Preclinical testing of the splice modulating oligonucleotide LSP-GR1

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Country

USA

Title of project or programme

Preclinical testing of the splice modulating oligonucleotide LSP-GR1

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 885,576.15

Start date of award

01/08/2011

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Preclinical Testing, Amyotrophic Lateral Sclerosis, Oligonucleotides, RNA Splicing, Pharmacology and Toxicology

Research Abstract
DESCRIPTION (provided by applicant): AMPA glutamate receptors mediate the majority of fast

excitatory neurotransmission in the central nervous system. Four AMPA receptor subunits exist, GluA1-GluA4, with functional channels containing various combinations of these four subunits. Dysregulation of AMPA receptor expression has been reported in many neurological disorders, including amyotrophic lateral sclerosis (ALS), a devastating and fatal disease for which no good treatment exists. AMPA receptors are alternatively spliced, with the best-characterized splice variants being the flip and flop isoforms. AMPA receptors containing flip vs. flop cassettes have distinct channel properties. GluA1 flip and flop variants have similar kinetics but the flip isoform shows greater sensitivity to glutamate, increasing synaptic gain. Expression of flip channels is associated with greater vulnerability to excitotoxicity and hyperexcitability. Increases in GluA1 flip to flop ratio are found in motor neurons (MNs) of ALS patients and in a mouse model of the disease. Splice modulating oligonucleotides (SMOs) have unique chemistries and distinct advantages over classic antisense oligonucleotides and siRNA, and are in clinical trials for treating muscular dystrophy and spinal muscular atrophy. We have developed an SMO, LSP-GR1, that specifically and potently reduces GluA1 flip in vivo. LSP-GR1 increases longevity and delays disease progression in a mouse model of ALS. The goal of our Phase II SBIR is to perform IND- enabling preclinical pharmacology/toxicology and CMC studies to set the stage for clinical testing of LSP-GR1 in ALS patients. GLP pharmacology/toxicology studies will be done in rats and cynomologus monkeys to evaluate toxicity and biodistribution. Chemistry, Manufacturing and Controls (CMC) studies will be done to evaluate structure, stability, and impurities of LSP- GR1. These studies should lead to IND-enabling data to allow LSP-GR1 to move forward to clinical testing in ALS patients.

Lay Summary
PUBLIC HEALTH RELEVANCE: Project Narrative Amyotrophic lateral sclerosis (ALS) is a devastating and fatal disease with no cure and no effective drugs to improve quality of life and lifespan. The goals of this research are to test the safety of a compound, LSP-GR1 that has the potential to slow disease progression ALS patients. Ultimately the goal of our program is to determine whether LSP-GR1 is a safe and effective drug to treat patients with ALS.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

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