Poster Number **P58**

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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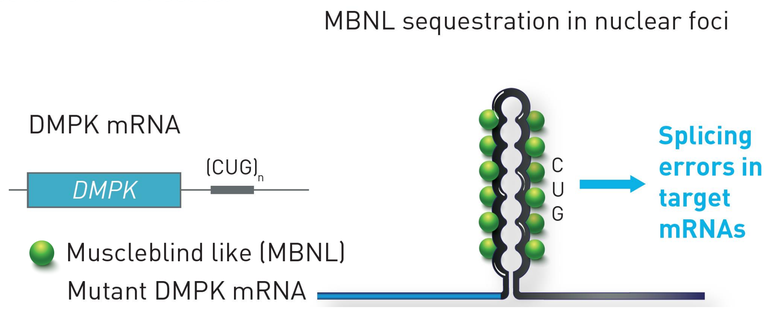
Background

- 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]

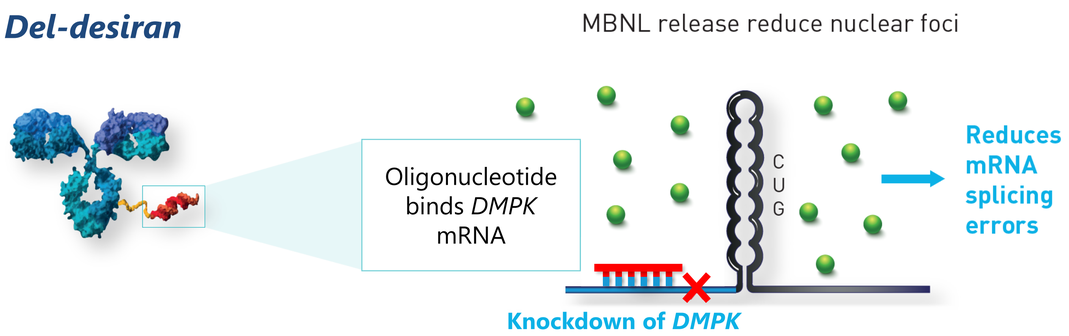
Figure 1. DM1 Mechanism of Disease.



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.

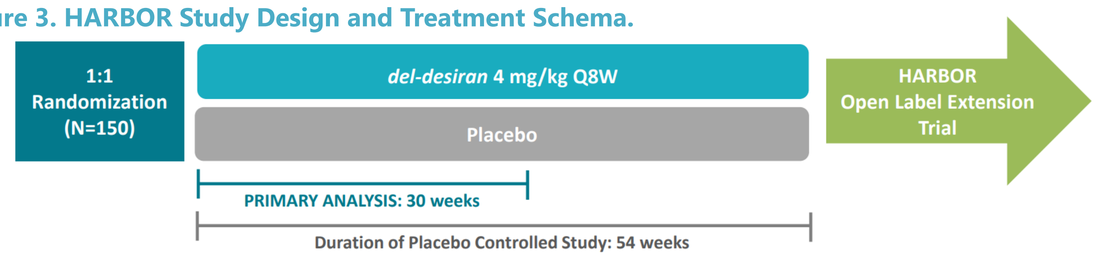
Secondary Objectives and Endpoints

- **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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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.

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