Patient reported outcomes in Friedreich's Ataxia after withdrawal from Idebenone

Arron Cook MBBS[1], Sylvia Boesch MD[2], Suzette Heck MD[3], Ewout Brunt MD[4], Thomas Klockgether MD[5] , Ludger Schöls MD[6, 6a], Angela Schulz MD[7], Paola Giunti MD[1]

1. Department of Molecular Neuroscience, Ataxia Centre, UCL Institute of Neurology, Queen Square, London, WC1N 3BG

2. Neurologische Klinik, Universitätsklinik Innsbruck, Anichstrasse 35, A-6020 Innsbruck, Austria

3. Dept. of Neurology, Klinikum Grosshadern, Marchioninistr. 15, 81377 Munich, Germany

4. Department of Neurology, UMC Groningen, PB 30.001, 9700 RB Groningen, Netherlands

5. Department of Neurology, University of Bonn and DZNE Bonn, Sigmund-Freud-Str. 25, D-53105 Bonn, Germany

6. Department of Neurodegeneration and Hertie Institute for Clinical Brain Research, University of Tübingen, Hoppe-Seyler-Str. 3, D-72076 Tübingen, Germany

6a. German Center for Neurodegenerative Diseases (DZNE), 72076 Tübingen, Germany

7. Specialty Clinic for Degenerative Brain Diseases, Children's Hospital, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

Correspondence to: Professor Paola Giunti
Ataxia Centre
Department of Molecular Neuroscience
UCL Institute of Neurology
Queen Square
London WC1N 3BG
p.giunti@ucl.ac.uk

Short title: Idebenone withdrawal in Friedreich's Ataxia

Objectives

Friedreich's ataxia is the most common inherited ataxia, and pathogenesis is known to involve mitochondrial oxidative stress. Idebenone is a potent antioxidant which has already been evaluated in several clinical trials in FRDA, with reports of symptomatic benefit but inconclusive objective results. Following patient consultation on design, we have completed a treatment withdrawal study to establish whether patients could correctly determine their treatment allocation to placebo or idebenone. Our aim was to capture subjective experiences of symptoms such as, for example, fatigue, which can be difficult to measure with questionnaires or semi-quantitative scales, particularly in chronic, slowly progressive conditions.

Materials and Methods

Patients taking idebenone for at least 12 months as part of the open-label MICONOS Extension Study were randomised to receive either placebo or idebenone continuation for two-month treatment cycles. The primary endpoint was patient assessment of treatment assignment.

Results

A total of 29 patients were randomised, forming the idebenone group (n=16) and the placebo group (n=13). No significant differences were detected between the idebenone and placebo groups on assessment of treatment assignment or early study withdrawal. A small but significant difference in ataxia rating scale scores was detected between treatment groups when considering ambulatory patients only.

Conclusions

This study provides no data to suggest that FRDA patients could correctly determine their treatment assignment over a 2-month period. We hope that this study design will help inform future trials so that patients' experiences of symptoms are more reliably measured.

Keywords: Friedreich**'**s ataxia, idebenone, patient reported outcomes

Introduction

Friedreich's ataxia (FRDA) is the most common inherited ataxia, with an estimated prevalence of 3-4 cases per 100 000 individuals[1]. Neurological features include slowly progressive gait and limb ataxia, dysarthria, areflexia, reduced vibration and joint position sense, extensor plantar responses, and distal extremity weakness. Symptoms typically manifest before adulthood, and most patients are wheelchair-bound by the third decade. Non-neurological features include cardiomyopathy, diabetes mellitus, scoliosis and pes cavus. Cardiac complications, including concentric and asymmetrical left ventricular hypertrophy, develop in at least 60% of patients and contribute significantly to disability and premature death[2]. The pathogenic mutation in FRDA affects the *FXN* gene mapped to chromosome 9q21.11, with approximately 97% of patients expressing homozygous GAA repeat expansions within the first intron, and a small number of patients expressing compound heterozygous expansions with point mutations or deletions[3]. The FRDA mutation reduces expression of frataxin, a mitochondrial protein integral to iron metabolism[4]. The pathological consequences of frataxin deficiency include reduced activity of iron-sulphur cluster (ISC) containing enzymes, mitochondrial iron overload, and increased susceptibility to oxidative stress and lipid peroxidation[5-7]. These changes precipitate progressive neuronal atrophy, primarily affecting the dorsal root ganglia, posterior columns, spinocerebellar tracts and dentate nuclei[8].

Idebenone (2,3-dimethoxy-5-methyl-6-(hydroxydecyl)-1,4-benzoquinone) is a short-chain synthetic benzoquinone distinct to but derived from ubiquinone (co-enzyme Q10). It has been shown to support ATP production by acting as an electron carrier between ISC-containing respiratory chain complexes I and II, and complex III[9]. Furthermore, the molecule is a potent antioxidant that retards lipid peroxidation, thereby protecting mitochondria against oxidative stress[9]. These supportive and protective functions have made idebenone an attractive therapeutic prospect for respiratory chain diseases such as FRDA. Early low-dose (5mg/kg/day) open-label trials of idebenone in adult and paediatric FRDA patients demonstrated improvements in various cardiac measures, including inter-ventricular septal thickness and left-ventricular mass[10-12]. Neurological outcomes have primarily been measured using the International Cooperative Ataxia Rating Scale (ICARS), and whilst some studies have demonstrated a stabilisation of neurological decline in paediatric FRDA patients taking idebenone, other studies have failed to reproduce any such effect[13-16]. Subsequent

larger randomised, double-blind, placebo-controlled trials using high-dose idebenone have revealed variable results. The first of these trials involved 48 patients aged 9-17 years over a 6-month period, and assessed a urinary marker of oxidative DNA damage (8OH2'dG) in addition to clinical and activities of daily living scales in four treatment groups (placebo; low-dose: 180mg/360mg; medium-dose: 450mg/900mg; high-dose: 1350mg/2250mg) stratified by weight (≤45kg/>45kg)[17]. No significant effect on 8OH2'dG was observed between groups, however a non-significant improvement in clinical scale scores was seen in the two higher dose groups. A pre-specified analysis excluding patients requiring wheelchair assistance revealed a significant improvement in ICARS score and demonstrated a dose-dependent response to ICARS, Friedreich's Ataxia Rating Scale (FARS) and Activities of Daily Living (ADL) scores in the two higher dose groups.

In the following IONIA phase III trial, 70 paediatric patients were again randomised to either placebo or weight-dependent idebenone doses of either 450mg/900mg or 1350mg/2250mg for 6 months[18]. No significant group differences were observed on ICARS, FARS or Friedreich's Ataxia Composite Tests. In addition, left ventricular mass index, left ventricular posterior wall thickness at diastole and ejection fraction were not improved by idebenone. Following a 12-month open-label extension study, an overall analysis demonstrated significant improvement on ICARS in the high-dose (1350mg/2250mg) idebenone group, which was best seen when the stance and posture sub-scores were excluded from the analysis. The phase III MICONOS trial included 232 primarily adult patients assigned to placebo, low-, medium-, or high-dose idebenone over a 12-month period. No significant differences were detected between placebo and treatment groups on either ICARS, FARS or echocardiographic parameters (Schulz et al., unpublished). Despite the failure to attain these objective study endpoints, a significant portion of patients on the MICONOS trial reported symptomatic improvements with idebenone, in particular with fatigue, speech and general functional performance. The present study was therefore designed to address the discrepancy between the patient's experiences on idebenone and the measured effects using clinical scales in the IONIA and MICONOS trials. Patient reported outcomes are increasingly recognised as integral measures of patient's perspectives in clinical research, and they have been effectively used in studies of FRDA patients previously[19,20,21].We therefore employed these measures in an attempt to capture patients' experiences of symptoms on and off treatment with idebenone. Furthermore, patients who had already been on idebenone on the MICONOS trial were invited to contribute to discus-

sions on study design. Ultimately, we developed a treatment-withdrawal study that primarily asked patients to identify whether they had been randomised to placebo or idebenone continuation.

Materials and Methods

Study design and patients

This was a double-blind, randomised, placebo-controlled, parallel-group, multi-centre withdrawal study involving patients who had already received continuous high-dose idebenone (1350mg/day if ≤45kg or 2250mg/day if >45kg) for at least 12 months in the open-label MICONOS Extension Study (MES). The estimated sample size of up to 80 patients for this study was based on the number of eligible patients in the MES. Seven European centres provided data for this trial (one in the UK, one in the Netherlands, one in Austria, and four in Germany), from April 2011 to July 2012. Approximately half of the sample was recruited from the UK.

All patients on the MICONOS trial at the UK site were invited to discuss the study protocol in ad hoc interviews with researchers and Sponsor study coordinators. Whilst the basic treatment withdrawal design had been finalised by this point, patients were asked to offer their suggestions on specific components of the study, for example treatment cycle duration, study endpoints, and methods of assessment. The outcomes of these interviews were reviewed and, where possible, incorporated into the final study design. Patients meeting inclusion criteria (genetically confirmed diagnosis of FRDA, completion of ≥12 months on the MES, body weight ≥25kg) were randomised in a 1:1 ratio to either continue receiving high-dose idebenone or to receive placebo, for a cycle length of 2 months. Whilst recruitment was offered to all patients on the MICONOS trial, including both homozygous and heterozygous patients, this study only included homozygous patients. Randomisation codes were prepared by an independent statistician, and randomisation was stratified by centre and ambulatory status. Following a 2 month treatment period patients then returned to the MES. In all, patients were offered the opportunity to enter the study on two separate cycles, each being separated by at least a 6-month period of treatment with high-dose idebenone on the MES. Exclusion criteria included significant adverse events considered to be attributable to idebenone whilst on MES, clinically significant abnormalities of haematology or biochemistry, and pregnancy or breast-feeding.

Each 2 month cycle comprised two visits: baseline and follow-up. At each study visit patients underwent physical examination, standardised electrocardiogram (ECG), vital signs assessment, blood sampling (haematology, biochemistry), urine analysis, urine pregnancy test for women of childbearing age, and completion of specific assessments including a yes/no question on treatment assignment (primary endpoint); other patient reported outcomes including status and change questionnaires; Modified Fatigue Impact Scale (MFIS), 9-Hole Peg Test (9-HPT), speech assessments (Assessment of Intelligibility of Dysarthric Speech (AIDS), Maximum Phonation Time and Diadochokinetic Rate), Clinical Global Impression of Change (CGI-C; follow-up visit only), and ICARS.

The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, Directive 2001/20/EC, Guideline for Good Clinical Practice CPMP/ICH/135/95. Independent ethics committees and institutional review boards at each study site reviewed the protocol and all amendments. This trial is registered with ClinicalTrials.gov, number NCT01303406.

Study endpoints

The primary endpoint was patient assessment of treatment assignment, which was to be measured as a comparison of the proportion of patients randomised to idebenone and placebo who assessed that they received idebenone. This was ascertained with a simple yes/no question at the follow-up visit. The key secondary endpoint was a comparison of the proportion of patients randomised to idebenone and placebo who withdrew early due to recurrence or worsening of FRDA symptoms. Other secondary endpoints included patient reported outcomes (status questionnaire, change questionnaire, and patient diary entries), change in fatigue level as assessed by the MFIS, change in 9-HPT time, change in speech capability, change in CGI-C, investigator impression of treatment assignment, and change in ICARS score[22-27]. The Status Questionnaire assessed general status and included questions specific to symptoms and activities of daily living. Patient were asked to comment on any perceived change to each component of the Status Questionnaire at the follow-up visit, with available responses of much better/slightly better/as expected (no worsening); and slightly worse/much worse (worsening) (Change Questionnaire). The CGI-C comprised a numerical scale used by the investigator to quantify any impression of

change in clinical state between visits (1 to 7, with 1 indicating marked improvement, 7 indicating marked deterioration, and 4 indicating no change). Investigators were asked for their impression as to which treatment the patient had been randomised.

Statistical analysis

Two populations were defined for analysis: the safety population and the intend-to-treat (ITT) population. Both populations included all randomised patients who received at least one dose of study medication. Data were analysed using a parallel design with data from the first cycle only (n=29; idebenone 16, placebo 13); the second cycle included too small a sample to warrant inclusion in the final analysis (n=7; idebenone 2, placebo 5). The primary and key secondary endpoints were analysed using logistic regression. Secondary endpoints MFIS, 9-HPT, speech assessments and ICARS were analysed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate. In a separate analysis, ambulatory status and baseline were covariates. Other secondary endpoints (CGI-C, Investigator's assessment of treatment assignment, change questionnaire, status questionnaire) were analysed using logistic regression.

Results

Baseline characteristics

A total of 29 patients were screened and randomised in the study, forming the idebenone group (n=16) and the placebo group (n=13) (Figure 1). Table 1 shows baseline demographic and clinical characteristics. Treatment compliance, as measured based on returned tablet counts and patient diary entries, was good and did not differ between groups.

Efficacy evaluation

For the primary endpoint using data from the first treatment cycle only, there was no statistically significant difference between idebenone and placebo in the proportion of patients who correctly assessed that they received idebenone: 8 patients (50.0%) in the idebenone group correctly assessed that they received idebenone and 6 patients (46.2%) in the placebo group incorrectly assessed that they received idebenone (odds ratio 1.17, 95.2% CI: 0.27, 5.12; p=0.8369). Analyses of the primary endpoint for patients who completed both

cycles and treating observations from the same patient as independent also demonstrated no statistically significant difference between treatments (odds ratio 1.65, 95.2% CI: 0.43, 6.39; p=0.4645). Ambulatory patients appeared to be more likely to correctly assess that they had received idebenone treatment than non-ambulatory patients but logistic regression analysis including ambulatory status in the model revealed no significant effect of ambulatory status (Table 2).

For the primary analysis set, for the comparison of ambulatory versus non-ambulatory patients the odds ratio was 1.54 (95.2% CI: 0.35, 6.76; p=0.5675) and for the comparison of idebenone versus placebo the odds ratio was 1.19 (95.2% CI: 0.27, 5.27; p=0.6166). No patients were withdrawn prematurely due to recurrence or worsening of FRDA symptoms (key secondary endpoint). One patient, while randomised to idebenone, reported symptoms of low energy levels and so prematurely withdrew from the study, two weeks before the end of the first treatment cycle. No significant differences were observed between treatments for other efficacy endpoints including Investigator's assessment of treatment assignment, MFIS, 9-HPT, and CGI-C. The AIDS speech capability test revealed a statistically significant difference between the treatment groups in favour of idebenone (p=0.0446). For ICARS, the mean difference (-2.2 points) between idebenone and placebo for the analysis using observed cases was not statistically significant, but for ambulatory patients the mean difference between treatments (-6.4 points) was statistically significant (p=0.0121) in favour of idebenone (Table 3). For the Change and Status questionnaires, the majority of patients reported no worsening in all categories, irrespective of their treatment.

Safety

No patients were discontinued from study treatment prematurely due to adverse events. Adverse events considered to be drug-related were reported by 7 patients treated with idebenone and 6 patients treated with placebo. Fatigue (4 patients treated with idebenone and 1 patient treated with placebo) and falls (4 patients treated with idebenone and 2 patients treated with placebo) were the adverse events most commonly considered by the Investigator to be treatment-related.

Discussion

This randomised, double-blind, placebo-controlled, withdrawal study was set up to investigate apparently contradictory outcomes of clinical trials of idebenone in FRDA, with reports of the benefit of idebenone use on a number of parameters made by patients and treating physicians. The study included patient reported outcome measures, and patients were encouraged to draw on their previous experience of idebenone use on MICONOS to make suggestions on the study design. This is the first time that such an approach has been used in a clinical drug trial in the FRDA population.

The projected sample size for this study was 80 patients, however data from only 29 patients were available. As such, this sample size limits the power of the analyses and the conclusions that can be drawn. For the primary endpoint, no significant differences were observed on assessment of treatment between groups. In agreement with previous trials, there was some evidence that ambulatory patients were better at assessing their treatment allocation (9 of 15 ambulatory patients [60%] made a correct assessment), although no significant differences were seen between treatments[17,18]. These ambulatory patients had a shorter disease duration and may have a larger capacity for improvement[15]. It could be argued that this improvement is more noticeable since it is likely to have a greater impact on quality of life and general level of function when compared to non-ambulatory patients.

No significant differences were observed between treatment groups for most secondary endpoints including patient withdrawal, Investigator's assessment of treatment assignment, MFIS, 9-HPT, CGI-C and most speech assessments. The AIDS speech capability test, which was only performed in the UK Ataxia Centre as a result of the discussions with patients on study design and assessments, showed a statistically significant difference between treatments in favour of idebenone. This assessment involves articulating a series of randomly selected standardised sentences, which are then rated for intelligibility by specialists. There is limited evidence for this specific assessment in FRDA[25], however broader measures of speech intelligibility have been validated[28]. As such, we would argue that these findings warrant further investigation in larger cohorts as part of more comprehensive speech assessments. For ICARS, although the observed cases analysis showed no significant difference between idebenone and placebo for all patients, the analysis of ambulatory patients showed a statistically significant difference in favour of idebenone, although the number of patients in this subgroup was small. Of note, these group differences were not reflected in the patients' assessments of treatment received. One reason for this discrepancy could be that the duration of this study was too short for patients to appreciate

small changes. Also, patients with longer disease durations might find it difficult to appreciate these minor improvements. It is worth noting that two-month treatment cycles might be considered too short a period against which to measure any change in clinical state, particularly in slowly progressive diseases like FRDA[29,30]. However, our primary intention was not to detect changes in clinical scale scores but to base our measurements on subjective reports of symptoms including fatigue and speech. As such, we felt that we could justify these shorter treatment cycles, which were in-keeping with pre-study discussions with patients. Of note, patient assessments of treatment allocation and CGI-C were completed prior to the ICARS at study visits, and as such one might argue for a potential assessor bias whereby these allocation discussions influenced raters scores. Study treatment was well-tolerated and no clinically important safety issues were identified during the study.

In conclusion, although this study failed to detect any significant differences between groups on ~~the~~ primary and key secondary endpoints, a number of relevant observations can be highlighted that should ~~serve to~~ inform subsequent drug trials in FRDA patients. Of particular interest are the differences in self-assessment between ambulant and non-ambulant patients, and the potential clinical benefits of idebenone in ambulatory patients, as measured by the ICARS. As such, future trials should consider ambulatory status as a group stratification variable. In addition, subsequent trials should include comprehensive speech assessments since idebenone use was associated with a significant improvement in intelligibility in a small subgroup of patients. We believe that semi-quantitative scales, including those measuring fatigue, should be validated for FRDA patients, so that they can be reliably used in future trials. Furthermore, the viability of subjective reports as endpoints is important to consider, particularly in the context of short-term assessment periods and small changes in clinical symptoms and signs. Several approaches to disease modification in FRDA have now been evaluated in clinical trials (Table 4, reference 31), with clinical scales often forming the basis of neurological endpoints. We feel that this study demonstrates an innovative attempt at capturing data on symptomatic benefits, by incorporating patient suggestion into study design, and utilising patient-reported outcomes amongst some of the key study endpoints. We hope this design will help inform future trials so that patient's experiences of symptoms can be reliably measured and analysed in the context of novel treatments.

Acknowledgements

We would like to thank Dr Will Andrews, Dr Gunther Meier and Dr Günther Metz of Santhera Pharmaceuticals, for their support and guidance throughout the study. We are grateful to Ataxia UK and to all the patients who participated in the study, and took part in the discussions on study design.

Conflict of Interest and Sources of Funding Statement

The study was funded by Santhera Pharmaceuticals. Paola Giunti and Arron Cook work at University College London Hospitals/University College London which receives a proportion of its funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. Paola Giunti received funding from the EC (HEALTH-F2-2010-242193; FP7 Grant) and NIHR, Department of Health. Sylvia Boesch received funding from European Friedreich Ataxia Consortium for Translational Studies (EFACTS), FP7 Health (HEALTH-F2-2010-242193). Suzette Heck and Ewout Brunt have no financial disclosures or conflicts of interest to declare. Thomas Klockgether receives/has received research support from the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF), the Robert Bosch Foundation and the European Union (EU). He serves on the editorial board of The Cerebellum and the Journal of Neurology. He has received consulting fees from Biohaven, ICON Clinical Research and Atheneum. Ludger Schöls receives funding from the EC (FP7 grant to Neuromics, F5-2012-305121), the Deutsche Forschungsgemeinschaft (DFG, grant SCHO754/5-2), the German Ministry for Education and Research (BMBF, JPND grant 01ED16028), the HSP-Selbsthilfegruppe Deutschland e.V. and the Förderverein für HSP-Forschung e.V. Angela Schulz has received research support from BioMarin, where she works as a consultant.

Data Sharing

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Schulz JB, Boesch S, Bürk K, et al. **Diagnosis and treatment of Friedreich ataxia: a European perspective.** *Nature Reviews Neurology* 2009;5(4):222-234.

2. Dürr A, Cossee M, Agid Y, et al. **Clinical and genetic abnormalities in patients with Friedreich's ataxia.** *New England Journal of Medicine* 1996;335(16):1169-1175.

3. 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(5254):1423-1427.

4. Pandolfo M, Pastore A. **The pathogenesis of Friedreich ataxia and the structure and function of frataxin.** *Journal of Neurology* 2009;256(Suppl)1:9-17.

5. Delatycki MB, Camakaris J, Brooks H, et al. **Direct evidence that mitochondrial iron accumulation occurs in Friedreich ataxia**. *Annals of Neurology* 1999;45(5):673-675.

6. Cavadini P, O'Neill HA, Benada O, Isaya G. **Assembly and iron-binding properties of human frataxin, the protein deficient in Friedreich ataxia.** *Human Molecular Genetics* 2002;11(3):217-227.

7. Puccio H, Simon D, Cossée M, et al. **Mouse models for Friedreich ataxia exhibit cardiomyopathy, sensory nerve defect and Fe-S enzyme deficiency followed by intramitochondrial iron deposits.** *Nature Genetics* 2001;27(2):181-186.

8. Pandolfo M. **Friedreich ataxia: the clinical picture.** *Journal of Neurology* 2009;Suppl. 1:3-8.

9. James AM, Cocheme HM, Smith R, Murphy MP. **Interactions of mitochondria-targeted and untargeted ubiquinones with the mitochondrial respiratory chain and reactive oxygen species.** *Journal of Biological Chemistry* 2005;280:21295-21312.

10. Hausse AO, Aggoun Y, Bonnet D, et al. **Idebenone and reduced cardiac hypertrophy in Friedreich's ataxia.** *Heart* 2002;87(4):346-349.

11. Buyse G, Mertens L, Di Salvo G, et al. **Idebenone treatment in Friedreich's ataxia: neurological, cardiac, and biochemical monitoring.** *Neurology* 2003;60(10):1679-1681.

12. Ribaï P, Pousset F, Tanguy ML, et al. **Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up.** *Archives of Neurology* 2007;64(4):558-564.

13. Pineda M, Arpa J, Montero R, et al. **Idebenone treatment in paediatric and adult patients with Friedreich ataxia: long-term follow-up.** *European Journal of Paediatric Neurology* 2008;12(6):470-475.

14. Artuch R, Aracil A, Mas A, Colomé C, Rissech M, Monrós E, Pineda M. **Friedreich's ataxia: idebenone treatment in early stage patients.** *Neuropaediatrics* 2002;33(4):190-193.

15. Mariotti C, Solari A, Torta D, Marano L, Fiorentini C, Di Donato S. **Idebenone treatment in Friedreich patients: one-year-long randomized placebo-controlled trial.** *Neurology* 2003;60(10):1676-1679.

16. Brandsema JF, Stephens D, Hartley J, Yoon G. **Intermediate-dose idebenone and quality of life in Friedreich ataxia.** *Paediatric Neurology* 2010;42(5):338-342.

17. Di Prospero NA, Baker A, Jeffries N, Fischbeck KH. **Neurological effects of high-dose idebenone in patients with Friedreich's ataxia: a randomised, placebo-controlled trial.** *Lancet Neurology* 2007;6(10):878-886.

18. Meier T, Perlman SL, Rummey C, Coppard NJ, Lynch DR. **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.** *Journal of Neurology* 2012;259(2):284-291.

19. Purks JL, Wilhelm EE, Shoulson I, et al. **Inaugural Conference on Incorporating Patient-Reported Outcomes and Patient Preference Information into Clinical Research, Clinical Care, and Risk-Benefit Assessments for Neurodegenerative Diseases.** *Patient* 2017;10(5):541-544. doi: 10.1007/s40271-017-0257-5.

20. Tai G, Corben LA, Yiu EM, et al. **A longitudinal study of the SF-36 version 2 in Friedreich ataxia.** *Acta Neurologica Scandinavica* 2017;136(1):41-46.

21. Yiu EM, Tai G, Peverill RE, Lee KJ, et al. **An open-label trial in Friedreich ataxia suggests clinical benefit with high-dose resveratrol, without effect on frataxin levels.** *Journal of Neurology* 2015;262(5):1344-53.

22. Schiehser DM, Ayers CR, Liu L, Lessig S, Song DS, Filoteo JV. **Validation of the Modified Fatigue Impact Scale in Parkinson's disease.** *Parkinsonism and Related Disorders* 2012;19(3):335-338.

23. Lynch DR, Farmer JM, Tsou AY, et al. **Measuring Friedreich ataxia: complementary features of examination and performance measures.** *Neurology* 2006;66(11):1711-1716.

24. Folker JE, Murdoch BE, Cahill LM, Rosen KM, Delatycki MB, Corben LA, Vogel AP. **Articulatory kinematics in the dysarthria associated with Friedreich's ataxia.** *Motor Control* 2011;15(3):376-389.

25. Singh A, Epstein E, Myers LM, Farmer JM, Lynch DR. **Clinical measures of dysarthria in Friedreich Ataxia.** *Movement Disorders* 2010;25(1):108-111.

26. Brendel B, Ackermann H, Berg D, et al. **Friedreich ataxia: dysarthria profile and clinical data.** *The Cerebellum* 2013;12(4):475-484.

27. Metz G, Coppard N, Cooper JM, et al. **Rating disease progression of Friedreich's ataxia by the International Cooperative Ataxia Rating Scale: analysis of a 603-patient database.** *Brain* 2013;136(1):259-268.

28. Eigentler A, Rhomberg J, Nachbauer W, et al. **The scale for the assessment and rating of ataxia correlates with dysarthria assessment in Friedreich's ataxia.** *Journal of Neurology* 2012;259(3):420-6.

29. Reetz K, Dogan I, Costa AS, et al. **Biological and clinical characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS) cohort: a cross-sectional analysis of baseline data.** *Lancet Neurology* 2015;14(2):174-182.

30. Reetz K, Dogan I, Hilgers RD, et al. **Progression characteristics of the European Friedreich's Ataxia Consortium for Translational Studies (EFACTS): a 2 year cohort study.** *Lancet Neurology* 2016;15(13):1346-1354.

31. Cook, A, Giunti P. **Friedreich's ataxia: clinical features, pathogenesis and management.** *British Medical Bulletin* 2017;124(1):19-30.