Phase 1/2 Trial Evaluating AOC 1044 in Healthy Volunteers and Participants with DMD Mutations Amenable to Exon 44 Skipping (DMD44): EXPLORE44™ Trial Design

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Introduction

- DMD is a monogenic, X-linked, recessive muscular disease caused by mutations in the *DMD* gene that result in minimal or no expression of functional dystrophin protein[1]
- Lack of functional dystrophin leads to stress, inflammation, and tears of muscle cell membranes and dysfunction of the dystrophin associated protein complex, resulting in muscle cell death and progressive loss of muscle function[1]
- Progressive muscle degeneration, wasting, and paralysis generally leads to death via respiratory and/or cardiac failure in the third-to-fourth decade of life, even with recent advances in supportive care[1]
- In patients with specific frameshift-causing deletions, dystrophin protein expression can be restored through oligonucleotide-mediated exclusion of a particular DMD exon from the mature mRNA ("exon skipping") to restore the reading frame[2]
  - Around 7% of DMD skip-amenable patients have mutations amenable to exon 44 skipping (DMD44)
  - It is estimated that ~900 people in the US are exon 44 skip-amenable (ultra rare)
- Several oligonucleotides targeting different exons have been approved based on biomarker data, demonstrating increases in dystrophin levels.[3] Additionally, recent gene therapy has been approved based on micro-dystrophin data[4]

Avidity's Approach

Figure 1: AOC 1044, an Antibody Oligonucleotide Conjugate Targeting Exon 44 Skipping

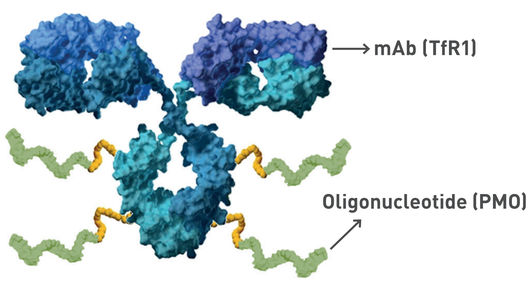
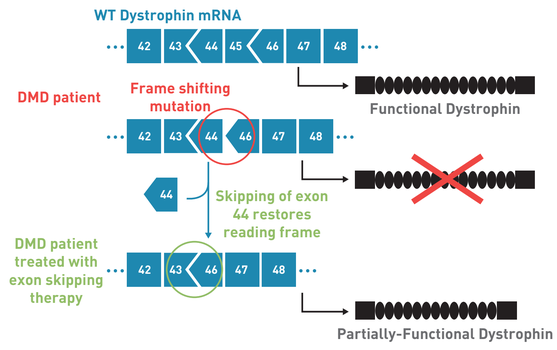


Figure 2: Example of a DMD patient with Exon 45 Deletion, Amenable to Exon 44 Skipping Therapy[5]



Trial Objectives

explore44™ Objectives

Part A: Healthy Volunteers	Part B: Participants Amenable to Exon 44 Skipping
Primary Objective • Safety and tolerability of single doses in healthy volunteers	**Primary Objective** • Safety and tolerability of multiple doses in DMD44 patients

Secondary Objective
• Pharmacokinetics
	Secondary Objective
	• Pharmacokinetics
	• Pharmacodynamics
	  - Exon 44 skipping
	  - Dystrophin levels

Key Exploratory Objectives
• Pharmacodynamics
  - Exon 44 skipping
	Key Exploratory Objectives
	• Measures of clinical activity
	  - Muscle function (NSAA, 10MWR, 4SC/4SD, PUL, 6MWT, DVA, and PFTs)
	• Patient-reported outcomes
	• Quality of life

Abbreviations

10MWR, 10-meter walk-run test; 6MWT, 6-minute walk test; 4SC, 4-stair climb; 4SD, 4-stair descend; AOC, antibody oligonucleotide conjugate; DMD, Duchenne muscular dystrophy; DMD44, Duchenne muscular dystrophy amenable to exon 44 skipping; DVA, Duchenne video assessment; mAb, monoclonal antibody; NSAA, North Star Ambulatory Assessment; OTC, over-the-counter; PFT, pulmonary function test; PMO, phosphorodiamidate morpholino oligomer; PUL, performance of upper limb; TfR1, transferrin receptor 1; WT, wild type.

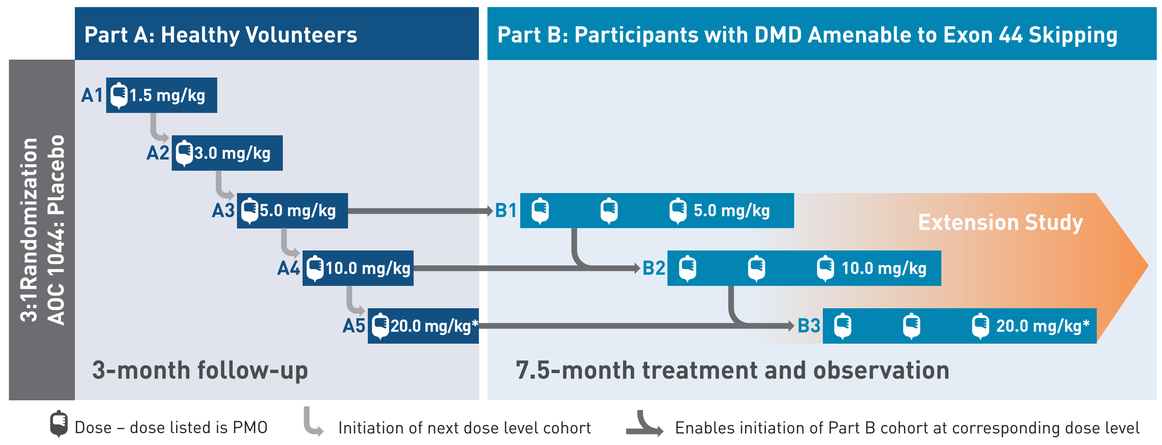
References

1. Duan D, et al. *Nat Rev Dis Primers*. 2021;7(1):13. **2.** Arechavala-Gomeza V, et al. *Curr Gene Ther*. 2012;12(3):152–60. **3.** Roberts TC, et al. *Nat Rev Drug Discov*. 2020;19(10):673–94. **4.** FDA News Release. https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy [Last accessed August 2023]. **5.** Aartsma-Rus A, et al. *BMC Med Genet*. 2007;8(43);2. **6.** Clinicaltrials.gov. NCT05670730 [EXPLORE44]. https://clinicaltrials.gov/ct2/show/NCT05670730 [Last accessed July 2023].

Trial Design

- EXPLORE44™ (AOC 1044-CS1) is a randomized, placebo-controlled, double-blind phase 1/2 trial conducted in two parts
  - Part A assesses the effects of AOC 1044 in five single-dose cohorts of healthy volunteers, who are monitored for 3 months
  - Part B will assess the effects of AOC 1044 in three multiple-ascending dose-level cohorts of participants with DMD44, dosed no more frequently than once every 6 weeks for 3 months
    - Eligible participants from Part B will have the option to enroll in a planned open-label extension study
    - If a participant chooses not to enter the planned extension study, they will have 3 months of follow-up
- Muscle biopsies will be conducted in later cohorts of Part A and in all cohorts of Part B
- Clinicaltrials.gov identifier: NCT05670730[6]

Figure 3: EXPLORE44™ Trial Design

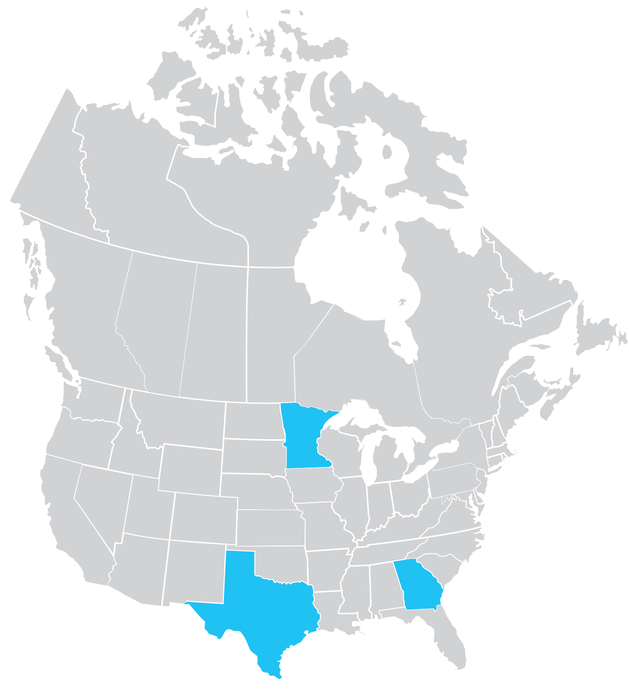


*Maximum; actual dose level TBD based on emerging data

Key Inclusion and Exclusion Criteria

Part A[6]	Part B[6]
Inclusion Criteria • 18 to 55 years of age (inclusive) • Body mass index of 18.5 to 32.0 kg/m^2	**Inclusion Criteria** • 7 to 27 years of age (inclusive) • Clinical diagnosis of DMD or clear onset of DMD symptoms at or before the age of 6 years • Confirmation of DMD gene mutation amenable to exon 44 skipping • Weight ≥23 kg • Ambulatory or non-ambulatory • PUL 2.0 entry item A ≥3 • If on corticosteroids, stable dose for 30 days
Exclusion Criteria • Elevated blood pressure >130/80 mmHg • Tests of renal, hepatic, and hematologic health outside of normal ranges • Regular use of prescription or OTC medications	**Exclusion Criteria** • Biceps brachii muscles unsuitable for biopsy • Serum hemoglobin less than lower limit of normal • Uncontrolled hypertension or diabetes • Prior treatment with any cell or gene therapy • Prior treatment with another exon 44 skipping agent within 6 months prior to informed consent

Map of Planned Trial Sites



Additional sites are planned.

2023 Neuromuscular Study Group Annual Scientific Meeting | Caribe Royal Hotel | Orlando, FL | September 22–24, 2023