QurAlis to Present Data That Show its Splice-Switching ASOs Restore UNC13A Function in ALS and Frontotemporal Dementia

UNC13A is an essential regulator of neurotransmitter release at synapses; mis-splicing is a critical RNA alteration occurring in up to 63 percent of all ALS patients and up to one-third of all FTD cases

Preclinical data to be featured in a poster presentation at AD/PD™ 2024

CAMBRIDGE, Mass., *March 4, 2024* – QurAlis Corporation, a clinical-stage biotechnology company driving scientific breakthroughs into powerful precision medicines that will alter the trajectory of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and other neurodegenerative diseases, today announced preclinical data that showed the company's UNC13A splice-switching antisense oligonucleotides (ASOs) modulate UNC13A splicing and restore normal synaptic activities in ALS and FTD. QurAlis' ASOs prevented cryptic exon inclusion in UNC13A transcripts, increased UNC13A protein levels, and normalized localization of UNC13A protein at the synapse.

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease characterized by the loss of neurons in the spinal cord, brainstem, and brain. A defining feature of both sporadic and familial disease is the cytoplasmic mis-localization of TAR DNA Binding Protein-43 (TDP-43). TDP-43 pathology is implicated in 95 percent of ALS cases and 50 percent of FTD cases.

UNC13A is an essential regulator of neurotransmitter release at synapses and is one of a number of pre-mRNAs that becomes mis-spliced due to loss of nuclear TDP-43 in disease. Up to 63 percent of ALS patients and up to one-third of FTD patients carry a single nucleotide polymorphism in the UNC13A gene or show TDP-43 pathology which greatly exacerbates UNC13A mis-splicing leading to loss of function of the UNC13A protein.

"There are currently no cures for ALS or FTD and limited therapeutic options are available for ALS and FTD patients who are in desperate need for effective therapies," said Dan Elbaum, Ph.D., chief scientific officer of QurAlis. "QurAlis has identified ASOs that modulate UNC13A splicing and restore normal synaptic activities. We believe that correction of UNC13A splicing can provide therapeutic benefit in relevant patient populations."

These data will be featured in a poster presentation at the AD/PD™ 2024 International Conference on Alzheimer's and Parkinson's Diseases and Related Neurological Disorders being held March 5-9, 2024 in Lisbon, Portugal. Details of the presentation are as follows:

Title: UNC13A Targeting Splice Switching ASOs Ameliorate TDP-43 Dependent Mis-splicing Phenotypes in FTD and ALS

Date(s)/Time: Thursday, March 7, 2024, and Friday, March 8, 2024 at 1:50-3:50PM CET
Poster and Abstract Number: P1214 / 2851
Poster Topic: FTD, ALS: TDP43, C9orf72, and TMEM106B 1
Session: D02 Therapeutic Targets, Mechanisms for Treatment
Location: Auditorium VIII
Presenter: Marisa Kamelgarn, Ph.D., senior scientist, QurAlis

Splice-switching oligonucleotides targeting UNC13A were screened via quantitative polymerase chain reaction (qPCR) and a small subset demonstrated correction of splicing and rescue of protein. From those rescue experiments, ASOs were used for functional assay testing.

Using in-house models of induced pluripotent stem cell (iPSC) motor and cortical neurons, QurAlis established a phenotype to demonstrate the cellular consequences of UNC13A mis-splicing due to TDP-43 loss of function.

TDP-43 mediated UNC13A loss partially disabled SNARE complex assembly and evoked synaptic vesicle release in human motor neurons. QurAlis' ASOs restored all or some aspects of SNARE complex assembly and synaptic vesicle fusion and release.

About QurAlis' FlexASO™ Splice Modulator Platform
Incorporating its proprietary FlexASO™ Splice Modulator Platform, QurAlis' ASOs correct UNC13A mis-splicing, restore UNC13A protein production, and reduce cryptic exons that may contribute to disease progression. The QurAlis FlexASO Splice Modulator Platform was developed to generate splice-switching ASOs with improved potency and an increased therapeutic index. In addition to UNC13A, QurAlis is currently exploring this ASO technology for multiple other disease targets.

About QurAlis Corporation
At QurAlis, we are neuro pioneers on a quest to cure. We work with a relentless pursuit of knowledge, a precise attention to craft, and an optimistic mindset to discover and develop effective precision medicines that will alter the trajectory of amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and other neurodegenerative diseases. Founded by an internationally recognized team of neurodegenerative biologists from Harvard Medical School and Harvard University, QurAlis is advancing a pipeline with therapeutic candidates that target specific components of ALS and FTD pathology and defined patient populations based on both disease-causing genetic mutation(s) and clinical biomarkers. For more information, please visit www.quralis.com or follow us on Twitter @QurAlisCo.

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