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Positive Early Results For Addex Parkinson's Drug Dipraglurant Spur Hopes For Deal

In a small, short Phase IIa study, an oral inhibitor of mGluR5 proved effective at reducing dyskinesia caused by levodopa. If future trials are positive, the drug would have a significant positive impact on Parkinson's patients, says the Michael J. Fox Foundation.

Addex Therapeutics' successful Phase IIa study of dipraglurant (ADX48621) builds on a body of evidence supporting mGluR5 as a target for dyskinesia caused by the standard of care generic Parkinson's treatment levodopa, and it may help the Swiss biotech attract a partner.

The market for Parkinson's disease is largely dominated by generics, including levodopa (*"Parkinson's Disease At A Crossroad: Deals And Emerging Therapeutics" — "The Pink Sheet," Jun. 13, 2011*). But while levodopa is effective it has the troublesome side effect of dyskinesia, a movement disorder characterized by the inability to control movements that affects about 80% of patients after prolonged treatment.

Announcing top-line results from a Phase IIa study in 76 Parkinson's patients with moderate-to-severe PD-LID on March 21, Addex said the candidate had proved safe and well-tolerated, satisfying the trial's primary objective of safety and tolerability as well as showing efficacy in reduction of LID severity, an exploratory secondary objective in the trial.

News about safety is reassuring to investors, considering that another candidate from the company with the same mechanism of action – ADX10059 – was terminated in 2009 due to unexpected safety problems related to effects on the liver, Jefferies analyst Peter Welford commented in a March 22 note. But dipraglurant has a different molecular scaffold than its predecessor so "worries" were "misplaced," the analyst wrote.

Furthermore, the analyst concluded, the positive data could be a catalyst for a partnership.

In an interview, Addex CEO Bharatt Chowrira said that the company hopes to partner the compound by the end of the year. He said the firm has had "broad outreach" with companies involved in CNS and Parkinson's. Potential partners will need the full results to assess the candidate; these should be released in early summer.

The next steps for development will depend partly on the partner. Addex may decide to run a small dose-ranging study and then two pivotal studies. It's not clear whether an even lower dose than was used in the Phase IIa trial might be efficacious, Chief Medical Officer Charlotte Keywood said in an interview. Alternatively, the next step might be a large pivotal dose-ranging study, the first of two Phase III trials.

Filling A Pressing Need

Currently, there are no FDA-approved options for levodopa induced dyskinesia (LID). Some patients need expensive surgical treatment, and physicians may reduce the dose of levodopa, but efficacy may be sacrificed in the process. An oral therapy would meet a pressing demand.

"Right now, patients are faced with this balancing act. They are taking a drug and getting a benefit, but they also get these side effects and in the end they wind up under-medicating," Todd Sherer, CEO of the Michael J. Fox Foundation, said in an interview. The foundation funded the Addex study via a $900,000 grant (*"Addex Wins Michael J. Fox Foundation Funding To Take Its Dopamine Side Effect Therapy Into Phase II Testing" — "The Pink Sheet" DAILY, Sep. 7, 2010*).

Dipraglurant is an oral small molecule allosteric modulator that selectively inhibits the metabotropic glutamate receptor 5 (mGluR5), a glutamate that has been shown to be linked to dyskinesia in preclinical research. Novartis AG also has a drug with the same mechanism of action in Phase II, called AFQ056.

"A lot of evidence is building around this mechanism," said Sherer, commenting on Addex and Novartis' candidates, as well as extensive animal studies.

Sherer noted that developing treatments for LID is a high priority for the foundation, as such a drug would have a

"significant impact for management of disease" and improving patients' quality of life.

Finding a successful treatment to limit this side effect would "do more overnight for the PD community than any other type of drug," Bill Langston, scientific director and CEO of the Parkinson's Institute in Sunnyvale Calif., said in an interview about the trial results posted on the foundation website.

The potential impact was not lost on the market, which rewarded Addex well on the news, sending the stock price up by CHF 5.44, or 84%, to CHF 11.90 on March 22.

Meeting Trial Objectives

The four-week, double-blind Phase II study randomized 52 patients to the test drug and 24 to placebo. Those on the study drug were given 50 mg doses from day 1 to day 14, followed by 100 mg from days 14 to 28.

Efficacy was measured using the modified abnormal involuntary movement scale (mAIMS), patient diaries documenting off-time (impaired voluntary movement) and on-time (with or without dyskinesia and sleep). Additional endpoints include the Unified Parkinson's Disease Rating Scale, the clinician and patient global impression of change (CGIC and PGIC) and an evaluation of patients' mood using the hospital anxiety and depression score.

There were no significant changes in safety parameters and no changes in liver function tests for either group, Addex reported. Rates of adverse events were similar: 88.5% for the test drug compared to 75% for placebo. The dipraglurant side effects, which included vertigo, visual disturbance, and reports of feeling drunk, were seen in less than 10% of patients and were not severe or dose limiting.

Both the 50 mg and 100 mg doses showed significant reduction in LID. Based on mAIMS, LID was significantly reduced on day 1 (50 mg, $p = 0.042$) and on day 14 (100 mg $p= 0.038$). A 30% reduction in mAIMS or a 20% separation from placebo was achieved on days 1, 14 and 28. The magnitude of reduction in mAIMS was maintained for dipraglurant on day 28 (100 mg) but was not statistically significant on the final day due to an increase in the placebo response that day.

The drug was effective at reducing dystonia severity in addition to chorea, the two main components of LID.

Patient diaries also suggested a significant reduction in LID severity, based on reports of "on" and "off" time. Patients and clinicians tended to favor treatment with the test drug, with a higher percentage reporting improvement on the test drug based on PGIC and CGIC. Those on dipraglurant had up to 70 minutes more of "on" time compared to those on placebo.

Importantly, UPDRS motor scores show that the improvement in dyskinesia did not come at the expense of levodopa efficacy.

It's difficult to ask more from a Phase IIa clinical trial, Ladenburg Thalmann analyst Juan Sanchez commented in a March 22 note.

"Future trials will determine whether the strong signal seen in this trial will be maintained (or improved) once more patients are treated for longer periods using reported outcomes as primary instruments;" the analyst wrote.

By Emily Hayes