Poster Number **226P**

Phase 3, Randomized, Global Study Assessing Efficacy and Safety of *Del-desiran*™ for the Treatment of Myotonic Dystrophy Type 1: HARBOR™ Trial Design

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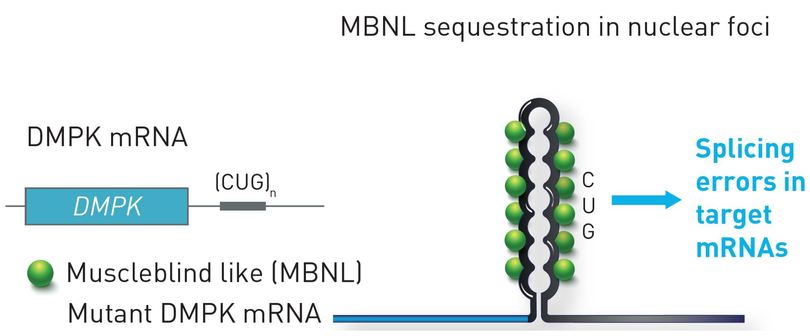
Background

- Myotonic dystrophy type 1 (DM1) is a rare, dominantly inherited, progressive neuromuscular disease caused by a toxic gain-of-function mutation in the DM1 protein kinase (*DMPK*) gene.[1,2]
- DM1 is characterized by myotonia along with progressive muscular weakness and wasting, leading to deficits in hand function, immobility, respiratory insufficiency, dysarthria, and dysphagia, among other multisystemic impacts.[1,3]
- Delpacibart etedesiran (*del-desiran*™, formerly AOC 1001) is an antibody-oligonucleotide conjugate (AOC) comprised of a *DMPK*-specific small interfering RNA (siRNA) conjugated to a humanized antibody targeting human transferrin receptor 1 (TfR1).[4,5]
  - This unique conjugate facilitates targeted delivery of the siRNA to skeletal, cardiac, and smooth muscle cells, mediating degradation of the *DMPK* mRNA.[6]
- *Del-desiran* is currently being investigated for the treatment of DM1 as a potential therapy to address the underlying cause of the disease.
- In the Phase I/II MARINA® trial and its open-label extension, *del-desiran* has shown (**1**) consistent long-term safety and tolerability in adults with DM1[4] and (**2**) directional improvement in measures of myotonia, muscle strength, muscle function, and patient-reported outcomes.[7]

DM1 Pathophysiology

- In unaffected individuals, there are fewer than 50 CTG repeats within the 3′ untranslated region of the *DMPK* gene.[8]
- DM1 is caused by a mutation in the *DMPK* gene in which the CTG repeats are expanded to hundreds or thousands of repeats. When the mutant *DMPK* gene is transcribed into RNA, the subsequent expanded CUG repeats fold into aberrant hairpin structures.[8]
- This sequesters various RNA-binding proteins in the muscleblind-like protein (MBNL) family, reducing their function (**Figure 1**).[6]
- Reduced MBNL protein function results in misregulated alternative splicing and subsequent abnormal protein production, leading to multisystemic disease manifestations.[6]
  - Mis-splicing of muscle-related genes leads to myotonia, muscle weakening, and atrophy of the muscle tissue.[8]

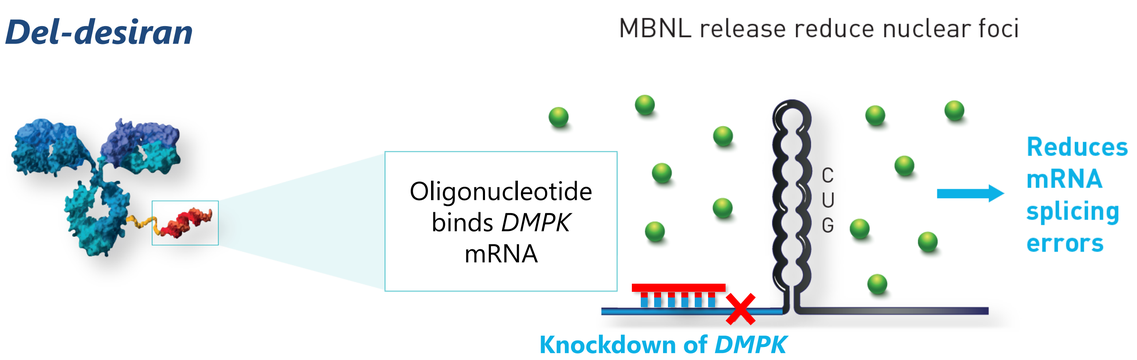
Figure 1. DM1 Mechanism of Disease.



Del-desiran Mechanism of Action

- *Del-desiran* consists of a proprietary monoclonal antibody that binds to TfR1 conjugated to a siRNA that targets the *DMPK* mRNA for degradation by RNA interference.[9]
- Targeted delivery of *del-desiran* to skeletal, smooth, and cardiac muscle cells addresses the underlying cause of DM1 by:
  1. Degrading *DMPK* mRNA.
  2. Releasing MBNL proteins from sequestration.
  3. Correcting RNA mis-splicing (**Figure 2**).
  4. Addressing multisystemic impacts of DM1, including improvements in muscle function.

Figure 2. *Del-desiran* Mechanism of Action.



Trial Objectives[10]

HARBOR™

Primary Objective and Endpoint

- **Objective**: To evaluate the efficacy of *del-desiran* on hand opening time.
- **Endpoint**: Change from baseline in video hand-opening time at Week 30.

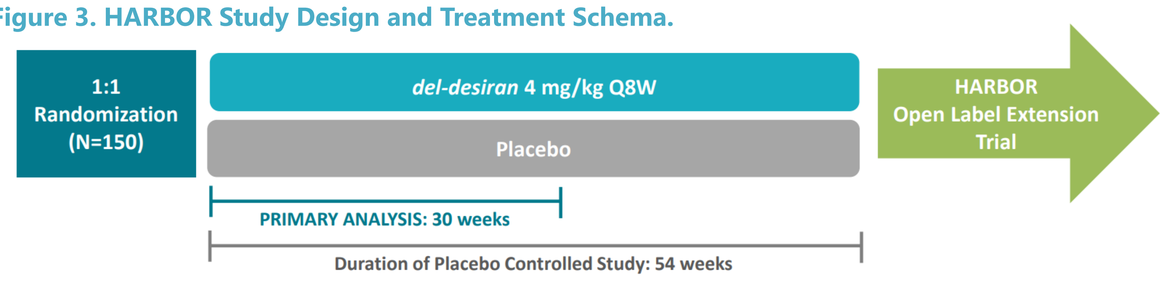
Secondary Objectives and Endpoints

- **Objectives**: To evaluate the efficacy of *del-desiran* on mobility, muscle strength, muscle function, and activities of daily living.
- **Endpoints**: Hand grip strength by dynamometer, quantitative muscle testing composite score by dynamometer, and scores on the DM1 Activity and Participation Scale C (DM1-Activ^{C}).

HARBOR Trial Design[10]

- The HARBOR trial will assess the efficacy and safety of *del-desiran* in the treatment of DM1.
- This phase 3, randomized, double-blind, placebo-controlled, 54-week study is actively recruiting and will be conducted across ~40 global sites.
- This study will enroll participants aged 16-65 years with a clinical and genetic diagnosis of DM1 (*DMPK* CTG repeats ≥ 100).
- Participants will be randomized 1:1 to receive either *del-desiran* or placebo administered intravenously every 8 weeks (**Figure 3**).
- Primary analysis will take place at Week 30. Eligible participants will have the option to enroll in a future open-label extension trial.

Figure 3. HARBOR Study Design and Treatment Schema.



Inclusion and Exclusion Criteria[10]

Key Inclusion Criteria

- Clinical and genetic diagnosis of DM1 (CTG repeats ≥ 100).
- Ability to walk independently (orthoses and ankle braces allowed) for at least 10 meters at screening.

Key Exclusion Criteria

- Breastfeeding, pregnancy, or intent to become pregnant during the study.
- Unwilling or unable to comply with contraceptive requirements.
- Abnormal lab values, conditions or diseases that would make the participant unsuitable for the study.
- Diabetes that is not adequately controlled.
- History of decompensated heart failure within 3 months of screening (participants with preexisting pacemaker/implantable cardioverter defibrillator are not excluded).
- Body Mass Index > 35 kg/m^2 at screening.
- Recently treated with an investigational drug or biological agent.
- Treatment with anti-myotonic medication within 5 half-lives or 14 days of baseline, whichever is longer, before baseline.

Note: *Additional protocol-defined Inclusion and Exclusion criteria apply.*

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Disclosures and Acknowledgements

Nicholas Johnson has received grants or contracts from NINDS, FDA, and CDC; his institution has received grants or contracts from Avidity Biosciences, Dyne Therapeutics, Wyck Foundation, Coalition to Cure Calpain 3, Muscular Dystrophy Association, Cure Rare Diseases, Novartis, Pfizer, AMO Pharma, ML Bio, Fulcrum Therapeutics, PepGen, Vertex, Sarepta, AskBio, Takeda, and Arthex Biotech; He has received royalties or licenses from the University of Rochester; He has received consulting fees from Novartis, Sarepta, AskBio, Vertex, Dyne Therapeutics, AMO Pharma, Rgenta Therapeutics, and Kate Therapeutics; He has received personal compensation for serving on the data safety monitoring board for Biogen and Fulcrum Therapeutics. He has received stock or stock options from Angel Therapeutics and Juvena Therapeutics.

John Day has received research funding from Avidity Biosciences, AMO Pharma, Ionis Pharmaceuticals, Biogen, Muscular Dystrophy Association, and Myotonic Dystrophy Foundation; he has received royalties or licenses from Athena Diagnostics; he has received consulting fees from Avidity Biosciences, Biogen, Kate Therapeutics, Pepgen, Vertex Pharmaceuticals, and Muscular Dystrophy Association; he has participated in leadership or fiduciary role in other board, society, committee or advocacy group as board of directors of Myotonic Dystrophy Foundation and Cure Congenital Muscular Dystrophy.

Authors BM, MF, BK, TB, KG, SH, and EA are employees of Avidity Biosciences and have stock or stock options. L-TJ is a former employee of Avidity Biosciences.

We thank Alexander Schwartz and Lauren Todd from Sixsense Strategy Group for medical writing support.

Avidity Biosciences, Inc. provided funding support for the HARBOR trial and medical writing.

29th Annual Congress of the World Muscle Society | Prague, Czechia | October 8th – 12th, 2024