Interim Results from FORTITUDE™, a Randomized Phase 1/2 Trial Evaluating AOC 1020 in Adults with FSHD

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Introduction

- **Facioscapulohumeral Muscular Dystrophy (FSHD) is a rare, progressive, and often asymmetrical genetic disorder caused by the abnormal activation of the DUX4 transcription factor in skeletal muscles, triggering a cascade of events that ultimately lead to muscle degeneration and wasting.[1-3]**
- ***Del-brax*™ (AOC 1020) is an antibody-oligonucleotide conjugate (AOC) comprised of a *DUX4*-targeting siRNA conjugated to a humanized anti-transferrin receptor 1 (TfR1) antibody to facilitate delivery to muscle tissue.[4,5]**
- ***Del-brax* is being investigated for the treatment of FSHD in the FORTITUDE trial, a first-in-human, phase 1/2 randomized, double-blind, placebo-controlled trial in adult patients with FSHD.[6]**

FSHD is caused by aberrant activation of the DUX4 transcription factor. *Del-brax* is designed to correct the underlying cause of FSHD by directly targeting and silencing *DUX4* mRNA, and thus has the potential to slow or halt disease progression.

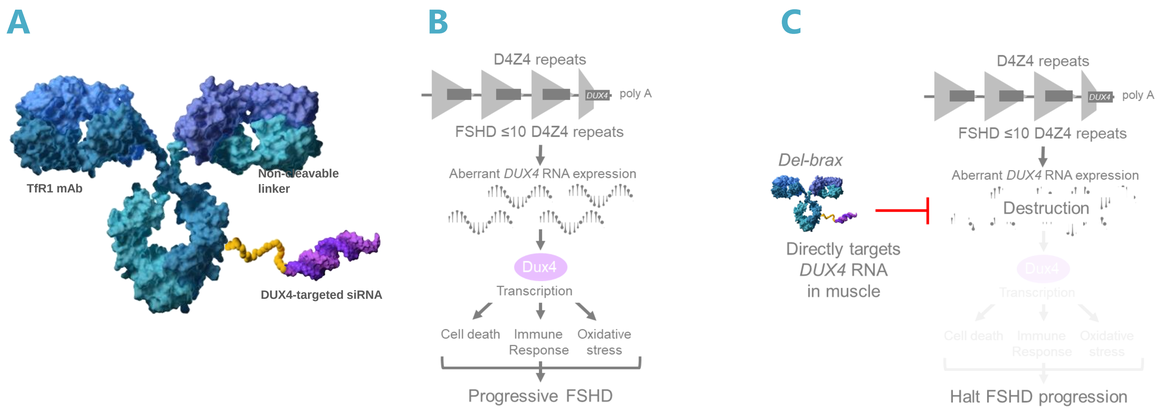


Figure 1. (**A**) Schematic of *Del-brax* (AOC 1020) comprising a humanized TfR1-targeting antibody, a non-cleavable MCC maleimide linker, and a stabilized siRNA targeting *DUX4* mRNA. (**B**) FSHD disease pathology and (**C**) *Del-brax* mechanism of action.

Study Design

- FORTITUDE (AOC 1020-CS1) is a randomized, placebo-controlled, double-blind, global trial designed to evaluate the safety and tolerability of *del-brax* in adult patients with FSHD. The trial is being conducted in four parts:
  - **Part A**: A single cohort dose titration group evaluating a 2 mg/kg dose.
  - **Part B**: A single cohort evaluating a 4 mg/kg dose.
  - **Part C**: A single cohort for biomarker analysis.
  - **Part D**: A single cohort for functional analysis.
- All participants will be followed for 12 months, and eligible participants have the option to enroll in an open-label extension (OLE) study.

The FORTITUDE trial is designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of *del-brax* in adults with FSHD.

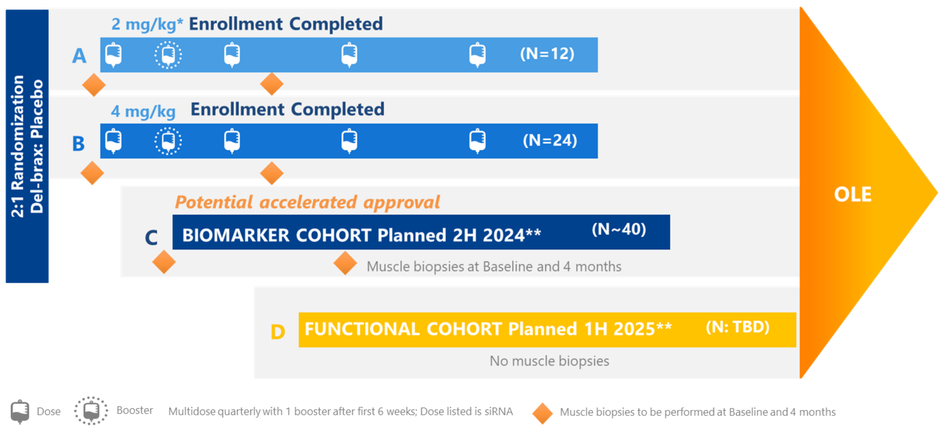


Figure 2. FORTITUDE trial design. *Participants receive a first dose of 1 mg/kg and then receive the 2 mg/kg dose for the remainder of the study. **Dose and schedule to be determined in Q3 2024.

The data herein present interim results for Cohort A (2 mg/kg) after a 4-month follow-up.

Key Information	Cohort	Primary & Secondary Objectives	Key Exploratory Objectives

• Randomized, double blinded, placebo controlled
• Age 18-65
• 12-month multiple dose treatment/follow-up period
• Biopsies at Month 4
	• Cohort A: First dose at 1 mg/kg; all subsequent doses at 2 mg/kg	• Safety and tolerability of ascending doses of *del-brax* in participants with FSHD
		• Pharmacokinetics
			• Pharmacodynamics
			  • Biomarkers
			• Measures of clinical activity
			  • Muscle strength
			  • Muscle function
			  • Muscle composition (MRI)
			• Patient and Clinician reported outcomes

Figure 3. Key information about the FORTITUDE trial design underlying the interim results presented herein. *Note: The primary and key objectives relate to cohorts A and B only.*

Interim Results

Baseline demographics were generally well matched between groups and *del-brax* demonstrated favorable safety and tolerability profile at month 4 at the two dose levels studied.

A

Baseline Demographics	Cohort A Placebo N=4 % or mean (SD)	*Del-brax* 2 mg/kg* N=8 % or mean (SD)
Sex, % Male	75	62.5
Age, years	53.5 (10.15)	51.6 (11.62)
Genetic Diagnosis, % FSHD 1	100	100
FSHD Clinical Score	9.3 (1.71)	9.3 (2.31)
D4Z4 Repeat Number	5.0 (2.45)	5.8 (2.60)
Age at First Symptom Onset (y)	25.3 (13.5)	28.6 (17.75)
Reachable Workspace RSA with weight (Q1+Q3) Reachable Workspace RSA without weight (Q1+Q3)**	0.118 (0.0661) 0.156 (0.0810)	0.088 (0.0598) 0.138 (0.0750)
Quantitative Muscle Testing - Percent Predicted Normal	33.97 (16.42)	30.14 (11.58)

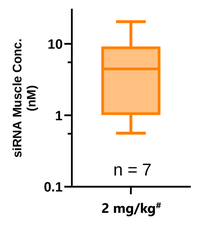
B

Subjects with ≥ 1 AE n (%)	Placebo N=13	2 mg/kg* N=8	4 mg/kg N=18
Any AE	11 (84.6%)	8 (100%)	17 (94.4%)
Related to study drug	3 (23.1%)	4 (50%)	9 (50%)
Severe AE	0	0	0
Serious AE (SAE)	0	0	0
AE leading to study discontinuation	0	0	0
AE leading to death	0	0	0

Table 1. (**A**) *Participants received a first dose of 1mg/kg and then received the 2mg/kg dose for the remainder of the study. **Participants in FORTITUDE had >50% reduction in reachable workspace in Q1 & Q3 at baseline compared to normal controls. Reachable Workspace (RWS) Relative Surface Area (RSA) (Q1+Q3) with or without weight was calculated using the average of both arms. (**B**) Data from FORTITUDE as of June 2024. The most common related AEs occurring in 2 or more participants were fatigue, rash, hemoglobin decrease/anemia, and chills.

Interim Results (Continued)

***Del-brax* showed consistent and effective delivery of siRNA to muscle.**



***Del-brax* showed consistent >50% reductions in DUX4-regulated genes as measured by multiple gene panels.**

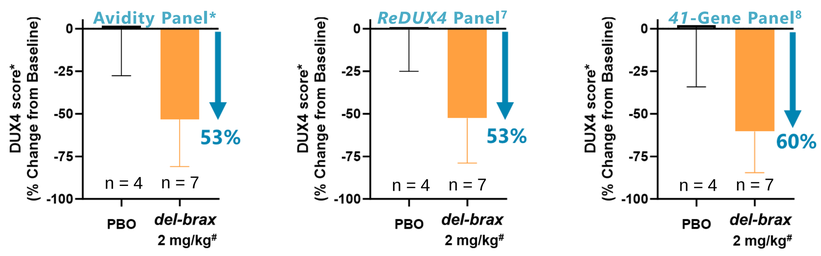
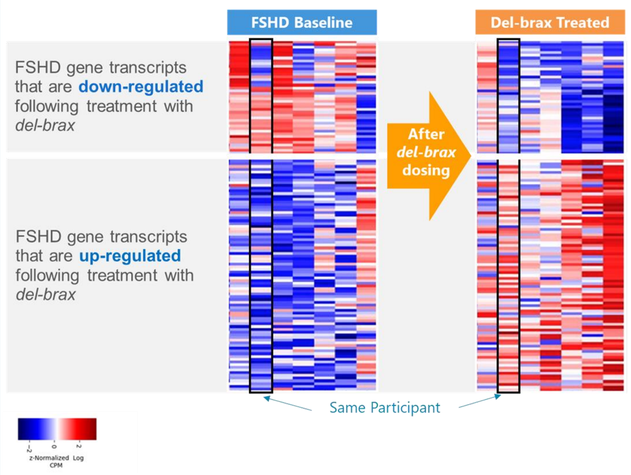


Figure 4. Muscle biopsies were collected in leg muscles (vastus lateralis, vastus medialis, tibialis anterior, gastrocnemius medialis or gastrocnemius lateralis) with fat fraction 15-40%, 4 weeks after 3rd dose. #Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92). One participant in the *del-brax*-treated group did not undergo a post-dose biopsy (n=7).

Figure 5. *DUX4* scores in MRI-informed muscle biopsy were determined utilizing qPCR (*Avidity panel [LEUTX, TRIM43, MBD3L2, and KHDC1L]) or RNA-Seq (ReDux and 41-Gene Panels). Reference genes = TBP and STATA5. *DUX4* score was calculated as cumulative expression of each gene and data are presented as change at 4M treatment relative to cohort normalized baseline. Mean ± SEM, n=7 for *del-brax* and n=4 for placebo (PBO). One participant in the *del-brax*-treated group did not undergo a post-dose biopsy. #Doses were 1 mg/kg (D1), 2 mg/kg (D43 and D92).

***Del-brax* impacts underlying FSHD disease biology.**



***Del-brax* demonstrated a consistent and confirmatory decrease in a DUX4-regulated biomarker and creatine kinase.**

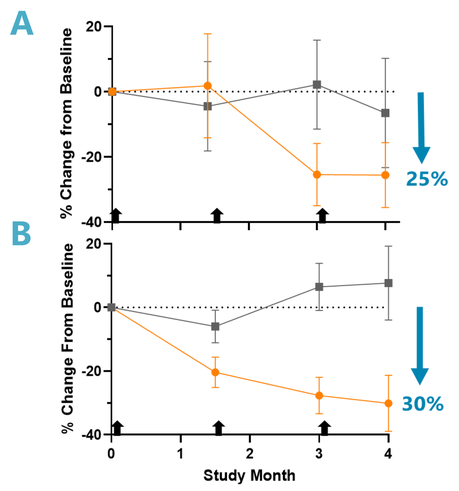


Figure 6. Each column shows a participant's disease signature at baseline compared to 1-month post-third dose. Differential gene expression (excluding DUX4-regulated genes) in muscle utilizing RNA-Seq (n=7).

Figure 7. *Del-brax* dose is shown by black arrows (1 mg/kg D1, 2 mg/kg D43 and D92). *Del-brax* demonstrated a decrease in (**A**) a novel DUX4-regulated biomarker and (**B**) a creatine kinase biomarker, an indicator of muscle damage. n=8 for *del-brax* and n=4 for placebo; mean ± SEM.

***Del-brax* showed trends toward improved muscle strength in both upper and lower limbs and reachable workspace when compared to placebo.**

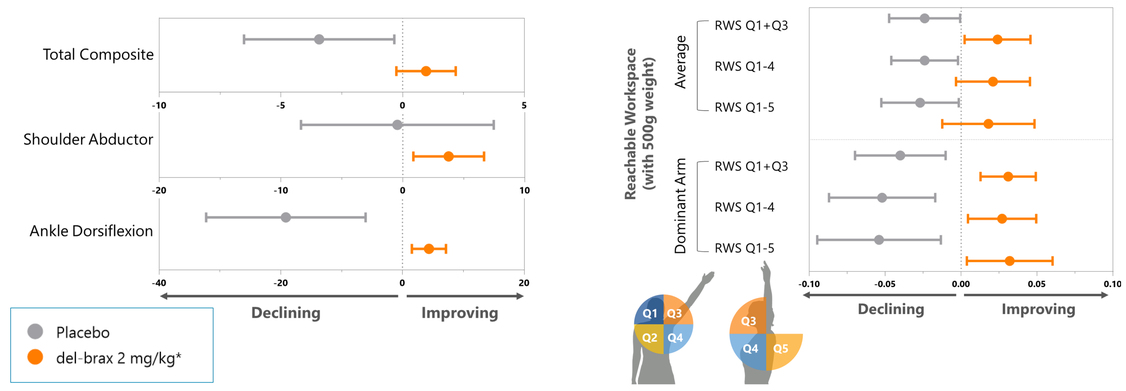


Figure 8. (**A**) Change from baseline to month 4 (mean ± SEM) in percent predicted normal QMT assessed by hand-held device. Total composite score reflects measurement of shoulder abductors, shoulder external rotators, elbow flexors, elbow extensors, knee flexor, knee extensor, and ankle dorsiflexion. (**B**) Change from baseline to month 4 (mean ± SEM) in relative surface area. n=8 for "average" and n=7 for "dominant arm" in the *del-brax* group. One participant's RWS dominant side Month 4 results were not included in the analysis due to injury. This decision was based on the consistency with instructions in the Clinical Evaluator Manual * Participants received a first dose of 1 mg/kg and then received the 2 mg/kg dose for the remainder of the study.

Conclusions

- **Effective muscle delivery with unprecedented and consistent >50% reduction in DUX4-regulated gene panels – impacting underlying FSHD disease biology**
- **Decrease in circulating biomarkers (novel and creatine kinase) indicate whole-body response**
- **Trends for improvements in clinical measures of disease:**
  - Muscle strength
  - Function: Reachable workspace compared to both placebo and natural history data
  - Patient and clinician reported outcomes
- **Favorable safety and tolerability with no serious AEs or patient discontinuation**
- **These data support rapidly advancing the clinical evaluation of *del-brax* in registrational cohorts within FORTITUDE (NCT05747924; biomarker and functional cohorts), in patients with FSHD**

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