Gene therapy in MND

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MND
MND
MND – Not one disease
Tofersen

- A genetic therapy for familial MND caused by SOD1 mutation
- 1% of all MND
Special case of Familial MND
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Phase 1–2 Trial of Antisense Oligonucleotide Tofersen for SOD1 ALS

 Faulty SOD1 DNA → Faulty SOD1 mRNA → Faulty SOD1 protein

Treatment with Tofersen (Antisense Oligonucleotide)

Enzymatic degradation

X
**Objective:** to evaluate the safety, tolerability, PK, PD, and exploratory efficacy of an antisense oligonucleotide tofersen (BIIB067/IONIS-SOD1Rx) designed to degrade superoxide dismutase 1 (SOD1) mRNA to reduce levels of SOD1 protein in people with ALS with SOD1 gene mutation (SOD1-ALS)

**Population**
- > 18 years old
- Weakness attributed to ALS
- Documented SOD1 mutation
- FVC ≥ 50% of predicted value

**MAD Study**

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose</th>
<th>Placebo</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>tofersen 20 mg</td>
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<tr>
<td>2</td>
<td>tofersen 40 mg</td>
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<tr>
<td>3</td>
<td>tofersen 60 mg</td>
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<tr>
<td>4</td>
<td>tofersen 100 mg</td>
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**Endpoints**

**Primary**
- Safety and tolerability
- PK measures of tofersen (plasma and CSF)

**Secondary**
- Change from baseline in CSF levels of SOD1 protein

**Exploratory endpoints include**
- Changes from baseline of clinical function measures: ALSFRS-R scores, SVC, and HHD megascore

- 50 participants world-wide, randomized 3:1 tofersen:placebo in each cohort
- 7 from Sheffield
- Five doses of study treatment (tofersen or placebo)
- Approximately 31 weeks including: up to 7-week screening period, 12-week dosing period, and 12-week follow-up period
• 37% lowering of SOD1 in CSF at highest dose 100 mg vs. no reduction in placebo group, p=0.002

** First identification of biomarkers of therapeutic efficacy
Other Positive Findings

Decline in function slowed

Breathing strength maintained

Limbs remain strong
Phase 2/3 study enrolled

.reporting 2021
What does this mean for the other 99%?

MND could be treatable

• For 10% with familial MND multiple promising gene trials
  • C9orf72 underway

• For 90% with sporadic MND
  • Understanding of sporadic MND has made major advances in recent years with many potential new treatments ready to be tested
  • Faster and smarter clinical trials using biomarker readouts and platform trial designs
  • Learning from familial MND
Sporadic MND

Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS

Andrew C. Elder, Hyung-Jun Kim, Michael P. Hart, Alice S. Chen-Plotkin, Brian S. Johnson, Xiaodong Fang, Maria Armakola, Felix Geser, Robert Greene, Min Min Lu, Arun Padmanabhan, Dana Clay-Falcone, Leo McCluskey, Lauren Elman, Denise Juhr, Peter J. Gruber, Udo Rüb, Georg Aebischer, John Q. Trojanowski, Virginia M.-Y. Lee, Viviana M. Van Deerlin, Nancy M. Bonini & Aaron D. Gitler

Nature 466, 1063–1075 (2010) | Cite this article

Therapeutic reduction of ataxin-2 extends lifespan and reduces pathology in TDP-43 mice

Lindsay A. Becker, Brenda Huang, Gregor Berl, Rosanna Ma, David A. Knowles, Paymaan Jafar-Nejad, James Messing, Hong Joo Kim, Armand Soriano, Georg Aebischer, Stefan M. Pulet, J. Paul Taylor, Frank Rigo & Aaron D. Gitler

Nature 544, 367–371 (2017) | Cite this article
Sporadic MND

A Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB105 in Participants With Amyotrophic Lateral Sclerosis With or Without Poly-cytosine-adenine-guanine (CAG) Expansion in the Ataxin-2 Gene
Reasons to be hopeful

- Gene therapies for types of MND are showing promise
- Advances in understanding of biology
- Trial design and execution