PsychoGenics Inc.
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Organization and Team Overview

PsychoGenics is a primarily a preclinical CRO that provides a full complement of partnered drug discovery capabilities with a focus on psychiatric, cognitive and neurodegenerative disorders, pain, inflammation, spinal cord and traumatic brain injury.

As part of its hybrid business model, PsychoGenics also has partnered and internal drug discovery efforts using proprietary, high-throughput behavioral testing platforms that combine expertise in behavioral neurobiology with the power of bioinformatics to rapidly screen compound libraries for CNS activity.

Eltoprazine is one of three assets that was developed internally; the other two assets are a nicotinic alpha-6 program and an dual A1a/A2a adenosine antagonist program for the treatment of Parkinson’s Disease.

Opportunity Overview

Eltoprazine is a partial agonist at 5-HT\textsubscript{1A} and 5-HT\textsubscript{1B} receptors. This compound was originally developed by Solvay Pharmaceuticals, Inc. for the treatment of aggression associated with psychiatric and cognitive disorders. PsychoGenics has licensed exclusive, worldwide rights to develop and commercialize this compound. There is extensive non-clinical and clinical data on eltoprazine.

Single dose toxicity of eltoprazine has been investigated in mice, rats, and dogs. Six-month toxicity studies in male and female rats and dogs have also been completed. Eltoprazine was not mutagenic in the \textit{in vitro} bacterial reverse mutation assay, \textit{an in vitro} assay in cultured Chinese hamster ovary (CHO) cells, or in the \textit{in vitro} CHO cell forward mutation assay. Eltoprazine was negative \textit{in vivo} in males and females in the mouse bone marrow micronucleus assay. Teratology studies in rats and rabbits revealed no evidence of embryo lethality or teratogenicity.

The pharmacokinetics of eltoprazine in healthy subjects has been defined. After oral administration, eltoprazine is completely absorbed with no significant first pass metabolism. Eltoprazine is excreted primarily through renal mechanisms, with approximately 40% of the drug excreted in the urine unchanged. Binding to human plasma proteins is relatively low (15%). There is no CYP inhibition.

The mean plasma half-life ($t_{1/2}$) is approximately 8 hours. After oral administration, the maximum concentration ($C_{max}$) and area under the concentration-time curve (AUC) are essentially linear in the range of 5 to 30 mg.

In all, over 600 humans have been treated with eltoprazine in clinical studies in single dose and multiple dose studies. Patients have been dosed with single and multiple doses of eltoprazine ranging between 0.25 and 30 mg. Overall, the compound was safe and well-tolerated.

Experiments in 6-OHDA rodent model of PD indicate that eltoprazine is highly effective, both acutely and sub-chronically in suppressing dyskinesias in the rat PD model, giving a complete block of established dyskinesias, and blockade of development of dyskinesias in drug-naïve animals, already at a dose of 0.3 mg/kg, with a 50% reduction at 0.1 mg/kg. These doses are about 10-fold lower than the standard effective dose previously used in rodent experiments on aggressive behavior.

The sub-chronic rodent study also indicates:
- Protection against development of dyskinesia (potential neuro-protective effect)
- No tolerance to eltoprazine over the time period tested.
- Suppression of existing dyskinesia symptoms

Similarly, eltoprazine reduced dyskinesias at low doses of 0.5 mg/kg and 0.75 mg/kg in MPTP monkeys.

Other non-clinical studies also show potential for eltoprazine to treat non-motor symptoms of PD, such as depression and cognitive deficits. PsychoGenics is pursuing a separate clinical study to assess the effect of eltoprazine in improving the cognitive impairment in schizophrenic patients and expects that the results of this study could provide the basis for assessing cognition in PD patients as well.
Details of MJFF Grant

The Michael J. Fox Foundation provided partial funding for a double-blind, randomized, placebo controlled, dose finding study of oral eltoprazine for treatment of levodopa-induced dyskinesias (LID) in Parkinsons Disease in a levodopa challenge-dose setting. The study was conducted in collaboration with Anders Bjorklund, MD, Ph.D, professor at Lund University, Sweden.

Two sites in Sweden (Lund University and Karolinska University) participated. A total of 22 patients completed the study. Each patient was exposed to all five treatment arms – baseline placebo (Visit 1) and four randomized treatment visits consisting of 3 acute doses of eltoprazine (2.5 mg, 5 mg and 7.5 mg) and a second placebo. At each visit, the patients were assessed for PD and dyskinesia symptoms (using the UPDRS-III, CDRS and Rush Scales) every 30 minutes post-dose, for up to 3 hours and video-taped.

In order to prevent bias, the video tapes were blinded and assessed by two independent raters. The mean values of the two raters was used in the analysis.

Results and Potential Next Steps

Data from this study shows that eltoprazine showed a statistically significant reduction in LID at the 5 mg dose (p = 0.0007) and the 7.5 mg dose (p = 0.0467), without adversely affecting levodopa efficacy. Eltoprazine was also well tolerated in this study and there were no serious adverse events.

The data also showed a clear reduction in Parkinsonian symptoms and no difference from the placebo treatment, attesting to the continued efficacy of levodopa.

PK parameters showed that the Cmax were linear and dose-dependent; the Cmax in this patient population was similar to that in healthy volunteers, indicating a lack of drug-drug interaction. The Tmax of L-dopa (~1.5 hours) and the Tmax of eltoprazine (~2 hours) make it ideal for co-administration.

Based on this data and the sub-chronic rodent data, PsychoGenics believes that the effect seen with acute dosing will be replicated in chronic studies.

PsychoGenics intends to continue development of this compound in LID and other additional indications, with the help of a partner who has the infrastructure to conduct large trials. The main focus of PsychoGenics business is preclinical services in the CNS therapeutic area. As such, we do not maintain the infrastructure to conduct large pivotal trials and commercialize the product. We anticipate using the positive data generated to partner with a pharma/biotech company that has the resources to advance this program to late stage clinical and commercialization.

Intellectual Property Status

PsychoGenics has generated and/or in-licensed intellectual property to provide protection for eltoprazine to treat both the motor and non-motor symptoms of the disease.