Severe & Rare/Neurodegenerative Franchise: Discovering New Options for Underserved Patients

**Neurodegenerative Diseases**

- Huntington's Disease
- Myotonic Dystrophy
- Amyotrophic Lateral Sclerosis
- Spinal Muscular Atrophy
- Trinucleotide Repeat Diseases

**Targeting RNA for Spinal Muscular Atrophy (SMA)**

- **Practice Examples**
  - Huntingdon's disease: is an inherited neurodegenerative disease
  - Myotonic dystrophy:
    - Genetically unstable & can become part of their genetic code
  - Huntingdon's disease:
    - Muscle weakness, wasting, and death

**Optimization of Human Clinical Candidates**

- Thoracic ASO A, 4 µg, n=24, 6 months after treatment
- Lumbar ASO A, 4 µg, n=24, 6 months after treatment

**Intrathecal Delivery Solutions Are Available Today**

- Intrathecal delivery allows for direct CNS administration
- Avoids the need for peripherally administered neurotoxic drugs

**ISIS-SMNRx Increases Survival & Behavior in a Mouse Model of Huntington's Disease**

- **BACHD Mice**
  - Human Htt expression when infused into the occipital cortex
  - 100,000 µg/g

**SOD1 Oligo: Onset 107+/-4, Survival 156+/-12**

- ISIS-SOD1Rx selected as first-in-man antisense drug
- Directly targets the known cause of this form of ALS

**Antisense Drugs Show Promise for the Treatment of a Wide Range of Diseases**

- Diseases that result from selective loss of neurons
- More common forms of neurodegenerative diseases that do not have an approved therapy
- Diseases severe enough to support direct CNS administration
- Diseases with an identified genetic cause
- Neurodegenerative diseases that are refractory to standard therapies

**Summary**

- Antisense drugs do not cross an intact blood-brain barrier
- Antisense drugs do not bind to RNA in the bloodstream
- Antisense drugs do not require delivery to the CNS

**Clinical Potency & Pharmacology**

- Safety: 1 2 3 4 5 6 8 SMN-2 mRNA
- Pharmacokinetics: IT injection or IT infusion

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**Neurodegenerative Disease Strategy**

- Directly targets the known cause of this form of ALS
- ISIS-SMNRx Increases Survival & Behavior
- ISIS-SOD1Rx advances in development

**Neurodegenerative Disease Targets**

- Huntington's Disease
- ALS (Lou Gehrig's disease)
- Myotonic Dystrophy
- Spinal Muscular Atrophy
- Trinucleotide Repeat Diseases

**Phase 2 Proof-of-Concept**

- At which time GSK can license the drug
- ISIS-SMNRx Increases Survival & Behavioral Changes in Spinal Motor Neurons

**Key Attributes & Target Rationale**

- Transgenic mouse liver
- SC dosing for drugs to be administered systemically
- Antisense drugs can uniquely target transcripts with abnormal polyglutamine

**Molecular Pathology**

- SPLICING ABERRANT mRNA
- DM1 CLINICAL
- CNS Effects
- DM1 Molecular Pathology

**Aberrant Splicing in DM1**

- Aseptically resected muscle tissue from DM1 patients
- SPLICING ABERRANT mRNA
- CNS Effects
- DM1 Molecular Pathology