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Improvement in Upright Stability Subscale of mFARS With Vatiquinone Treatment in MOVE-FA: A Phase 3, Double-blind, Placebo-controlled Trial

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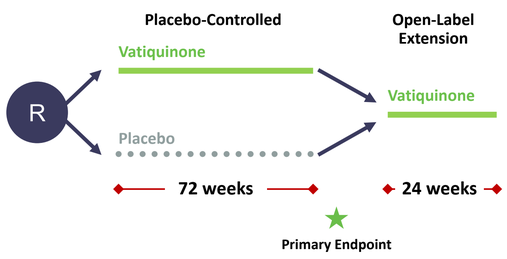
1. MOVE-FA Study Design

Friedreich Ataxia (FA), the most common inherited ataxia, is characterized by progressive neurological damage and loss of ambulation. Vatiquinone is an oral, investigational inhibitor of 15-lipoxygenase. MOVE-FA (NCT04577352), a global phase 3 trial, evaluated the safety and efficacy of vatiquinone in patients with FA. Here, we describe the results from the 72-week placebo-controlled phase.



Primary Analysis Population:
Ambulatory FA subjects 7-21 years old (n=61)
Overall Enrolled Population:
Ambulatory FA subjects ≥ 7 years old (n=62)

Primary Endpoint
Change from baseline in mFARS at 72 wks

Other Key Endpoints
Change from baseline at 72 wks:
Upright Stability Subscale
FARS-Activities of Daily Living
Modified Fatigue Impact Scale
1 minute walk test

Participating Countries
Australia, Brazil, Canada, France, Germany, Italy, Spain, New Zealand, USA

Key Inclusion Criteria

- Male or female patients aged 7 years or older
- Modified Friedreich Ataxia Rating Scale (mFARS) between 20 and 70 at baseline
- Must be able to ambulate at least 10 feet in 1 minute with or without assistance (non-wheelchair)
- FA diagnosis (homozygous for GAA repeat expansion in *FXN* gene) confirmed by clinical testing
- Difference in mFARS at screening and baseline of no more than 4 points
- Must be able to swallow capsules

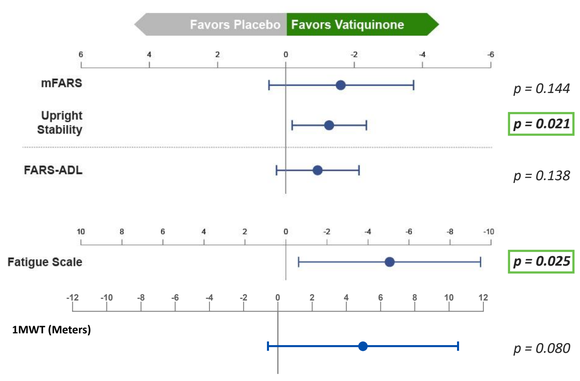
Key Exclusion Criteria

- Individuals with clinically diagnosed FA who have point mutations or deletions or other non-GAA expansions
- Previous treatment with vatiquinone
- Ejection fraction <50%
- Serum creatinine ≥1.5 x upper limit of normal at time of screening
- Uncontrolled diabetes
- Participation in any other interventional clinical trial or receipt of any investigational drug in any other clinical trial within 60 days prior to baseline visit

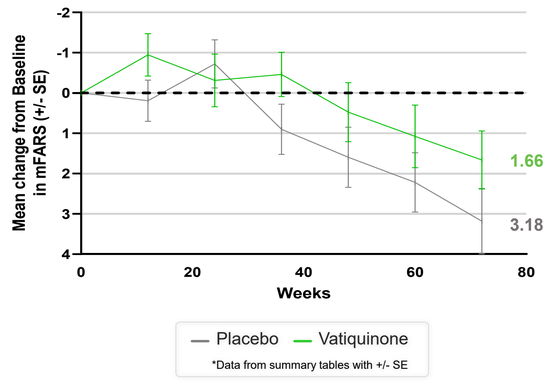
2. Topline Results from MOVE-FA

- Vatiquinone treatment benefit versus placebo was observed across the primary, secondary, and exploratory endpoints.
- In the mITT population, there was a -1.61 (p=0.144) change in mFARS at 72-weeks relative to placebo.
- Notably, there were nominally significant benefits recorded in the Upright Stability subscale (USS/FARS E) of mFARS (-1.26 [p=0.021]), a relevant metric of disease progression in younger, ambulatory FA patients, and the Modified Fatigue Impact Scale (MFIS), -5.05 (p=0.025).

Primary Analysis (mITT) Population
(LS Mean with 95% CI)



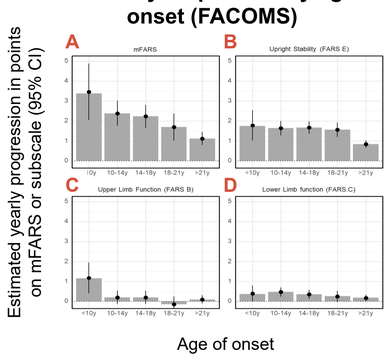
Primary Analysis (mITT) Population
(change from baseline in mFARS)



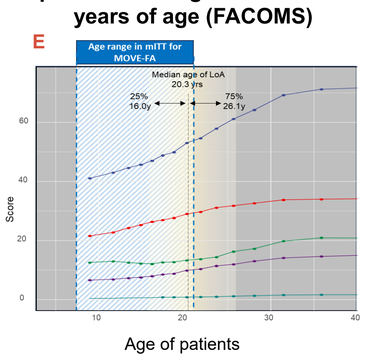
3. Disease Progression in Ambulatory FA Patients

- The FA Clinical Outcome Measures Study (FACOMS) represents the most comprehensive natural history database of patients with FA. It has enrolled more than 1300 participants to date, with data from over 6400 visits, and includes patients with FA of all ages, ages of onset, severities, and disease durations
- Patients with earlier disease onset are more likely to display rapid neurological progression as measured by mFARS. [1]
- USS assesses functions related to balance, stance, and mobility
- USS is primary and most stable driver of decline in mFARS for ambulatory patients with age of onset between 10 and 21 years of age (*Figure 3a and 3b*)
- USS has the largest contribution to overall mFARS score in typical onset, ambulatory FA subjects and is relatively stable through loss of ambulation (LoA) (*Figure 3e*) [1]

Mean annual change in ambulatory FA patients by age of onset (FACOMS)



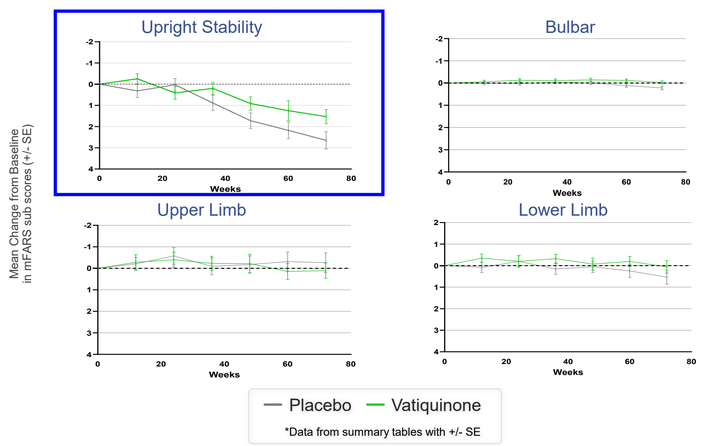
Contribution of subscales in FA patients with age of onset <15 years of age (FACOMS)



4. USS Subscale Is Only mFARS Component Sensitive to Treatment Effect in the MOVE-FA Patient Population

- USS was the only one of the four subscales of mFARS in which there was evidence of progression in the primary analysis population of MOVE-FA
- USS was the only component of the mFARS capable of registering treatment effect on the slowing of disease progression in this population

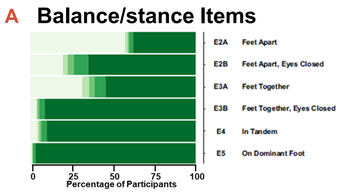
Primary Analysis Population (mITT)



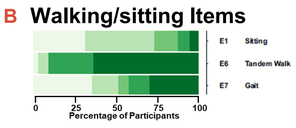
5. Stepwise Loss of Mini-milestones in FA Patients

- USS captures clinically relevant functional tasks that can be tied directly to the ability to ambulate independently
- USS includes 2 types of assessments: 6 stance/balance items (E2A, E2B, E3A, E3B, E4, and E5) and 3 walking/sitting items (E1, E6, and E7).
- Stance items demonstrate a distinct bimodal distribution where patients transition between being able to performing a task and failing the task very quickly (*Figure 5a and 5b*) [2]
- There is a unique and reproducible pattern of functional loss in the USS stance/balance items during FA progression
- These 3 steps (E2B, E3A, and E2A) act as mini-milestones of disease progression and occur in a defined and reproducible pattern that predictably precede LoA (*Figure 5c ad 5d*) [2]

A Balance/stance Items



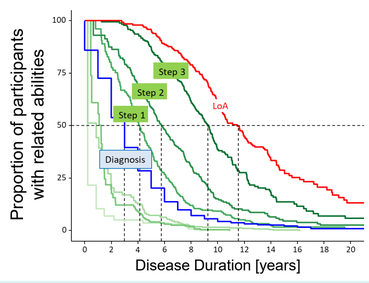
B Walking/sitting Items



C Time to Event from first signs of disease

Stance Capability/Function	Step	Time (y) (25, 75 percentiles)
Diagnosis		3.0 (1.0, 5.0)
Stance with feet apart, eyes closed (E2B)	1	4.1 (2.6, 6.1)
Stance with feet together (E3A)	2	5.8 (3.6, 8.7)
Stance with feet apart (E2A)	3	9.3 (6.7, 12.2)
LoA		11.5 (8.6, 16.2)

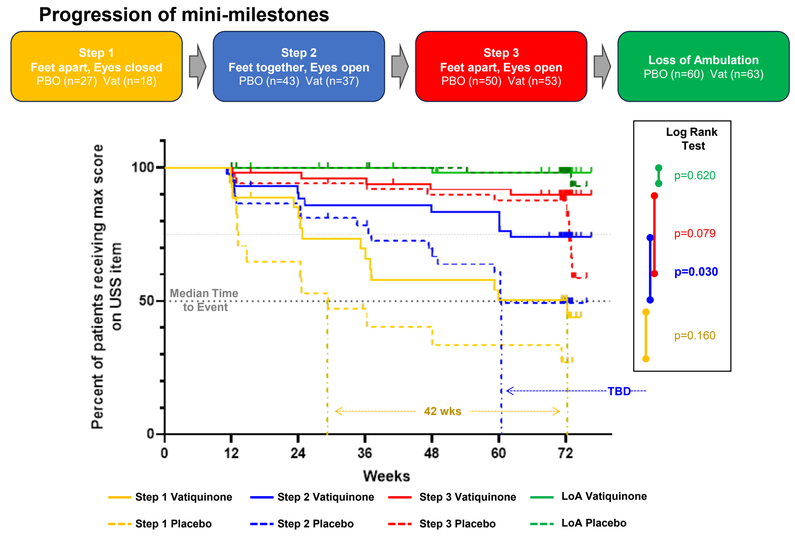
D FA Disease Mini-milestones



6. Loss of Mini-Milestones in the MOVE-FA Study

- Vatiquinone treatment delayed loss of two mini-milestones
  - Step 1 (E2B) and Step 2 (E3A)

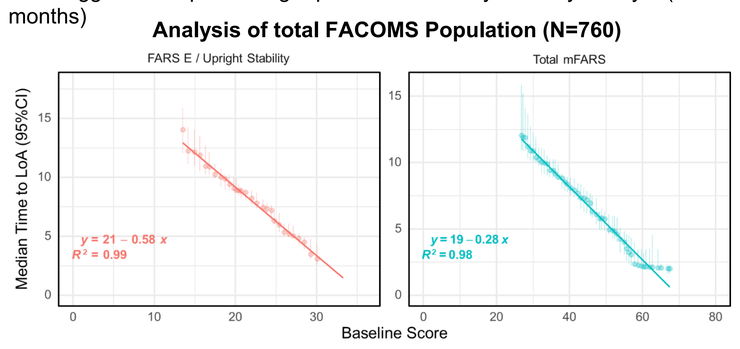
Progression of mini-milestones



7. Predictive Relationship Between mFARS/USS Score and LoA

- Long term natural history data allow the correlation of time to LoA with a subject's mFARS and USS scores at enrollment.
- Median time to LoA was estimated based on subgroups of patients with specific disability ranges (USS or mFARS scores). The resulting times were plotted versus mean baseline scores.
- The resulting slope indicates a delay in time to loss of ambulation, achieved by preserving one point in USS (or mFARS, respectively).
- This suggests that preserving 1-point in USS delays LoA by 0.58 yrs (6.9 months)

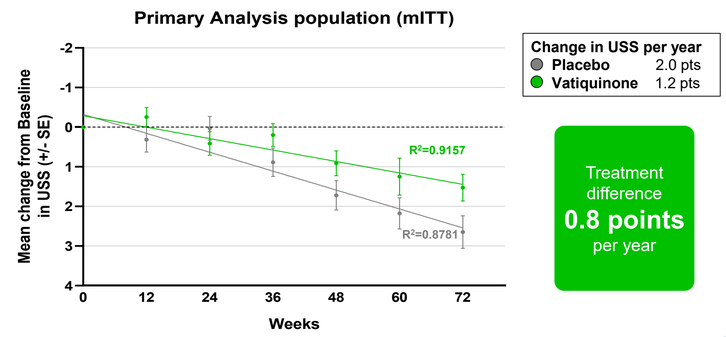
Analysis of total FACOMS Population (N=760)



8. Vatiquinone Treatment Effect on USS Predicts 40% Yearly Reduction in Progression

- Extrapolations of the rate of change in the USS were performed with longitudinal data in the mITT population
- USS changed at a rate of 2.0 points per year in the placebo group. That change is consistent with the increase in USS observed in ambulatory patients <15 years for FACOMS [1]
- Vatiquinone treatment slowed progression by 0.8 pts per year
- The 1.26 pt difference in USS at week 72 would corresponds to 9 month delay in loss of ambulation

Primary Analysis population (mITT)



CONCLUSION

- Upright Stability subscale (USS/FARS E) is the subscale of mFARS that is most sensitive to change in pediatric and adolescent ambulatory FA patients
- Vatiquinone demonstrated statistically significant treatment benefit on USS and delayed mini-milestones of disease progression associated with loss of ambulation
- The treatment benefit predicts a 40% reduction in disease progression and a delay in time to loss of ambulation of approximately 9 months

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2. Rummey, C, Farmer, JM and Lynch, DR. Predictors of Loss of Ambulation in Friedreich's Ataxia. EClinicalMedicine 2020;18:100213.

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