OBJECTIVE: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progressive paralysis caused by degeneration of motor neurons. There is no known treatment for ALS. The only approved drug for ALS is riluzole, a compound that reduces motor neuron excitability and has marginal benefit. Over the last decade, insight into the pathogenesis of ALS has been provided by studies of genetic forms of the disease. In particular, one familial form, has been convincingly ascribed to mutations in a gene that makes a protein anti-oxidant known as superoxide dismutase or SOD 1. Knowledge of these mutations has greatly abetted the search for ALS treatments, leading to the development of both animal and in vitro models of ALS. The ALS mice have been invaluable for testing candidate drugs. In general, those drugs that have failed in human ALS trials have failed in the ALS mice. For this reason, we believe that drugs that are efficacious in the ALS mice should be considered as candidate drugs for human ALS. We propose to build upon exciting and novel findings in the ALS mice generated at the Bedford VA and to translate these into human studies.

Research Design/Methodology: The long-term goal is to determine the tolerability and efficacy of sodium phenylbutyrate (NaPB) in human subjects with ALS. We first propose to establish the safety and tolerability of 9,18 and 27 grams per day of NaPB in 40 participants with ALS treated for 20 weeks. Each participant will have the dosage increased over a period of 12 weeks to the maximum anticipated dosage of 27 grams/day, then maintained on that dosage until Week 20. Serum levels of NaPB will be assessed at the studied dosages. Results from this will be used to determine dosing for a prospective NaPB efficacy trial in ALS patients.

Since many patients are unwilling to stop taking riluzole, riluzole will need to be included as a background treatment in medication trials with other agents. Because compounds often have multiple mechanisms of action, effects of combined therapies cannot be predicted. We will identify optimal doses for phenyl butyrate and riluzole and examine their combined therapeutic effects in transgenic ALS mice and compare efficacies with regards to behavioral and neuropathological phenotype in the ALS mice. We will assess temporal outcome measures in treated and non-treated transgenic ALS mice analyzing behavioral correlates, survival, neuronal measurements of injury, toxicity, and pharmacokinetics. We will model medication trials in ALS mice initiating treatment before and after symptoms are present.

The outcomes of the proposed aims will contribute greatly to the planning of future clinical trials using phenylbutyrate alone or in combination with uncontrolled compounds, such as riluzole, in ALS patients.