# AOC 1001–Mediated Reduction of DMPK Leads to Increase in Functional MBNL Levels, Improving Muscle Function in Patients with DM1

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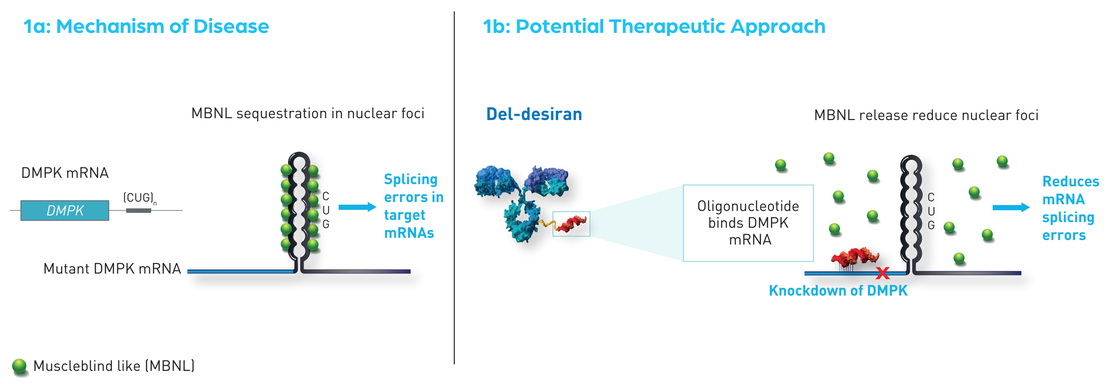
## Introduction

- Myotonic dystrophy type 1 (DM1) is a rare, autosomal dominant, progressive neuromuscular disease with no FDA-approved therapies. The cause of DM1 is a mutation in myotonic dystrophy protein kinase (*DMPK*) mRNA that contains expanded (>50) CUG repeats (Figure 1a).[1–5] Mutant *DMPK* is a toxic gain of function mRNA that leads to nuclear retention (nuclear foci) and sequestration of splicing factors (e.g. muscleblind like (MBNL)) resulting in global splicing dysregulation.[6]
- Given the challenges with delivery of oligonucleotides to muscle, we utilized transferrin receptor 1 (TfR1)-mediated endocytosis to deliver siRNA to skeletal muscle and heart. Thus, delpacibart etedesiran (del-desiran; formerly AOC 1001) is an antibody oligonucleotide conjugate (AOC™) comprised of a siRNA targeting *DMPK* mRNA (siDMPK) conjugated to a humanized monoclonal antibody (mAb) targeting human TfR1 that is designed to reduce *DMPK* mRNA in muscle tissue and subsequently correct splicing events that are responsible for DM1 disease manifestation (Figure 1b).

### Figure 1: Avidity's Approach to Treating DM1




## Methodology

- Pharmacodynamic activity of del-desiran was evaluated in the Phase 1/2 MARINA® study (Clinicaltrials.gov identifier: NCT05027269)[7] to determine target engagement and subsequent modulation of mis-splicing in evaluable muscle biopsies from tibialis anterior pre- and post-treatment. Post-treatment timepoints are 6 weeks post 1 dose (1 mg/kg cohort) or 2 doses (2 and 4 mg/kg cohort). Muscle biopsy from tibialis anterior from healthy volunteers were obtained as controls.
- RNA sequencing analysis of splicing events was performed and the intracellular concentration of functional MBNL ([MBNL]inf) value was inferred from splicing levels.[8]

## Results

### Figure 2: Reduced Functional MBNL Levels in MARINA® Participants at Baseline

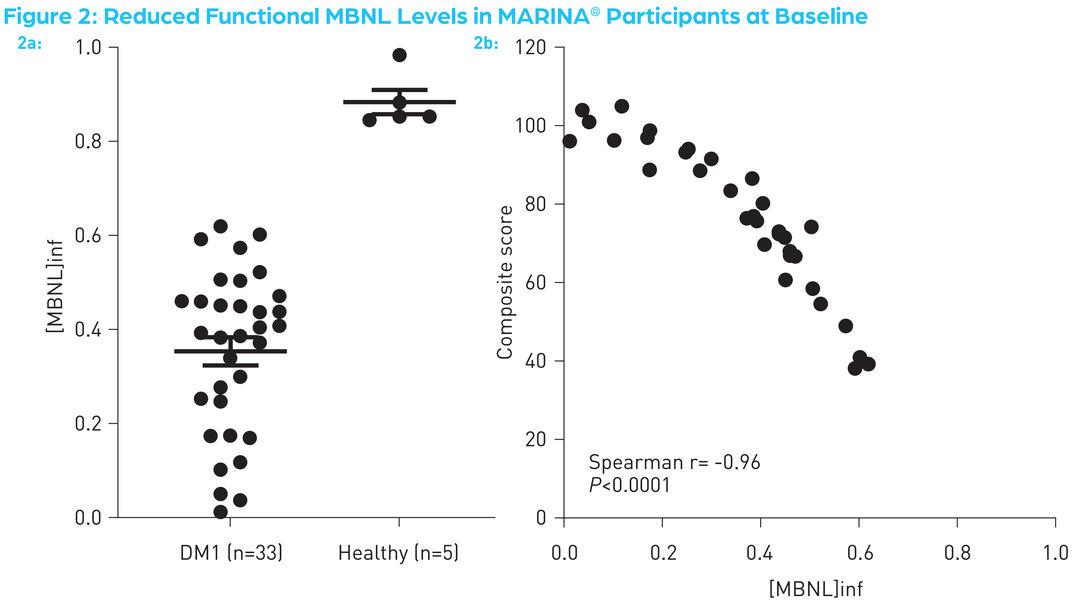



**Figure 2:** Reduced functional MBNL levels ([MBNL]inf) in skeletal muscle in MARINA® participants compared to healthy volunteers (2a). Inverse correlation of functional MBNL levels and spliceopathy score from 22 splicing events (2b).

### Figure 3: Reduced MBNL Levels Associated With Deficits in Multiple Muscle Functions at Baseline

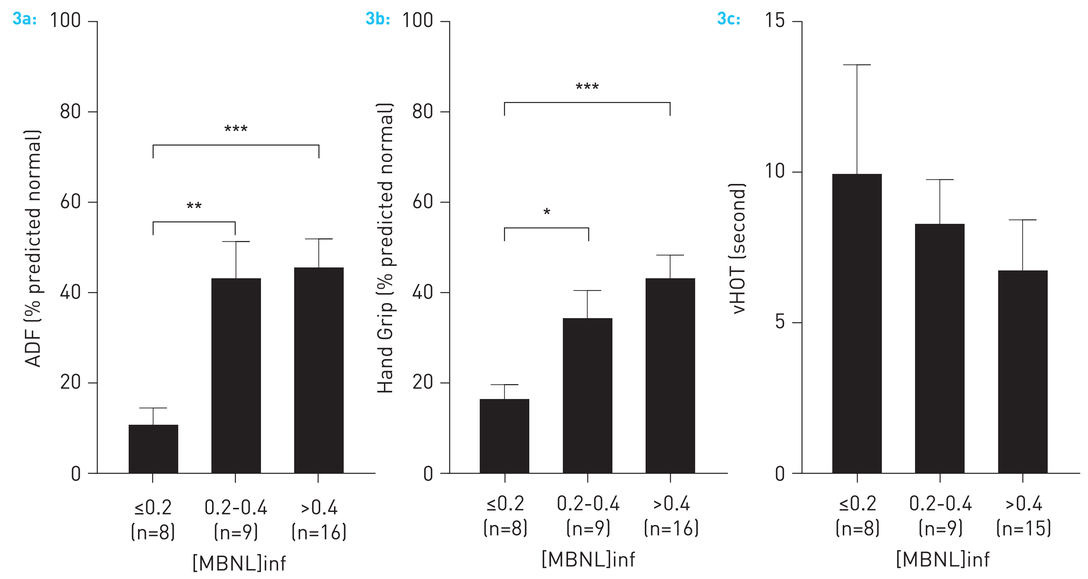



**Figure 3:** Baseline functional MBNL levels associates with multiple muscle strength measures including ankle dorsiflexion strength (3a) and hand grip (3b). Baseline functional MBNL levels inversely associates with myotonia measured as vHOT (3c). Data shown as mean and standard error. *$P$<0.05, **$P$<0.01, ***$P$<0.001, unpaired t-test.

## Results (Continued)

### Figure 4: Treatment of Del-desiran Results in Dose-Dependent Improvement of Functional MBNL Levels

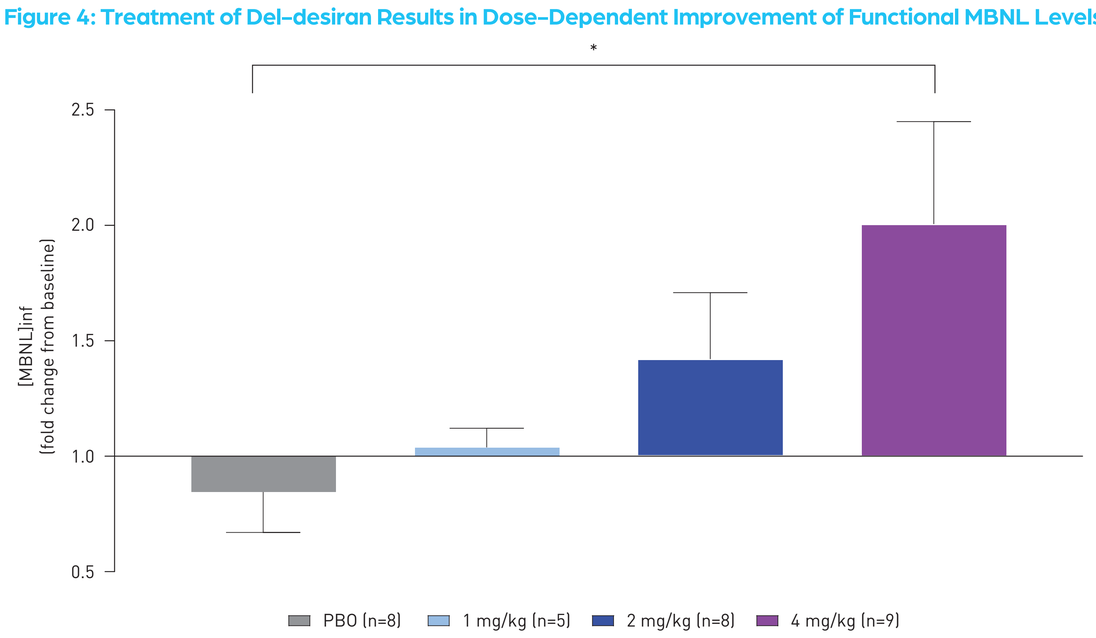



**Figure 4:** Data shown as mean and standard error. Fold change is calculated per subject as post-treatment relative to baseline. *$P$<0.05, unpaired t-test.

### Figure 5: Del-desiran Reduces *DMPK* mRNA Expression in DM1 Participants

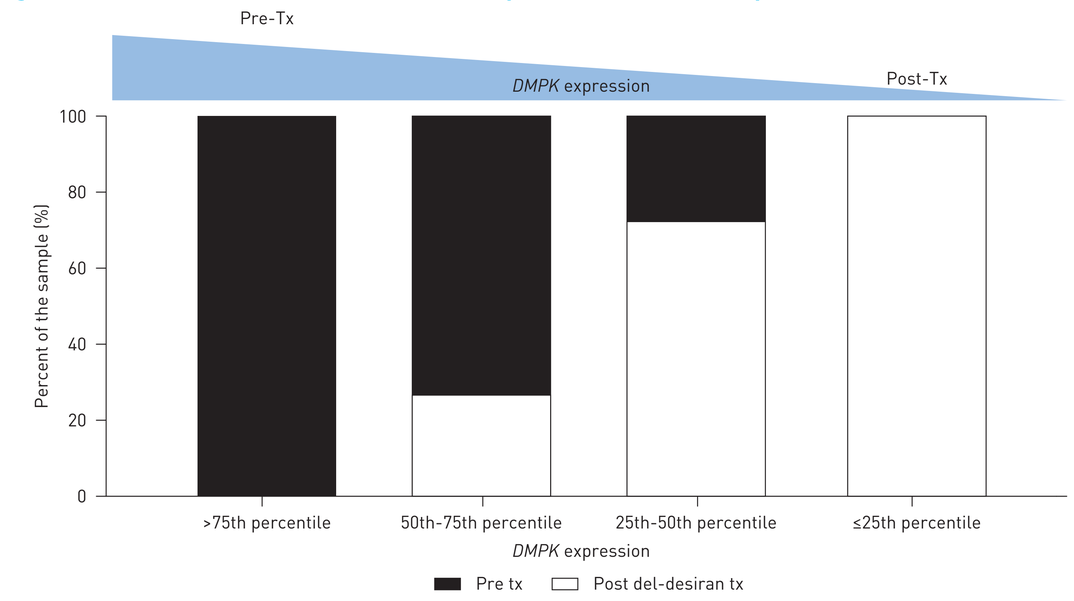



**Figure 5:** Data represented as the % of participants in each quartile of *DMPK* expression. Analysis includes 22 subjects on active arm with matching baseline and post-tx biopsies.

### Figure 6: Lower *DMPK* Expression Associates With Higher Functional MBNL Level

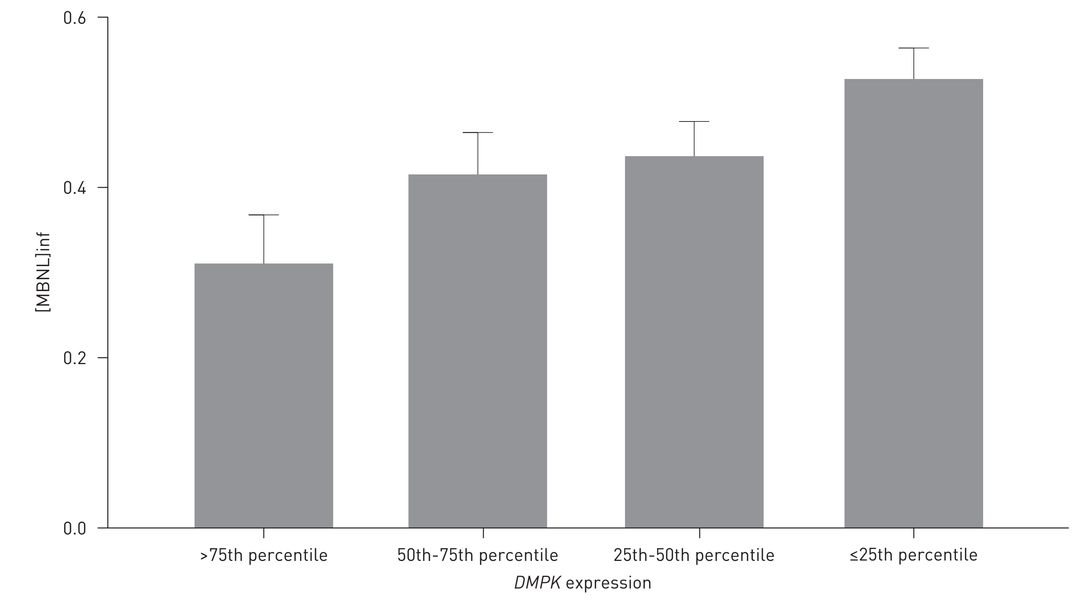



**Figure 6:** Data represented as mean and standard error of [MBNL]inf in each quartile of *DMPK* expression. Analysis includes 22 subjects on active arm with matching baseline and post-tx biopsies.

## Conclusions

These data demonstrate that functional MBNL levels associate with deficits in multiple muscle functions. Treatment with del-desiran leads to dose-dependent increases in functional MBNL levels, which correlates with reduced *DMPK* mRNA expression. Altogether the data support the mechanism of action of del-desiran to increase functional MBNL and improve muscle functions in DM1 patients.

## References & Abbreviations

**1.** Thornton CA, et al. *Lancet Neurol*. 2023;22(3):218-28. **2.** Hale MA, et al. *Hum Mol Genet*. 2022; 32(9):1413-28. **3.** Ashizawa T, et al. *Neurol Clin Pract*. 2018;8(6):507-20. **4.** Brook JD, et al. *Cell*. 1992;68(4):799-808. **5.** Lin X, et al. *Hum Mol Genet*. 2006;15(13):2087-97. **6.** Lee JE, Cooper TA. *Biochem Soc Trans*. 2009;37(Pt 6):1281-6. **7.** Clinicaltrials.gov. NCT05027269 [MARINA]. https://clinicaltrials.gov/ct2/show/NCT05027269. Accessed February 2024. **8.** Wagner SD, et al. *PLoS Genet*. 2016;12(9):e1006316.

ADF, ankle dorsiflexion; AOC, antibody oligonucleotide conjugate; DM1, myotonic dystrophy type 1; DMPK, myotonic dystrophy protein kinase; FDA, US Food and Drug Administration; mAb, monoclonal antibody; MBNL, muscleblind like; [MBNL]inf, inferred MBNL levels; mRNA, messenger ribonucleic acid; siRNA, small interfering ribonucleic acid; TfR1, transferrin receptor 1; tx, treatment; vHOT, video hand opening time.

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