

**SynAgile Corporation
Prof. Adam Heller (Lead PI)****Organization and Team Overview**

SynAgile was founded by Ephraim Heller and Adam Heller in January, 2011. Ephraim and Adam were previously the founders of TheraSense, a glucose monitoring company, which was sold to Abbott for \$1.2 billion. After TheraSense Ephraim was the founding CEO of AngioScore, a privately held balloon angioplasty company, 2011 revenues of ~\$40M. Prior to TheraSense, Adam co-developed one of the first commercial lithium batteries. He is a professor at University of Texas at Austin. In a White House ceremony President Bush presented him with the 2007 US National Medal of Technology and Innovation, the top technology award in the United States.

Opportunity Overview

SynAgile is developing DopaFuse, a L-DOPA prodrug, based on the API L-DOPA ethyl ester (LDEE). DopaFuse is continuously, subcutaneously infused using a simple insulin infusion pump. DopaFuse will enable patients with Parkinson's disease (PD) to achieve near-constant plasma levels and dramatically reduce their motor fluctuations.

All PD patients eventually end up on L-DOPA therapy. The pharmacokinetics of oral L-DOPA are very poor, with erratic absorption and a half life of only 60-90 minutes. Advanced PD patients routinely cycle between the "off" state (underdosing) and dyskinesias (overdosing), often spending many hours per day with severe motor fluctuations. Today the only alternative available in the United States is deep brain stimulation, an expensive and highly invasive surgical procedure. Numerous studies of continuous intravenous and intrajejunal infusion of L-DOPA have demonstrated that stabilizing plasma L-DOPA concentrations results in dramatic reductions in off time and dyskinesias; however, the risk of complications and inconvenience of these routes of administration precludes long term use at home by most patients. While theoretically superior, subcutaneous L-DOPA infusion therapy has not been feasible due to the poor solubility of L-DOPA, requiring infusion of more than one hundred mL/day.

LDEE is a highly soluble prodrug of L-DOPA, making it suitable for continuous subcutaneous infusion. LDEE is rapidly enzymatically hydrolyzed to L-DOPA and ethanol in the body. SynAgile has reduced the volume of a typical daily dose of 1,000 mg L-DOPA to a amount that can be conveniently infused subcutaneously.

DopaFuse is a reformulation of LDEE, a safe, proven, oral compound, into a subcutaneously infusible solution. In two Phase III clinical trials conducted by Teva and in earlier studies, oral LDEE was demonstrated to have safety and efficacy equivalent to that of L-DOPA in over 700 patients with PD (400 treated with LDEE, 300 treated with L-DOPA controls). However, oral LDEE was never submitted for marketing approval because it was not superior to L-DOPA. Two further clinical studies of subcutaneous injection of LDEE aqueous solutions in 23 patients with advanced PD demonstrated efficacy of injected LDEE in turning patients "on" and that subcutaneous delivery of LDEE was well tolerated. SynAgile has acquired exclusive rights to the Teva IND data.

Details of MJFF Grant

The Michael J. Fox Foundation for Parkinson's Research has awarded SynAgile a grant to support a Phase 2A clinical study of DopaFuse in patients with advanced PD.

Results and Potential Next Steps

Results in an animal model demonstrate that: (a) DopaFuse is well tolerated; (b) there is negligible systemic exposure to the prodrug; (c) high plasma L-DOPA concentrations can be maintained with low variability; and (d) transport from the subcutaneous tissue to the plasma is rapid.

DopaFuse was subcutaneously infused at a constant rate for 8 hours in an animal model using a Medtronic Paradigm insulin pump. The design of the experiment is presented in Table 1.

Table 1
Experimental Design

Treatment Day	Low Dose Rate	High Dose Rate
Day 1	1.6 mg LDEE/kg/hr (equal to 1.4 mg L-DOPA/kg/hr) at Site L1	10 mg LDEE/kg/hr (equal to 8.8 mg L-DOPA/kg/hr) at Sites L1 and L2
Day 8	1.6 mg LDEE/kg/hr (equal to 1.4 mg L-DOPA/kg/hr) at Site R1	10 mg LDEE/kg/hr (Site L1) (equal to 8.8 mg L-DOPA/kg/hr) Reinfusion at Sites L1 and L2

The low dose rate is 1.6X greater than a typical dose rate in a patient. The high dose rate is 10X greater than a typical dose rate in a patient.

The animals received oral carbidopa 25 mg at 12 hours prior to the start of the infusions and at t = 0 and 4 hours during the infusion. Infusion sites were monitored for skin reactions for 14 days post-infusion. Venous blood was sampled and the plasma assayed for LDEE and L-DOPA during the infusions at t = 0, 20 minutes, 40 minutes, and 1, 2, 4, 8 hours (end of infusion), 8 hours 40 minutes, 9 hours 40 minutes and 10 hours 50 minutes.

Conclusions

DopaFuse infusions were safe and well tolerated. No safety issues or adverse events were observed. Four infusions at the low dose rate (2 de novo sites and 2 reinfusions at these sites) resulted in no infusion site reactions at any time. Sixteen infusions at high dose rate (8 de novo sites and 8 reinfusions at these sites) resulted in no site reactions in 13 infusions and mild, transient site reactions in 3 infusions, all of which fully resolved.

Plasma LDEE concentrations were extremely low at all times, as desired. LDEE was below the limit of detection at all times during the 0.9 mg/hour per kg L-DOPA equivalent infusions. The highest concentration observed during the high dose infusions (where plasma levels of L-DOPA reached 14,000 ng/mL) was below 20 ng/mL.

Plasma L-DOPA profiles exhibited low variability, increasing monotonically from the start of the infusion until t=4 hours, then remaining approximately constant or rising slowly until t=8 hours. Importantly, plasma L-DOPA profiles exhibited no major concentration drops at any time. Extremely high plasma L-DOPA concentrations, up to ~14,000 ng/mL, were maintained.

Rapid transport of drug from the subcutaneous tissue to the plasma without depot formation was demonstrated by the prompt drop in L-DOPA concentrations upon cessation of the LDEE infusion.

Intellectual Property Status

Based on SynAgile's intellectual property position, we believe SynAgile will be the only company with the ability to subcutaneously infuse any L-DOPA prodrug. To the best of our knowledge, DopaFuse has clear freedom to operate. Aqueous LDEE solutions are typically unstable, decomposing within hours. DopaFuse is a proprietary, stable formulation that enables continuous infusion of a concentrated LDEE solution over a 24-hour period.