MJFF PARTNERING PROGRAM

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

Amicus Therapeutics
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Organization and Team Overview

Amicus Therapeutics (Nasdaq:FOLD) is a biopharmaceutical company at the forefront of developing therapies for rare and orphan diseases. The Company is developing orally-administered, small molecule drugs called pharmacological chaperones, a novel, first-in-class approach to treating a broad range of diseases including lysosomal storage disorders and diseases of neurodegeneration. Amicus' lead program with migalastat HCl is in Phase 3 for the treatment of Fabry disease. Amicus is a fully integrated drug-development company with resources covering medicinal chemistry, pre-clinical discovery, in vitro and in vivo pharmacology, bioanalysis, toxicology, and clinical development.

Mutations in GBA1 are the most common genetic risk factor for Parkinson's disease identified to date. By leveraging our research and development of pharmacological chaperones (PC) for Gaucher disease, Amicus has developed new, orally-available PCs that can cross the blood-brain barrier and increase the enzyme activity of GCase (GBA1).

Opportunity Overview

Cellular levels of α-synuclein are maintained by balancing expression with lysosomal degradation. Epidemiological data (Sidransky et al., NEJM 2009) show that mutations in GBA1, which result in reduced activity or trafficking of the enzyme acid-β-glucocerebrosidase (GCase), a lysosomal enzyme that catalyzes the hydrolysis of the sphingolipid glucosylceramide (GlcCer), are a major risk factor for PD. A feed-forward pathological loop between mutant GCase and α-synuclein provides a mechanism for the increased risk of PD among carriers of mutant GBA1 alleles, and also suggests a role for GCase deficiency in sporadic PD (Mazzulli et al., Cell 2011). Indeed, GCase deficiency promotes accumulation of α-synuclein, whereas increased α-synuclein impairs the trafficking of GCase to lysosomes, thus resulting in the accumulation of α-synuclein to pathological levels. Overexpression of GCase has been shown to reduce the accumulation and aggregation of α-synuclein and improves neuronal function in vitro and in vivo (Sardi et al., PNAS 2011), further supporting increased GCase activity as a therapeutic target for the treatment of synucleinopathies.

Since 2002 Amicus has been developing pharmacological chaperones that increase the lysosomal activity of GCase. Based on early epidemiological evidence for an over-representation of Gaucher (GBA1) carriers among patients with sporadic Parkinson's, Amicus began research into a possible biochemical link between GCase and accumulation of α-synuclein. In 2006 we and others determined that mouse models of Gaucher disease have an abnormal accumulation of endogenous murine α-synuclein that is correlated with the accumulation of the GCase substrate, the sphingolipid glucosylceramide, in the brain. Early pre-clinical efficacy studies in mice that overexpress human α-synuclein treated with the pharmacological chaperone AT2101 demonstrated elevation of GCase activity in the brain and a concomitant prevention of α-synuclein accumulation.

In 2008, a medicinal chemistry campaign to find analogs of AT2101 that might have superior properties (such as greater brain penetration) identified a series of compounds that have improved bioavailability, greater CNS penetration, higher potency for the stabilization of GCase, improved specificity, and faster washout from both bulk tissue and the lysosome. From among several promising compounds, AT3375 was chosen as an IND development candidate. Pilot efficacy studies with AT3375 have confirmed reduction of α-synuclein in the brain and improvement in α synuclein-dependent behaviors in pre-clinical models. Additional efficacy studies are ongoing. In both the rat and monkey, 28-day sub-chronic toxicology and safety pharmacology have been completed for AT3375. GMP supplies of AT3375 are available to support Phase 1 studies.

It is estimated that between 5 and 7% of Parkinson's patients are carriers of mutations in GBA1, implying a population of 50,000 - 70,000 patients in the US. Large cohorts of PD patients who are GBA1 carriers have been identified in the US and Europe (Sidransky et al., NEJM 2009; Lesage et al., HMG 2010).

For additional information, please contact: ResearchPartnerships@michaeljfox.org

Details of MJFF Grant

Amicus has received funding from the MJFF on two occasions. First, in 2006 under the Therapeutics Development Initiative, for an efficacy study with a first-generation PC for GCase (GBA1) known as AT2101, and again in 2010 under the Alpha-synuclein Therapeutics Initiative for a second-generation PC, AT3375.

The 2006 award allowed a 12-week examination of AT2101 efficacy in the PDGFβ-human-α-synuclein overexpression mouse model. Administration of AT2101 was shown to prevent accumulation of α-synuclein in the hippocampus of these animals. This initial funding from the MJFF led to additional internal investment to support a 26-week study of AT2101 in the same PDGFβ mouse model as well as a pilot study in the Thy-1-human α-synuclein mouse model. In both cases prevention of α-synuclein accumulation in the hippocampus was demonstrated. Furthermore, a fully-powered study in the Thy-1-human α-synuclein mouse model, which was conducted in collaboration with Dr. Chesselet at UCLA, showed a reduction of α-synuclein in dopaminergic neurons of the substantia nigra and behavioral improvement. While these four studies showed the promise of PCs for preventing the accumulation of α-synuclein in the brain, they also revealed the limitation of a relatively narrow efficacious dose range.

This limitation of AT2101 was addressed by a medicinal chemistry campaign to synthesize and examine about 200 analogs of AT2101 for improved pharmacokinetic properties that may increase the effective dose range. The PC AT3375 was chosen for further development and a second award from the MJFF was obtained in 2010 to study the efficacy of AT3375 in the Thy-1-human-α-synuclein mouse model at UCLA in the laboratory of Dr. Chesselet.

The 2010 award covers a two-year period. In the first year, month-old Thy-1 (Line 61) mice were administered AT3375 for a period of 16-weeks over a range of doses. Both histological analysis of α-synuclein accumulation in dopaminergic neurons of the substantia nigra and behavioral measures of motor function demonstrated a positive effect of AT3375. Based on these results, the second year program has been initiated with the Chesselet laboratory. In this case, 10-month old Thy-1-human-α-synuclein mice are being administered AT3375 for a period of 16 weeks. The endpoints are the measurement of striatal dopamine, which decreases by half in untreated animals of this age, behavioral tests remediated by L-DOPA, and α-synuclein accumulation. Results from this study are expected in Q412.

Results and Potential Next Steps

AT2101 and AT3375 have demonstrated efficacy in multiple mouse models that overexpress human α synuclein. The efficacious dose range for AT2101 is limited and the advanced properties of AT3375 should address this limitation. A pilot study with AT3375 has shown efficacy at a limited range of doses to date and further optimization of dose and administration regimen are needed. In addition, the ongoing study in aged Thy-1 mice described above, additional PK and PD studies in the CSF, brain, and plasma of non-human primates will inform the translation of PK/PD relationships in pre-clinical models to human dosing. Additional GMP material for formulation, Phase 2 studies, and chronic toxicology will be synthesized.

Intellectual Property Status

Amicus Therapeutics has exclusive rights to patents covering AT2101 as a composition of matter and owns an issued patent covering the specific salt, AT2101-tartrate. A composition of matter patent application covering AT3375 is pending. Two method of use patents covering the use of pharmacological chaperones, including AT2101 and its derivatives, for the treatment of Parkinson's disease have also issued.

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