greater responsiveness of patients with an earlier disease stage to both placebo and idebenone did appear in the present study. The IONIA study differs in its design from the NICOSIA study in several ways. Two centers participated in the present study, with ratings performed by individuals highly experienced in grading Friedreich ataxia.[16] Future studies might include more sites, in which variability among raters will be an issue, but also could resolve the site specificity noted in the present study.

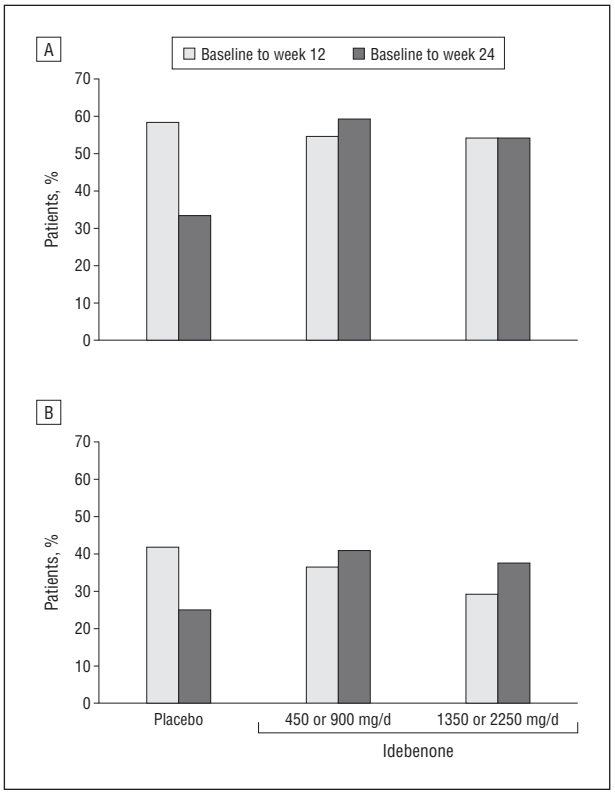

Figure 6. Responder analysis. Percentage of patients improving by 2.5 or more points (A) or 5 or more points (B) on the International Cooperative Ataxia Rating Scale.

The data from the present study show that the ICARS, FARS, and FACT-Z_3 composite are all likely to be useful in multicenter trials for Friedreich ataxia, as these measures all appeared to change in parallel, providing evidence of their concurrent validity. Thus, while the sensitivity of these scales to change is limited and each has a variety of limitations (including items that are redundant or irrelevant), they appear valid under clinical trial conditions. Still, although these measures change in parallel, the improvement in the placebo group was particularly prominent in the ICARS measurement. This had not been noted in the NICOSIA study.[14] As evaluations were performed more frequently in the present study than the NICOSIA study, one possible explanation would be practice effects in the performance of measures by the subject. This could be addressed in future studies by longer study durations, additional "run-in" visits, or different spacing of the efficacy evaluations. Another contributing factor is suggested by the greater improvement in all groups in younger patients. As ICARS scores improve by several units per year until roughly age 11 to 12 years, some of the improvement seen across all groups (including placebo) may reflect naturally occurring increases in motor abilities.[20] In addition, though the execution of this trial included systematic attempts to match assessment conditions at each visit, the high level of day-to-day variability in neurological function might have influenced results.

The improvement in the placebo group was particularly great from baseline to week 12, with a notable drop-

Table 2. Change in ICARS Scores in Patients With Friedreich Ataxia by ICARS Score at Baseline

	Mean (SEM) by Baseline ICARS Score								
	≤Median			>Median			*P* Value, ≤ vs > Median		
		Idebenone			Idebenone				
ICARS Score	Placebo (n=11)	450 or 900 mg (n=11)	1350 or 2250 mg (n=14)	Placebo (n=13)	450 or 900 mg (n=11)	1350 or 2250 mg (n=10)	Placebo	450 or 900 mg of Idebenone	1350 or 2250 mg of Idebenone
Baseline	29.2 (0.99)	30.3 (1.02)	28.1 (1.31)	41.1 (1.08)	41.6 (1.44)	42.1 (2.00)	.12	.19	.63
Change from baseline to week 24	–2.8 (1.07)	–4.3 (1.22)	–2.8 (1.43)	0.0 (1.30)	–0.7 (2.32)	–1.8 (1.28)			
P value[a]		.49	.97		.78	.49			

Abbreviation: ICARS, International Cooperative Ataxia Rating Scale.
[a] Comparison with placebo for change from baseline to week 24.

off in the level of improvement by week 24, while the improvement seen in the idebenone treatment groups increased from week 12 to week 24. If the study had been longer, a treatment effect may have been revealed. The study duration of 6 months in evaluating neuroprotection in a chronically progressive neurological disease may represent an important limitation.

Although idebenone did not significantly alter neurological function as measured in this study, idebenone treatment may affect features of Friedreich ataxia not captured in this study. Data from several studies indicate that idebenone can ameliorate cardiac hypertrophy of patients with Friedreich ataxia, but there is still insufficient evidence whether these improvements in cardiac anatomy translate into a demonstrable clinical benefit. Finally, in Friedreich ataxia, idebenone is commonly associated with a relief of the fatigue, a multifactorial symptom that may not necessarily be well captured in measures of ataxia.

While previous studies suggest that idebenone treatment results in a potential clinical benefit for patients with Friedreich ataxia, this study did not show statistically significant differences between placebo and idebenone treatment in neurological end points after treatment for 6 months. Larger studies of longer duration may be needed to assess neurological efficacy of drug candidates in Friedreich ataxia.

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Online-Only Materials: The eTable is available at http://www.archneurol.com.
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