RESEARCH ARTICLE

Results of a randomized double-blind study evaluating luvadaxistat in adults with Friedreich ataxia

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Abstract

Objectives: Friedreich ataxia (FRDA) is a rare disorder with progressive neurodegeneration and cardiomyopathy. Luvadaxistat (also known as TAK-831; NBI-1065844), an inhibitor of the enzyme D-amino acid oxidase, has demonstrated beneficial effects in preclinical models relevant to FRDA. This phase 2, randomized, double-blind, placebo-controlled, parallel-arm study evaluated the efficacy and safety of oral luvadaxistat in adults with FRDA. **Methods:** Adult patients with FRDA were randomized 2:1:2 to placebo, luvadaxistat 75 mg twice daily (BID), or luvadaxistat 300 mg BID for 12 weeks. The primary endpoint changed from baseline at week 12 on the inverse of the time to complete the nine-hole peg test (9-HPT^{-1}), a performance-based measure of the function of the upper extremities and manual dexterity. Comparisons between luvadaxistat and placebo were made using a mixed model for repeated measures. **Results:** Of 67 randomized patients, 63 (94%) completed the study. For the primary endpoint, there was no statistically significant difference in change from baseline on the 9-HPT^{-1} (seconds^{-1}) at week 12 between placebo (0.00029) and luvadaxistat 75 mg BID (−0.00031) or luvadaxistat 300 mg BID (−0.00059); least squares mean differences versus placebo (standard error) were −0.00054 (0.000746) for the 75 mg dose and −0.00069 (0.000616) for the 300 mg dose. Luvadaxistat was safe and well tolerated; the majority of reported adverse events were mild in intensity. **Interpretation:** Luvadaxistat was safe and well tolerated in this cohort of adults with FRDA; however, it did not demonstrate efficacy as a treatment for this condition.

Introduction

Friedreich ataxia (FRDA) is a rare hereditary disorder that affects approximately 5000 individuals in the United States.[1-3] FRDA is caused by mutations in the frataxin (*FXN*) gene. *FXN* is involved in the assembly of iron-sulfur clusters in the mitochondrial matrix; deficiency in *FXN* leads to mitochondrial dysfunction at the cellular level and results in neurodegeneration, cardiomyopathy, diabetes mellitus, and skeletal deformities.[1,4-10] Neurological symptoms that are prominent and highly penetrant include limb ataxia and dysarthria. Ataxia includes a sensory ataxia

component, which is associated with the loss of proprioceptive function and sensory neuropathy, as well as visual and hearing impairments.[4] A progressive destruction of the cerebellar dentate nucleus and the corticospinal tract can also be observed and contribute to cerebellar ataxia.[4]

While the initial symptoms of FRDA can present anytime between childhood and adulthood, a childhood onset is typically associated with a more rapid progression.[9] A progressive loss of coordination leads to motor incapacitation and, eventually, the full-time use of a wheelchair.[10] The most common symptoms that affect daily living included difficulties with walking or unsteady

gait; lack of balance and coordination; and inability to control movement in upper extremities.[11]

While a variety of agents are in development to reduce the mitochondrial dysfunction associated with *FXN* deficiency or to increase the levels of *FXN* within cells, no therapy is currently approved to treat FRDA.[8,12,13] Patients are currently managed with agents targeting their non-neurologic disorders, including cardiac arrhythmias and diabetes.[13,14] Unfortunately, effective treatments for the neurologic symptoms of FRDA, such as impaired coordination, dexterity, and speech, are lacking.[13] Consequently, there is an urgent need for interventions that address the neurological component of this progressive, multi-system disease.

Luvadaxistat (also known as TAK-831; NBI-1065844) is a highly selective and potent inhibitor of the D-amino acid oxidase (DAAO),[15] which mediates D-serine breakdown,[16,17] with IC_{50} of 3.6 ng/ml of human DAAO enzyme. D-serine is an N-methyl-D-aspartate-type glutamate receptor co-agonist and an agonist of the glutamate receptor delta 2, and it is highly expressed in the cerebellum.[17,18] D-serine is a critical mediator of the glutamate receptor-dependent functions of the cerebellum.[19]

Luvadaxistat increased the D-serine level in the cerebellum in a genetic mouse model (YG8sR) of FRDA.[15,20] In this model, improvements in the performance of a beam-crossing task after administration of luvadaxistat were observed.[15,20] Given the need to identify potentially effective treatments for patients with ataxias, we conducted a proof-of-concept study to evaluate the efficacy and tolerability of oral luvadaxistat in adults with FRDA.

The safety, tolerability, and PK of luvadaxistat have been evaluated in multiple phase 1 clinical studies in healthy subjects. Luvadaxistat was safe and well tolerated in single and multiple oral doses up to 1200 mg.[16] Both single and multiple dosing regimens showed dose-dependent luvadaxistat exposure increases in plasma and CSF. The estimated CSF to plasma concentration ratio is in the range of 0.62% to 1.72%.[16] At the 600 mg daily dose, TAK-994 concentration in CSF maintains 12 hours above IC50 of DAAO inhibition. The inhibitory effect of luvadaxistat on DAAO in humans was also demonstrated by means of dose-dependent increases in plasma and CSF D-serine levels, reaching nearly maximal D-serine elevation (approximately 150%) at 600 mg daily dose or higher. In both plasma and CSF, the elevation in D-serine persisted over the entire dosing intervals after multiple doses.

Methods

Study design

This study (ClinicalTrials.gov identifier, NCT03214588) was a phase 2, randomized, double-blind, placebo-controlled, parallel-arm study designed to evaluate the efficacy, tolerability, pharmacodynamic (PD) effects, and pharmacokinetics (PK) of two dose levels of oral luvadaxistat in adults with FRDA. The study was conducted from November 2017 through January 2019 in six specialized academic neurological centers in the USA with expertise in FRDA. This study was conducted according to the ICH E6 Good Clinical Practice guideline, with informed consent and under the oversight of Institutional Review Boards.

Patients were included if they were 18–55 years of age, had genetically confirmed FRDA, and had a disease stage of 2 to 5 as determined by a FRDA functional disability stage.

Patients were randomized in approximately a 2:1:2 ratio to receive placebo, a dose of luvadaxistat 75 mg twice daily (BID), or luvadaxistat 300 mg BID for 12 weeks (Fig. 1).[21] Permuted-block randomization was used, stratified by ambulatory status (ambulatory vs non-ambulatory) to balance the arms in a study population with heterogeneous disease stages. The randomization scheme was generated by a designee of the study sponsor and was stored in a secured area. At the first and subsequent visits in which drugs were dispensed, study personnel accessed an interactive response technology (IRT) system to request study drug for a subject. The IRT then provided the medication identification number of the study drug to be dispensed.

The selected doses of luvadaxistat were based on PK data from two phase 1 dose escalation studies (NCT02566759 and NCT03224325). A PK/PD modeling analysis showed that the higher dose regimen resulted in steady-state exposures associated with peak target occupancy of DAAO of > 90%.[15] The lower dose was chosen to provide at least a three-fold exposure difference from the higher dose to understand the dose–response relationship and potentially identify the no-effect dose.[15]

Outcomes and assessments

The nine-hole peg test (9-HPT) is a quantitative performance-based measure of the function of the upper extremities and manual dexterity. The primary endpoint changed from baseline on the inverse of the time to complete the 9-HPT (9-HPT^{-1}) at week 12 compared with placebo. Since it was not known whether fatigue and sequence of administration of the 9-HPT would affect the scores, two sets of assessments were conducted at each visit (one near the start and one at least 1 h later), with each set consisting of two trials for each hand. The first set of assessments was the primary endpoint.

The study included several neurologic and functional assessments as secondary endpoints, including changes from baseline compared with placebo on the modified
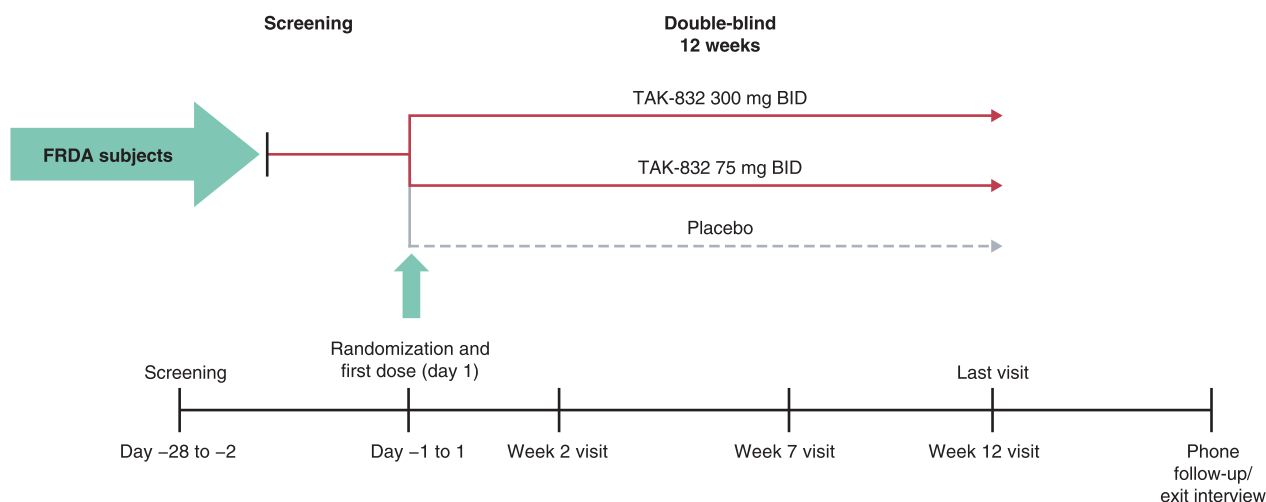
Figure 1. Study design. BID, twice daily; FRDA, Friedreich ataxia.

Friedreich Ataxia Rating Scale neurological examination (mFARS-neuro) total score, which provides a neurological functional assessment of patients;[21-23] a timed 25-foot walk (T25FW) for ambulatory participants only,[24,25] and the activities of daily living (ADL) component of the Friedreich Ataxia Rating Scale (FARS).[26]

In addition, patient assessments of disease severity and global improvement were measured using the Patient Global Impression-Severity scale (PGI-S), which requires patients to rate their disease severity on a five-point scale ranging from normal to extremely severe, and the Patient Global Impression-Improvement scale (PGI-I), which measures improvement due to treatment on a seven-point scale ranging from very much improved to very much worse. The PGI-S was used to measure both global severity and upper extremity functional severity separately, while the PGI-I also measured global improvement and upper extremity functional improvement separately. Investigators assessed disease severity and global improvement using the Clinical Global Impression-Severity scale (CGI-S), which measures illness severity on a seven-point scale, and the Clinical Global Impression-Improvement scale (CGI-I), which measures global improvement from treatment initiation on a similar seven-point scale. Similar to the patient-reported assessments described above, the CGI-S measured global severity and upper extremity functional severity and the CGI-I measured both global improvement and upper extremity functional improvement.

Other secondary endpoints included visual acuity, evaluated using low-contrast letter acuity (LCLA) testing with Sloan charts. PK and PD parameters, including measurements of plasma concentrations of luvadaxistat and D-serine, were also assessed. Lastly, exit interviews were conducted within 7 days of each patient's completion of the study to determine their overall experience with FRDA, focusing on the symptoms most meaningful to patients, as well as their perceived changes in FRDA symptoms related to study treatment.[27] These 60-minute interviews were conducted by interviewers who were blinded to the patients' treatment groups, and were semi-structured, recorded, transcribed, and analyzed using a coding framework developed from concepts of interests.[27]
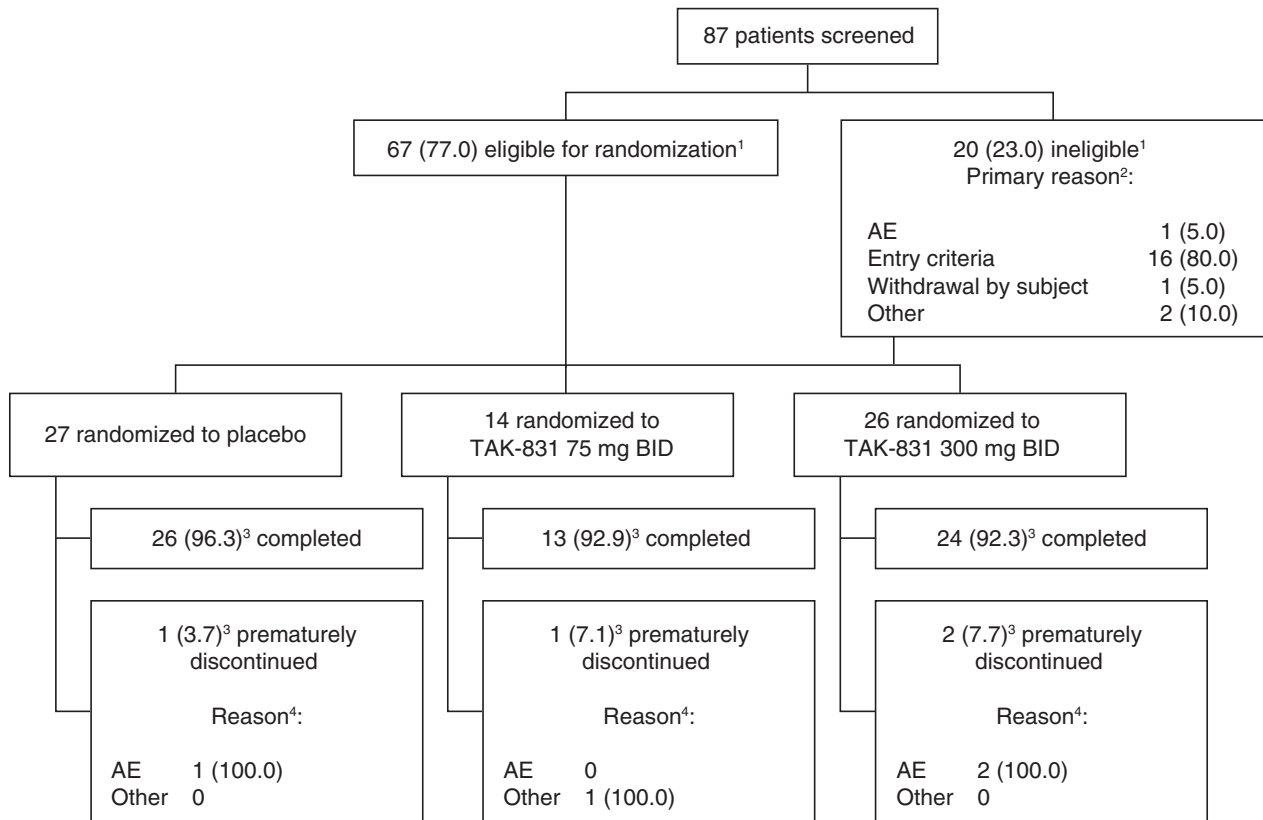
Safety, tolerability, and pharmacokinetics, and plasma D-serine levels were also measured.

Statistical analysis

Assuming an effect size (Cohen's d) of 0.6 for each dose of luvadaxistat, it was determined that a sample size of 60 evaluable patients would provide 77% power for at least one dose of luvadaxistat to be deemed superior to placebo and 54% power for both doses (overall $\alpha = 0.10$, one-sided). Comparisons between luvadaxistat and placebo were made overall time points using a mixed model for repeated measures with baseline 9-HPT^{-1} as a covariate; pooled site, visit, treatment, and ambulation status as fixed factors; and treatment-by-visit and baseline 9-HPT^{-1}-by-visit interactions. Multiplicity was controlled using the Holm method. Qualitative interviews were analyzed by generating concept-frequency tables in ATLAS II by tabulating the number of patients reporting each concept.[27]

Results

Of 67 patients who were randomized, 63 (94.0%) completed the study (Fig. 2). Patients were demographically well balanced across treatment arms (Table 1). Overall,

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                          │  87 patients screened   │
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     ┌──────────────────────────────┐   ┌──────────────────────────────────┐
     │ 67 (77.0) eligible for        │   │ 20 (23.0) ineligible[1]          │
     │ randomization[1]              │   │ Primary reason[2]:               │
     └──────────────────────────────┘   │                                  │
                                         │ AE                    1 (5.0)    │
                                         │ Entry criteria        16 (80.0)  │
                                         │ Withdrawal by subject 1 (5.0)    │
                                         │ Other                 2 (10.0)   │
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27 randomized to placebo	14 randomized to TAK-831 75 mg BID	26 randomized to TAK-831 300 mg BID
26 (96.3)[3] completed	13 (92.9)[3] completed	24 (92.3)[3] completed
1 (3.7)[3] prematurely discontinued Reason[4]: AE 1 (100.0) Other 0	1 (7.1)[3] prematurely discontinued Reason[4]: AE 0 Other 1 (100.0)	2 (7.7)[3] prematurely discontinued Reason[4]: AE 2 (100.0) Other 0

Figure 2. Patient disposition. Data represent the number of patients (%). All dosing is BID. Denominator is the number of patients [1]screened, [2]ineligible, [3]randomized, and [4]discontinued. AE, adverse event; BID, twice daily.

Table 1. Patient demographics.

Characteristic	Placebo (n = 27)	Luvadaxistat 75 mg BID (n = 14)	Luvadaxistat 300 mg BID (n = 26)
Mean age at screening, years (SD)	32.5 (11.0)	31.1 (11.3)	29.6 (8.9)
Sex, n (%)			
Female	17 (63.0)	5 (35.7)	15 (57.7)
Male	10 (37.0)	9 (64.3)	11 (42.3)
Mean body mass index, kg/m² (SD)	24.9 (4.9)	24.9 (4.4)	23.0 (3.9)
Ambulation status, n (%)			
Ambulatory	12 (44.4)	6 (42.9)	12 (46.2)
Non-ambulatory	15 (55.6)	8 (57.1)	14 (53.8)

BID, twice daily; SD, standard deviation.

the mean age was 31 years (range 18–55 years) and 37 patients (55%) were female.

For the primary endpoint, there was no statistically significant difference in change from baseline on the 9-HPT^{-1} at week 12 between placebo (0.00029) and luvadaxistat 75 mg BID (−0.00031) or luvadaxistat 300 mg BID (−0.00059) (Table 2). Differences in the least squares mean versus placebo (standard error) were −0.00054 (0.000746) for the 75 mg dose and −0.00069 (0.000616) for the 300 mg dose. The first and second assessments of performance on the 9-HPT^{-1} at each study visit produced similar results (Fig. 3).

Among the secondary endpoints, for the change in mFARS-neuro, all treatment arms showed a trend toward less impairment after 12 weeks, but the luvadaxistat arms did not differ statistically from placebo (Table 2). The luvadaxistat arms also did not statistically separate from placebo on the T25FW test, FARS ADLs, or PGI-S (Table 3). No statistically significant between-group differences in LCLA test scores or changes in CGI-I or CGI-S were observed. With respect to PK and PD, patients in the luvadaxistat 75 mg BID and 300 mg BID groups achieved the targeted luvadaxistat exposure (Table 4) and the expected elevations in plasma D-serine levels at steady-state (Table 5), as seen previously in healthy participants. Luvadaxistat plasma concentrations over time, an exploratory endpoint, are summarized in Table 4. The peak and trough plasma concentrations of luvadaxistat at the steady-state in patients were estimated at 1–2h post

Table 2. 9-HPT^{-1} and mFARS-neuro scores.

	Placebo (n = 27)	Luvadaxistat 75 mg BID (n = 14)	Luvadaxistat 300 mg BID (n = 26)
Mean 9HPT at baseline	66.37 (29.62)	79.64 (42.93)	66.43 (27.22)
9-HPT^{-1} (1/seconds)			
Baseline, mean (SD)	0.01711 (0.005489)	0.01571 (0.006871)	0.01778 (0.007747)
Mean at week 12 (SD)[1]	0.01798 (0.004780)	0.01538 (0.005804)	0.01750 (0.008345)
Mean change from baseline at week 12 (SD)	0.00029 (0.003071)	−0.00031 (0.001033)	−0.00059 (0.001611)
Difference in LS mean (SE) vs placebo at week 12	—	−0.00054 (0.000746)	−0.00069 (0.000616)
Adjusted one-sided p value vs placebo	—	1.00	1.00
mFARS-neuro total score			
Baseline, mean (SD)	50.83 (13.55)	51.01 (13.64)	51.12 (13.27)
Mean at week 12 (SD)[1]	46.79 (12.75)	49.27 (14.75)	50.20 (13.69)
Mean change from baseline at week 12 (SD)	−2.95 (3.14)	−1.00 (3.37)	−1.43 (3.77)
Difference in LS mean (SE) vs placebo at week 12	—	2.02 (1.27)	2.11 (1.05)
Adjusted one-sided p value vs placebo	—	0.942	0.975

A larger 9-HPT^{-1} score indicates better function; a negative change in 9-HPT^{-1} indicates worsened function. A negative change in mFARS-neuro indicates improvement.

9-HPT, nine-hole peg test; 9-HPT^{1}, inverse of the time in seconds to complete the nine-hole peg test; BID, twice daily; LS, least-squares; mFARS-neuro, modified Friedreich Ataxia Rating Scale neurological examination; SD, standard deviation; SE, standard error.

[1]At week 12, n = 24 for placebo, n = 12 for luvadaxistat 75 mg BID, and n = 24 for luvadaxistat 300 mg BID.
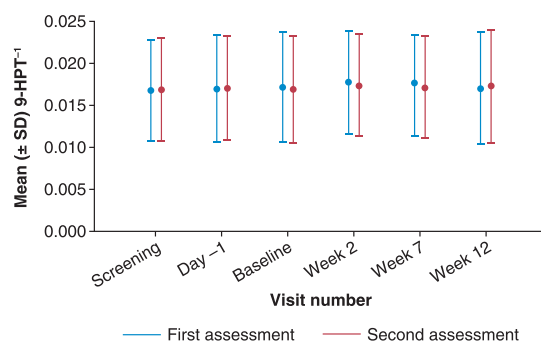
Figure 3. Mean 9-HPT^{-1} at first and second assessments at each visit for pooled treatment arms. 9-HPT^{-1}, inverse of the time to complete the nine-hole peg test; SD, standard deviation.

dose on week 2 and 4–8 h post dose on week 7 and week 12, respectively. The mean luvadaxistat concentration was 183.2 ng/ml for the 75 mg BID group and 1063 ng/ml for the 300 mg BID group after 1–2 h post dose at week 2. The mean luvadaxistat concentration after 4–8 h post dose at week 7 and week 12 were consistent (52.8–59.8 ng/ml for the 75 mg BID group and 312–340 ng/ml for the 300 mg BID group).

The changes from baseline to weeks 2, 7, and 12 on luvadaxistat plasma D-serine and L-serine levels, and ratios of D-serine to total serine after treatment with luvadaxistat, compared with placebo, were also determined as exploratory endpoints. At week 12, the mean increases from baseline in plasma D-serine and D-serine to total serine ratios were statistically significantly greater than placebo for both doses of luvadaxistat (Table 5). The mean plasma D-serine increases from the baseline were 65.6 ng/ml for the 75 mg BID group and 62.5 ng/ml for the 300 mg BID group, suggesting the plateau of D-serine elevation in the dose range.

To assess patients' experience with FRDA, 65 patients (placebo, n = 27; luvadaxistat 75 mg BID, n = 12; luvadaxistat 300 mg BID, n = 26) were interviewed. More than 80% of patients who were enrolled in the trial reported experiencing symptoms related to FRDA, including difficulties with walking or unsteady gait (100%); lack of balance and coordination (100%); inability to control movement in upper extremities (92%); speech difficulties (89%); fatigue (88%); and inability to control movement in the lower extremities (85%). Symptoms that most negatively affected daily life included: difficulties with walking or gait (65%); lack of balance or coordination (45%); inability to control movement in upper extremities (35%); fatigue/tiredness/lack of energy (31%); and difficulty speaking or slurred speech (22%) (Fig. 4). Areas of impact considered to be the most important to patients were difficulties in activities that require the ability to balance or coordinate (31%), engaging in physically demanding activities (28%), walking or walking properly (28%), having energy, and not being fatigued (27%), and communicating or speaking properly (23%) (Fig. 5 and Table S1). In addition, the most commonly reported functional challenges for patients included: the inability to perform household chores (91%); the inability to stand unassisted (89%); the inability to engage in physical

Table 3. Other secondary endpoints.

	Placebo (n = 27)	Luvadaxistat 75 mg BID (n = 14)	Luvadaxistat 300 mg BID (n = 26)
T25FW: change from baseline at week 12 (seconds)[1]			
Patients, n	11	5	10
Mean (SD)	−0.29 (0.73)	1.10 (2.57)	−1.25 (3.27)
Difference in LS mean (SE) vs placebo at week 12	—	2.18 (1.08)	0.78 (0.82)
One-sided p value vs placebo	—	0.972	0.825
FARS ADLs score: change from baseline at week 12[2]			
Patients, n	24	12	24
Mean (SD)	−0.40 (2.62)	−0.29 (2.19)	−0.52 (2.02)
Difference in LS mean (SE) vs placebo at week 12	–	0.24 (0.82)	0.37 (0.68)
One-sided p value vs placebo	—	0.616	0.708
PGI-S: change from baseline at week 12[3]			
Patients, n	24	12	24
Patients, n (%)			
Improved	6 (25.0)	5 (41.7)	5 (20.8)
No change	16 (66.7)	6 (50.0)	19 (79.2)
Worsened	2 (8.3)	1 (8.3)	0 (0.0)
One-sided p value vs placebo	—	0.194	0.408

BID, twice daily; FARS ADLs, activities of daily living component of the Friedreich Ataxia Rating Scale; LS, least-squares; PGI-S, Patient Global Impression-Severity scale; SD, standard deviation; SE, standard error; T25FW, timed 25-foot walk.

[1]T25FW was assessed only in participants who could walk. A negative change from baseline in T25FW indicates improvement.

[2]A negative change from baseline in FARS ADLs score indicates improvement.

[3]Change pertains to upper extremity functioning.

Table 4. The plasma concentration (ng/ml) of luvadaxistat at the steady state.

	Week 2 (1–2h)	Week 7 (4–8 h)	Week 12 (4–8 h)
75 mg BID			
Patients, n	13	13	12
Mean plasma concentration, ng/ml (SD)	183.2 (147.4)	59.8 (28.3)	52.8 (21.5)
300 mg BID			
Patients, n	25	22	24
Mean plasma concentration, ng/ml (SD)	1063 (632)	312 (159)	340 (294)

BID, twice daily; SD, standard deviation.

Overall, 85% of patients on luvadaxistat had at least one treatment-emergent adverse event (TEAE), compared with 93% on placebo (Table 6). The majority of TEAEs were mild in intensity. One patient in the luvadaxistat 75 mg BID group had a TEAE of severe flank pain that was deemed to be unrelated to treatment; all other TEAEs were mild or moderate. The most frequently reported TEAEs were headache, nausea, fall, cough, oropharyngeal pain, nasal congestion, and fatigue. A total of four patients (6%) had TEAEs that led to discontinuation of the study drug. No serious TEAEs or deaths occurred in the study.

Discussion

Although this study was properly powered for the primary outcome measure and patient retention in the study was excellent, luvadaxistat did not demonstrate efficacy as measured by the 9-HPT^{-1} as primary endpoint, and secondary endpoints mFARS-neuro, T25FW, FARS ADLs, or PGI-S assessments, using the specific dosage, duration, and population/disease severity.

Although both treatment groups achieved expected luvadaxistat exposure and maximized D-serine elevation with this dosing range, treatment with luvadaxistat did not show significant clinical benefit in the primary or secondary endpoints. The complexity of FRDA and its pathophysiology may explain the failure of luvadaxistat to significantly improve FRDA symptomatology.[13] For example, the deficiency of *FXN* in FRDA affects multiple biochemical pathways. Consequently, pharmacological agents affecting downstream targets may be limited in their ability to improve symptomatology, particularly if they only act on a single neurotransmitter system,[13] i.e., a single neurological pathway is insufficient to demonstrate benefit to a wide range of patients with FRDA, particularly if those patients are in different stages of the disease.[13] Owing to these complexities, it is possible that the benefits of luvadaxistat that have been demonstrated in a

activity (88%); the inability to continue in school or work (74%); the need to depend on others to carry out regular activities (69%); and the inability to drive (69%).

Nearly two-thirds (63%) of patients reported that study treatment did not help in the management of their FRDA symptoms, and there was no difference in patient-perceived changes in symptoms between those who received luvadaxistat and patients on placebo. However, 37% of patients reported an improvement in their upper-extremity motor function and manual dexterity during the trial.

In this study, luvadaxistat was found to be safe and well tolerated in this population of patients with FRDA.

Table 5. Plasma D- and L-serine and change from baseline (µg/ml).

	Placebo n = 27	Luvadaxistat 75 mg BID n = 14	Luvadaxistat 300 mg BID n = 26
Plasma L-serine (µg/ml)			
Baseline, observed mean (SD)	10.5 (2.99)	10.5 (3.31)	11.5 (3.53)
Final/week 12 change from baseline			
Patients, n	24	12	24
Mean (SD)	0.464 (1.982)	0.817 (2.851)	0.150 (2.274)
LS mean difference (SE), luvadaxistat versus placebo		0.184 (0.696)	−0.114 (0.574)
Plasma D-serine (µg/ml)			
Baseline, observed mean (SD)	0.142 (0.0360)	0.144 (0.0283)	0.157 (0.0460)
Final/week 12 change from baseline			
Patients, n	24	12	24
Mean (SD)	0.00383 (0.02874)	0.0656 (0.0340)	0.0625 (0.0514)
LS mean difference (SE), luvadaxistat versus placebo		0.0591 (0.0136)[1]	0.0554 (0.0113)[1]
Ratio of D-serine to total serine			
Baseline, observed mean (SD)	0.0138 (0.00358)	0.0144 (0.00433)	0.0141 (0.00484)
Final/week 12 change from baseline			
Patients, n	24	12	24
Mean (SD)	−0.0004 (0.00234)	0.0048 (0.00333)	0.0052 (0.00447)
LS mean difference (SE), luvadaxistat versus placebo		0.0052 (0.00121)[1]	0.0059 (0.00100)[1]

BID, twice daily; LS, least squares; SD, standard deviation; SE, standard error.
[1]Two-sided *p* value < 0.001.
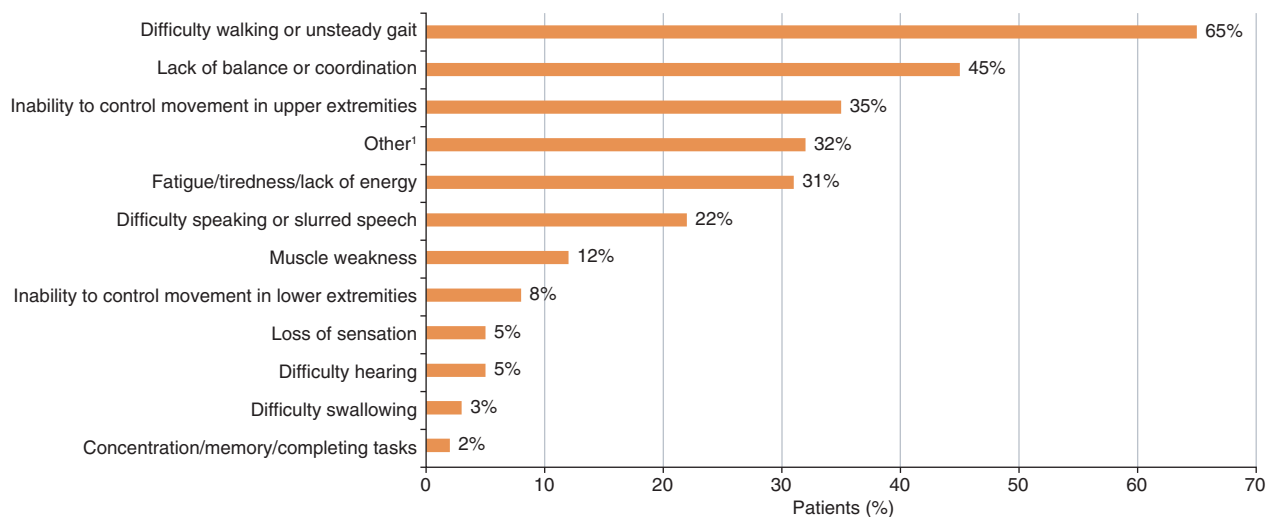
Figure 4. Symptoms that most negatively affect daily life. Note that all categories are not mutually exclusive. [1] Other includes: inability to transfer (n = 4); bladder symptoms (n = 3); need of assistance from others/independence (n = 3); mood/emotion such as stress and frustration (n = 3); inability to stand (n = 2); pain (n = 2); inability to drive (n = 1); neurological symptoms (unspecified, n = 1); mobility (unspecified, n = 1); loss of proprioception (n = 1); reduced movement speed (n = 1); and incontinence (n = 1).

preclinical genetic mouse model (increased D-serine level in the cerebellum and improved motor coordination) may not translate to clinical disease.[15,20] Therefore, combining evidence from behavioral models with data that demonstrate effects on cerebellar circuitry might be of value in the future to help to increase the confidence in translation and ultimately of identifying an effective treatment for FRDA.
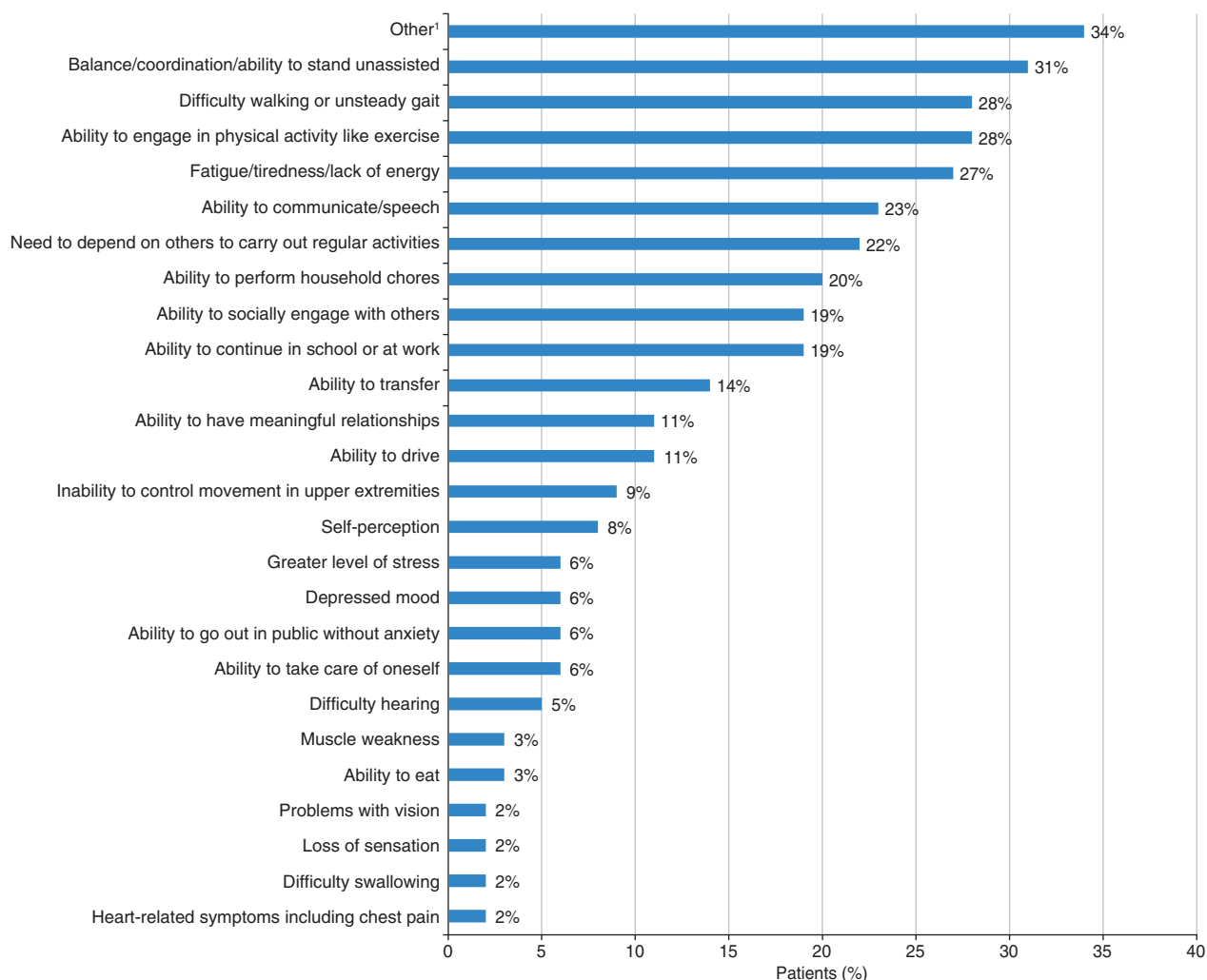
Figure 5. Areas of impact that are most important to patients. Note that all categories are not mutually exclusive. [1] Other includes: mobility/fine motor control/dexterity (unspecified, n = 4), ability to go out (unspecified, n = 4), emotional impact (unspecified/future outlook/ frustration, n = 3), ability to take care of family/take family to places/play with family (n = 3), pain (n = 2), ability to dress the way participant wants (n = 1), everyday living (unspecified, n = 1), financial impact (n = 1), ability to have children (n = 1), bladder (n = 1), travel (n = 1), ability to use bathroom (n = 1), and use of assistive device (n = 1).

Despite the failure of luvadaxistat to provide significant symptomatic relief to patients with FRDA, the study provided useful insight regarding the utility of various clinical assessments in FRDA. The lack of differences between the first and second 9-HPT assessments which are spaced at least 1 h in between at each visit suggests that the task has good intra-day stability, and that it may be less subject to the effect of fatigue than anticipated.

The study also utilized exit interviews to explore patient experiences in adults with FRDA. As expected, most patients enrolled in the trial reported that FRDA symptoms substantially affect their daily lives. While the results of our qualitative interviews indicated that the majority reported that luvadaxistat had no effect on FRDA symptoms related to their functional ability, the findings reinforced the need for treatments that will maintain, if not improve, upper extremity function related to daily activities that are essential to preserving the quality of life in patients with FRDA.

Based on the results of this study, we conclude that luvadaxistat was safe and well tolerated in adults with FRDA but is not effective as a treatment for this condition. Luvadaxistat did not demonstrate efficacy as measured by any of the neurologic and functional assessments included in our study.

Table 6. Treatment-emergent adverse events.

TEAE, n (%)[1]	Placebo (n = 27)	Luvadaxistat 75 mg BID (n = 14)	Luvadaxistat 300 mg BID (n = 26)	Luvadaxistat Overall (N = 40)
Any TEAE	25 (92.6)	10 (71.4)	24 (92.3)	34 (85.0)
Related to study drug	9 (33.3)	8 (57.1)	14 (53.8)	22 (55.0)
Not related to study drug	16 (59.3)	2 (14.3)	10 (38.5)	12 (30.0)
Mild	18 (66.7)	9 (64.3)	16 (61.5)	25 (62.5)
Moderate	7 (25.9)	0	8 (30.8)	8 (20.0)
Severe	0	1 (7.1)	0	1 (2.5)
Leading to study drug discontinuation	1 (3.7)	1 (7.1)	2 (7.7)	3 (7.5)
Serious TEAE	0	0	0	0
Death	0	0	0	0
Most frequent TEAEs (≥ 10% in either luvadaxistat arm)				
Headache	8 (29.6)	4 (28.6)	11 (42.3)	15 (37.5)
Nausea	4 (14.8)	1 (7.1)	8 (30.8)	9 (22.5)
Fall	6 (22.2)	1 (7.1)	6 (23.1)	7 (17.5)
Cough	2 (7.4)	1 (7.1)	5 (19.2)	6 (15.0)
Oropharyngeal pain	3 (11.1)	1 (7.1)	4 (15.4)	5 (12.5)
Nasal congestion	1 (3.7)	1 (7.1)	4 (15.4)	5 (12.5)
Fatigue	4 (14.8)	0	3 (11.5)	3 (7.5)
Pyrexia	0	0	3 (11.5)	3 (7.5)
Urinary tract infection	0	0	3 (11.5)	3 (7.5)

BID, twice daily; TEAE, treatment-emergent adverse event.
[1]Number of participants with at least one TEAE in the given category.

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Author Contributions

H.W., J.N., N.D., J.F. and D.L. contributed to the study design and acquisition of data. All authors contributed to analysis and interpretation of data, drafting, and review of the manuscript.

Conflicts of Interest

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Supporting Information

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

Table S1. Study participant quotes: areas of impact that are most important to patients.