



# Pre-Symptomatic ALS Clinical Trial Paves the Way for Early Intervention Strategies in Neurodegenerative Diseases

A groundbreaking clinical trial for unaffected individuals at risk for a genetic form of amyotrophic lateral sclerosis (ALS) could pave the way for early intervention strategies for other forms of ALS as well as a wide range of neurodegenerative diseases, according to researchers at the University of Miami Miller School of Medicine.



Dr. Michael Benatar

“Historically, ALS therapy development has been hampered by difficulty in targeting the cause of disease, which is unknown in most patients, and long delays in initiating experimental therapies,” said Michael Benatar, M.D., Ph.D., professor of neurology, the Walter Bradley Chair in ALS Research and



executive director of the ALS Center at the University of Miami.

The multi-center ATLAS clinical trial, designed by Dr. Benatar in collaboration with Biogen, will tackle both challenges in treating ALS, also known as Lou Gehrig's disease. This progressive, fatal neurological disease attacks the nerve cells responsible for controlling voluntary muscles. Mutations in the *SOD1* gene are responsible for about 2% of all ALS.

ATLAS will utilize the investigational drug tofersen (which targets SOD1) in a subset of *SOD1* mutation carriers who do not yet have clinical manifestations of disease. The trial will evaluate whether tofersen can delay the onset or slow the progression of ALS in this high-risk population.

The design of ATLAS is built upon the findings of the *Pre-fALS* study, led by Dr. Benatar and Joanne Wu, Sc.M., research associate professor of neurology and associate director of research at the University of Miami ALS Center. After studying pre-symptomatic ALS gene mutation carriers for more than a decade, the UM team and their collaborators discovered in 2017 that neurofilament light (NfL) levels in the blood are elevated prior to the emergence of clinical disease. In individuals with *SOD1* gene mutations associated with fast-progressing disease – the group that will be eligible to participate in ATLAS – the rise in NfL was observed as far back as 6-12 months before the onset of symptoms.

Together with data from Biogen's recently completed phase 3 study of tofersen among patients with clinically manifest *SOD1*-ALS, ATLAS's findings will inform the optimal timing of tofersen administration, and the relative benefits of treatment initiated before vs. after clinical onset of the



disease.

Dr. Benatar said the UM team has already enrolled the first 26 participants (as of mid-October) in the international ATLAS trial, which is sponsored by Biogen. Overall, ATLAS will enroll approximately 150 patients with the *SOD1* gene mutation and monitor them during the run-in phase of the study for changes in their neurofilament levels. If at any point during the run-in period a participant's NfL levels increase above a pre-determined threshold, the participant – if still clinically pre-symptomatic – will be randomly assigned to receive either tofersen or placebo. If any study participant develops clinical manifestations of ALS (during run-in or after randomization), they will transition to open label tofersen.

“ALS, like cancer, almost certainly begins at the molecular or cellular level, and may be quite advanced by the time symptoms or other outward manifestations of disease appear,” Dr. Benatar explained. Early detection and treatment are therefore essential. “ATLAS offers a unique opportunity to demonstrate the effectiveness of early, even pre-symptomatic, intervention with an experimental therapeutic that targets the underlying cause of disease. This approach, if successful, may have profound implications for how we approach the treatment of other genetic and non-genetic forms of ALS, as well as other neurodegenerative disorders.”

For more information about the ATLAS clinical trial, go to: <https://clinicaltrials.gov/ct2/show/NCT04856982>

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