Initial Results of the Phase 2 Open-Label Extension Study of AOC 1001 in Adults With Myotonic Dystrophy Type 1: MARINA-OLE™

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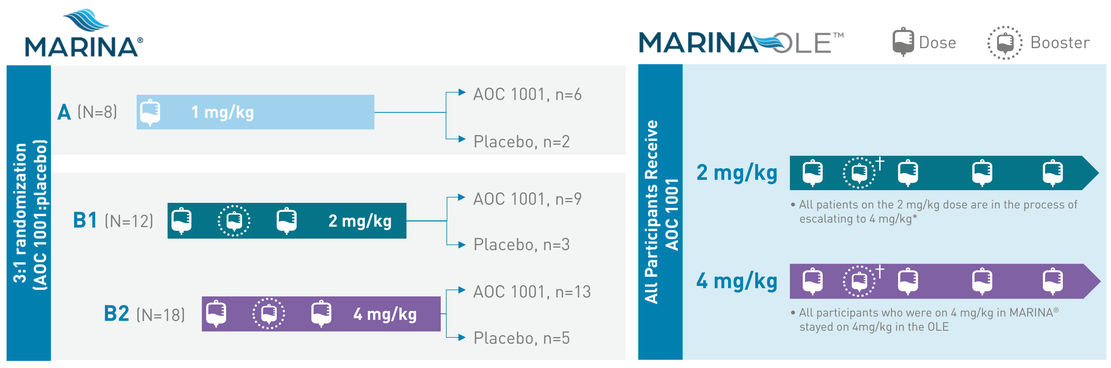
Introduction

- Myotonic dystrophy type 1 (DM1) is a rare, autosomal-dominant, progressive neuromuscular disease caused by the expansion of the CTG repeat in the 3' untranslated region of the *DM1 protein kinase (DMPK)* gene, leading to sequestration of RNA-regulating proteins, and consequently the mis-splicing of multiple downstream genes which results in multiorgan manifestations[1-7]
- DM1 is typically characterized by myotonia and muscle weakness leading to dysarthria, dysphagia, immobility, and respiratory insufficiency, which place a significant burden on patients[3,4,8,9]
- Current medical treatment for DM1 is focused on symptom management because there are no approved disease-modifying therapies[2]
- AOC 1001 is an antibody oligonucleotide conjugate (AOC™) comprised of[10]:
  - Antibody: human TfR1-targeting, effector function-null, humanized IgG1 monoclonal antibody (TfR1 mAb)
  - Non-cleavable linker
  - Oligonucleotide: double-stranded siRNA oligonucleotide complementary to both wild-type and mutant DMPK mRNA
- The TfR1 mAb targets muscles for delivery of siDMPK.19 into the cytoplasm and nucleus where it mediates DMPK mRNA degradation[10]
- AOC 1001 successfully delivered drug to muscle, resulting in *DMPK* reduction and increased estimated functional MBNL levels[11]

Study Design

Figure 1: MARINA® and MARINA-OLE™ Trials Designed to Evaluate Safety and Tolerability of AOC 1001*



*Under the terms of the partial clinical hold, the first dose of AOC 1001 must be less than or equal to 2 mg/kg.
†Booster dose was only given to participants who were in Cohort A1 and placebo B1/B2.
Dose listed is siRNA.

- All participants that completed MARINA® enrolled in the MARINA-OLE™
- All participants remain in the MARINA-OLE™

Results

Table 1: Summary of Treatment-Emergent Adverse Events (AEs)
AOC 1001 long-term safety data continue to demonstrate favorable safety and tolerability

	MARINA®				MARINA-OLE™
Subjects with ≥1 AE, n (%)	Placebo (N=10)	1 mg/kg (N=6)	2 mg/kg (N=9)	4 mg/kg (N=13)	All (N=37)
Any AE	8 (80%)	6 (100%)	9 (100%)	13 (100%)	35 (95%)
AE related to study drug	2 (20%)	1 (17%)	3 (33%)	10 (77%)	9 (24%)
Any serious AE (SAE)	0	0	1 (11%)	1 (8%)	4 (11%)
SAE related to study drug	0	0	0	1 (8%)	0
AE leading to study discontinuation	0	0	0	1 (8%)	0
AE leading to death	0	0	0	0	0

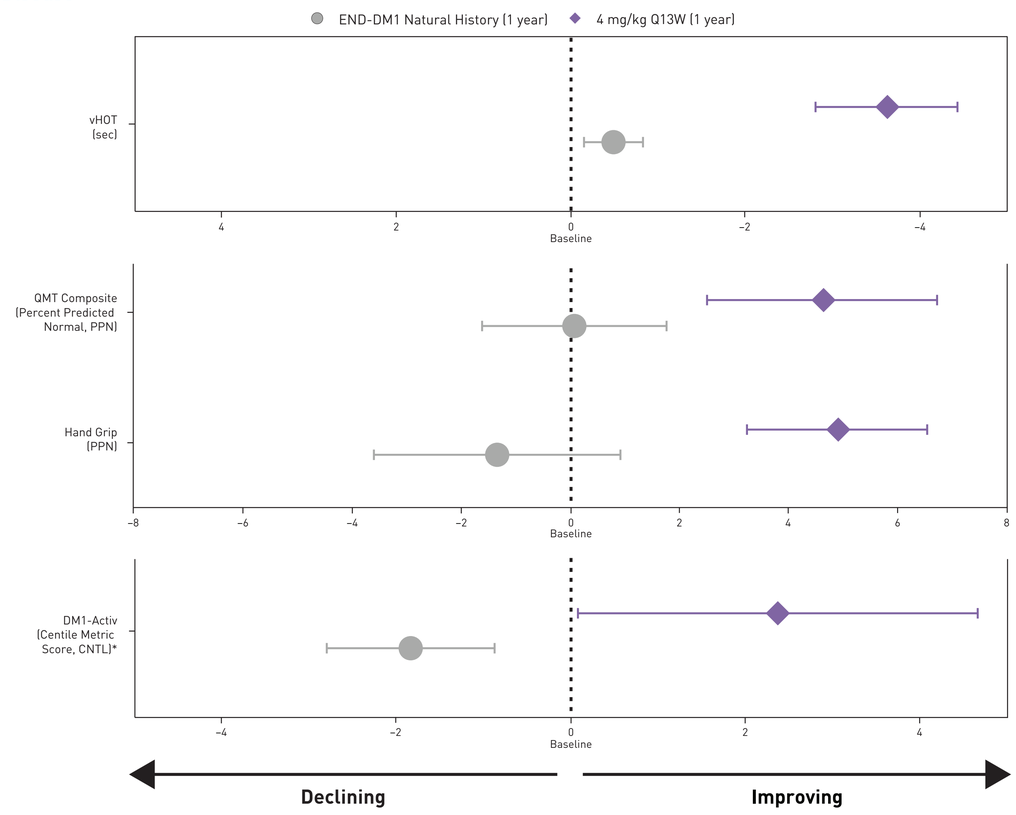
MARINA® and MARINA-OLE™

- **As of January 2024, over 265 infusions of AOC 1001 have totaled 61.1 patient-years of exposure**

MARINA-OLE™

- **All 37 participants enrolled remain on study**
- **All related AEs were mild or moderate**
  - Most common related AEs reported in 2 or more participants include nausea and headache
  - No discontinuations
  - No related SAEs; unrelated SAEs are consistent with DM1
  - SAEs considered unrelated to treatment included nausea/vomiting, worsening of atrial fibrillation, and chest pain. One participant had acute cholelithiasis and biliary pancreatitis.

Figure 2: MARINA®/MARINA-OLE™ Data Suggest Improvement in Disease Course Compared to Natural History of the Disease



Thanks to END-DM1 physicians for reviewing and approving use of this Avidity analysis. END-DM1 subpopulation based on MARINA® (n ~ 60; MIRS≥2 and 3.8<10MWRT<14 secs).
*N=11

Results (Continued)

Figure 3: AOC 1001 (4 mg/kg) Continues to Improve in Myotonia as Measured by vHOT at 1 Year on Treatment in MARINA-OLE™

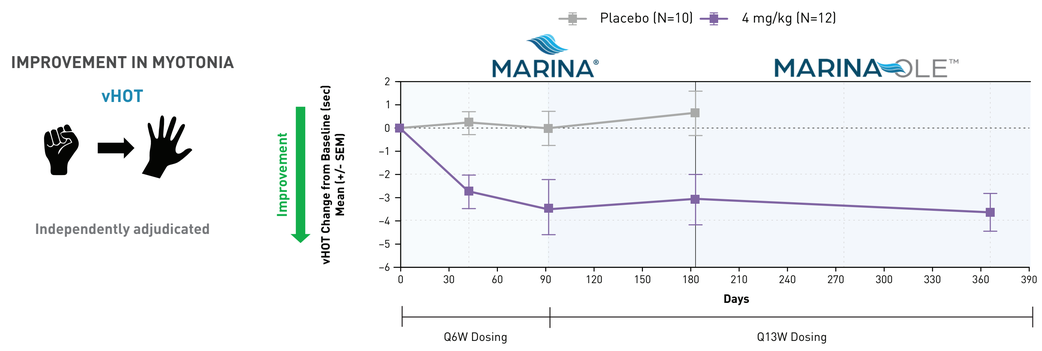


Figure 4: AOC 1001 (4 mg/kg) Shows Continued Improvement in Hand Grip Strength at 1 Year on Treatment in MARINA-OLE™

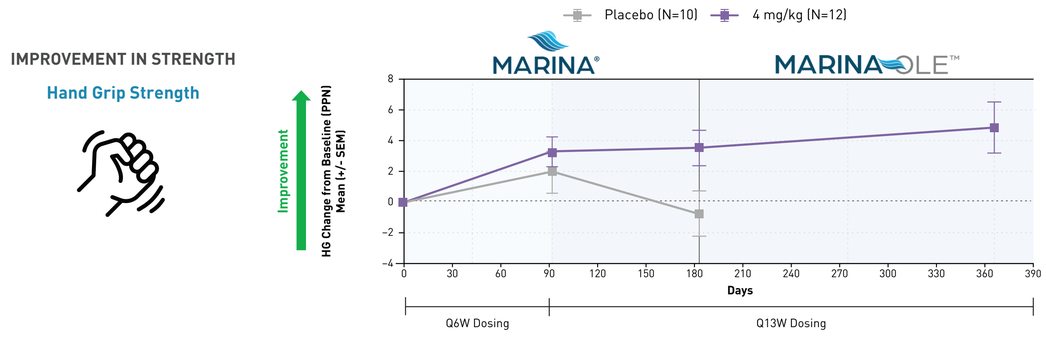


Figure 5: AOC 1001 (4 mg/kg) Shows Continued Improvement in Strength by 6-Muscle Composite QMT at 1 Year on Treatment in MARINA-OLE™

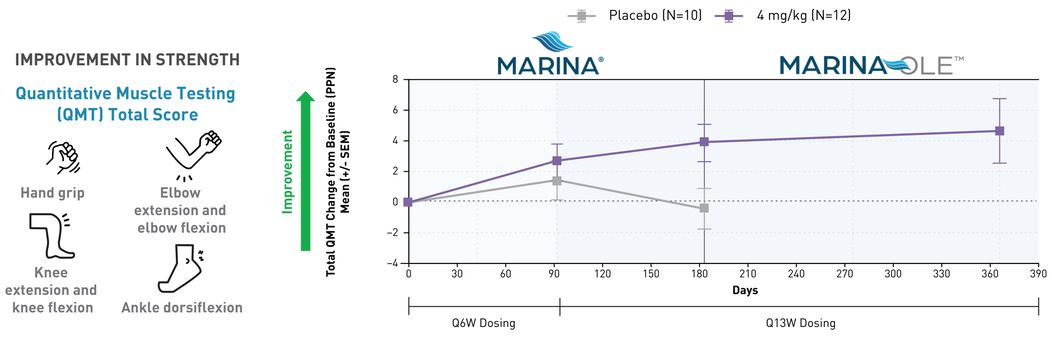
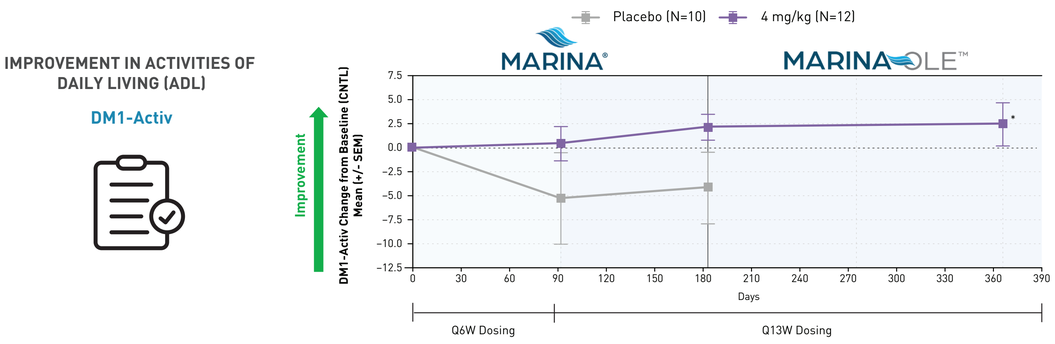


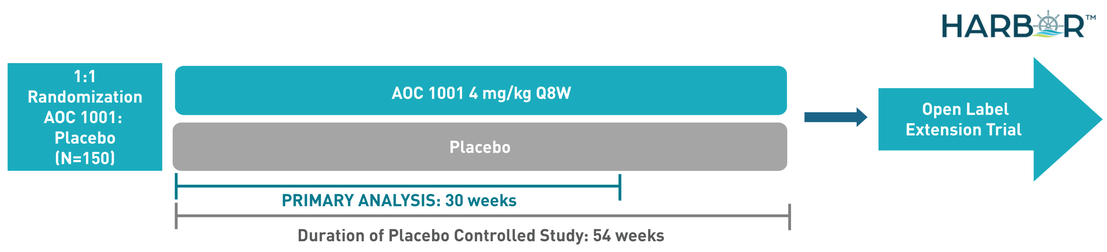
Figure 6: AOC 1001 (4 mg/kg) Maintains Improvement in DM1-Activ at 1 Year on Treatment in MARINA-OLE™



*Data summarized exclude one participant who experienced an injury impairing their ability to perform mobility measures.

Global Pivotal HARBOR™ Study

Figure 7: HARBOR™ Global Phase 3 Pivotal Trial



Key Information
- 4 mg/kg every 8 weeks; first dose of 2 mg/kg
- Ages 16+
- ~40 global sites

Primary Objective
- **vHOT**

Key Secondary Objectives
- **Hand Grip**
- **QMT**
- **DM1-Activ**

MARINA-OLE™ Data Summary

- AOC 1001 4 mg/kg demonstrates favorable long-term safety and tolerability with improvement in multiple clinical outcomes
- Data analysis shows improvement with AOC 1001 on multiple functional endpoints, including ADL, versus decline seen on the END-DM1 natural history study
- Global HARBOR Phase 3 pivotal study to commence enrollment Q2 2024

References and Abbreviations

1. LoRusso S, et al. *Neurotherapeutics*. 2018;15(14):872-84. **2.** Ashizawa T, et al. *Neurol Clin Pract*. 2018;8(6):507-20. **3.** Udd B and Krahe R. *Lancet Neurol*. 2012;11(10):891-905. **4.** Gourdon G and Meola G. *Front Cell Neurosci*. 2017;11:101. **5.** Brook JD, et al. *Cell*. 1992;68(4):799-808. **6.** Lin X, et al. *Hum Mol Genet*. 2006;15(13):2087-97. **7.** Lee JE and Cooper TA. *Biochem Soc Trans*. 2009;37(PT 6):1281-6. **8.** Hagerman KA, et al. *Muscle Nerve*. 2019;59(4):457-64. **9.** Landfeldt E, et al. *J Neurol*. 2019;266(4):998-1006. **10.** Johnson N. A Phase 1/2 Clinical Trial Evaluating the Safety and Pharmacokinetics of AOC 1001 in Adults with Myotonic Dystrophy Type 1 (DM1): MARINA® Study Design. Poster presented at: Muscular Dystrophy Association Clinical & Scientific Conference; Nashville, TN; 13-15 March 2022. **11.** Zhu Y et al. AOC 1001-mediated Reduction of DMPK Leads to Increase in Functional MBNL Levels, Improving Muscle Function in Patients with DM1. Poster presented at: Muscular Dystrophy Association Clinical & Scientific Conference; Orlando, FL; 3-6 March 2024.

ADL, activities of daily living; AE, adverse event; AOC, antibody oligonucleotide conjugate; CNTL, centile metric score; DM1, myotonic dystrophy type 1; DMPK, DM1 protein kinase; HG, hand grip; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MBNL, muscleblind like; mRNA, messenger ribonucleic acid; OLE, open-label extension; PPN, percent predicted normal; QMT, quantitative muscle testing; SAE, serious adverse event; SEM, standard error of the mean; siDMPK, small inhibitory DM1 protein kinase; siRNA, small inhibitory ribonucleic acid; TfR1, transferrin receptor 1; TUG, timed up and go; vHOT, video hand opening time.

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