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
- 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
- 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
- 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
- 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
- Additionally, recent gene therapy has been approved based on micro-dystrophin data

Trial Objectives

- Part A: Healthy Volunteers
  - Primary Objective
    - Safety and tolerability of single doses in healthy volunteers
  - Secondary Objective
    - Pharmacokinetics

- Part B: Participants with DMD Amenable to Exon 44 Skipping
  - Primary Objective
    - Safety and tolerability of multiple doses in DMD44 patients
  - Secondary Objective
    - Pharmacokinetics
    - Pharmacodynamics
    - Dystrophin levels
  - Key Exploratory Objectives
    - Measures of clinical activity
    - Muscle function (NSAA, 10MWR, 4SC/4SD, DVA, PFT)
    - 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 limbs; TfR1, transferrin receptor 1; WT, wild type.

Key Inclusion and Exclusion Criteria

Part A

- Inclusion Criteria
  - 18 to 55 years of age (inclusive)
  - Body mass index of 18.5 to 32.0 kg/m²

- 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

Part B

- 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
  - PL kinetics within specified range

- 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

References