From Myocyte to Patient: AOC 1001 Demonstrates DMPK Reduction and Spliceopathy Improvement in a Phase 1/2 Study in Myotonic Dystrophy Type 1 (DM1) (MARINA™)

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Background

Myotonic dystrophy type 1 (DM1) is a rare, autosomal dominant, progressive neuromuscular disease with no US Food and Drug Administration (FDA)-approved therapies. The cause of DM1 is a mutation in myotonic dystrophy protein kinase (DMPK), which encodes a nuclear serine/threonine kinase that phosphorylates numerous nuclear targets, including the heat shock protein (HSP) family, the neuronal mRNA-binding protein LOC8, and the RNA binding protein MALAT1. These effects lead to nuclear retention, nuclear repositioning, and cellular stress. In addition, DMPK regulates the activity of the muscleblind-like protein (MBNL), which is responsible for DM1 pathogenesis. DM1 patients experience a wide range of symptoms, including muscle weakness, joint contractures, and cognitive decline. Despite the availability of several drugs targeting human Tfr1 (e.g., muscleblind-like [MBNL]) resulting in global splicing dysregulation.

Avidity’s Approach to Treating DM1

- The activity of AOC 1001 was evaluated in vitro in DM1 patient myotubes and in a clinical trial of patients with DM1.
- DM1 patient myotubes were transfected with DMPK. Levels of DMPK mRNA and splicing events (RNA sequencing) as well as nuclear foci (immunohistochemistry) were evaluated.
- AVIDITY’s™ MARINA™ is a Phase 1/2 study (>70 patients) to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of AOC 1001 in adult patients with DM1. Twenty-two patients were enrolled, including nine AOC 1001:placebo, nine AOC 1001:2 mg/kg, and four AOC 1001:4 mg/kg. Dose escalation was performed in a phase 1 portion.

Results

- DM1 patients were aged between 18 and 65 years.
- AOC 1001: placebo, n=5
- AOC 1001: 2 mg/kg (n=9)
- AOC 1001: 4 mg/kg (n=9)
- Placebo: n=9

- Ascher et al., 2018; 8(6):507-520.
- Dunn et al., 2018; 15(4):872-884.
- Tanner MK, et al.

Conclusion

We demonstrate the translation of patient in vitro activity to proof-of-mechanism (DMPK reduction and spliceopathy improvement) of AOC 1001 in a final-in-human clinical study in DM1 patients, supporting AOC 1001 as a potential therapy addressing the underlying cause of DM1.

Acknowledgments

Investigators, and their families in MARINA™: Association Insitut de Myologie for providing central and DMS (cell lines). CHU de Quebec-Laval, Canada for providing DM1 patient-derived human primary myoblasts.

References


Abbreviations

AOC, antibody oligonucleotide conjugate; CPM, count per million; DM1, myotonic dystrophy type 1; DMPK, myotonic dystrophy protein kinase; FDA, US Food and Drug Administration; IV, intravenous; mRNA, messenger ribonucleic acid; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; PSI, percent spliced-in; PSD, percent spliced-out; SEM, standard deviation of the mean; sRNA, small interfering RNA; Tfr1, transferrin receptor 1.