



PRESS RELEASE

## Glutamate Receptor “mGluR5” Implicated in GERD

Data Published in *GUT* Shows Addex' ADX10059 Reduces GERD Symptoms in Patients

First Peer-Reviewed Publication of a Clinical Study of an mGluR5 Inhibitor in GERD

**Geneva, Switzerland, 27 May 2009** – Allosteric modulation company Addex Pharmaceuticals (SIX:ADXN) is pioneering a new approach to the treatment of gastroesophageal reflux disease (GERD), a common disorder affecting approximately 15 percent of people. GERD is the cause of commonly recognized unpleasant symptoms like heartburn, acid brash and reflux. By inhibiting metabotropic glutamate receptor 5 (mGluR5) signaling with ADX10059, a negative allosteric modulator (NAM) of mGluR5, Addex believes that the functioning of the lower esophageal sphincter can be normalized, thereby reducing exposure of the esophagus to acidic stomach contents and treating symptoms by addressing the cause of GERD.

Clinical data, published online in the peer-reviewed journal *GUT* and to be presented next week at the Digestive Disease Week conference (DDW, May 30 - June 4, Chicago), demonstrated that following administration of ADX10059 for a single day, patients reported fewer and shorter episodes of GERD symptoms compared to when they received placebo (2 versus 7 episodes, with a mean total duration of 5 minutes versus 14 minutes for placebo). This reduction in symptoms was associated with a statistically significant reduction in duration of esophageal acid exposure, during the 24 hour pH monitoring period, compared to placebo.

The researchers also found that night time reflux, which causes sleep disturbance and increased risk of esophageal damage, and reflux events following meals were also significantly reduced by ADX10059 therapy.

“About one-third of GERD patients have symptoms that remain inadequately controlled even after treatment with the best available medicines, which reduce acidity of stomach contents to treat symptoms,” said Jan Tack MD, co-author, leading GERD expert and chairman of the department of pathophysiology at the University of Leuven. “Thus, new approaches are needed that address the underlying cause of this common disorder. These clinical data suggest targeting glutamate signaling via negative allosteric modulation of mGluR5 using ADX10059 improves symptoms because it inhibits reflux, the cause of GERD.”

Data from a Phase I study of a modified release formulation of ADX10059, which supported the findings of the above study in GERD patients, also will be presented at DDW. This study in healthy volunteers showed that, compared to placebo, the new formulation of ADX10059 reduced the occurrence of reflux events on impedance pH monitoring, following intake of a refluxogenic breakfast. The modified release formulation also achieved the objective of improving the side effect profile seen previously with the immediate release formulation, and in reducing the dosing interval to twice daily from three times daily. Phase IIb trials with ADX10059 in GERD, both as a monotherapy and, separately, in combination with proton pump inhibitor (PPI) treatment are ongoing in the U.S. and EU.

“mGluR5 inhibition with ADX10059 represents a novel way of potentially treating GERD. These data published in *GUT* and to be presented at DDW represent some of our early clinical experience with ADX10059. Our Phase IIb studies are progressing well and we expect to report data on both the monotherapy and PPI combination studies late in 2009,” said Charlotte Keywood, chief medical officer at Addex.

**Note to Editors:** The *GUT* article, entitled, “A proof of concept study evaluating the effect of ADX10059, a metabotropic glutamate receptor-5 negative allosteric modulator, on acid exposure and symptoms in gastro-esophageal reflux disease,” is now freely available at the following link:

<http://gut.bmj.com/cgi/content/abstract/gut.2008.162040v1?paperoc>

The following will be presented at DDW:

**Abstract 774** (oral presentation): Effect of mGluR5 inhibition with ADX10059, on day and night time reflux and clinical symptoms, in patients with gastro-esophageal reflux disease (GERD): a proof of concept study. Charlotte Keywood, Addex Pharmaceuticals; Jan F. Tack, Katholieke Universiteit Leuven, Leuven, Belgium

Session: AGA Institute GERD Treatment: Beyond PPI, June 2, 2009 3:15 - 3:30 PM, McCormick Place, Room E350

**Abstract M1867** (poster presentation): Efficacy and Tolerability of ADX10059, a Negative Allosteric Modulator of mGluR5, On Gastro-Esophageal Reflux: a pH-Impedance Study in Healthy Subjects. Frank Zerbib, Hôpital Saint André CHU, Bordeaux, France; Charlotte Keywood, Addex Pharmaceuticals

Session: AGA Institute GERD: Pharmacological Treatment, June 1, 2009, 8:00 AM - 5:00 PM, McCormick Place, South Hall

**mGluR5 inhibition:** In GERD, inhibition of mGluR5 aims to restore normal function of the LES muscle thereby preventing reflux and addressing the underlying cause of the disease. Indeed, ADX10059 has been shown by Addex to reduce reflux events and reduce esophageal acid exposure in two separate clinical trials. Research has shown that mGluR5 inhibition improves LES function in animals. Reflux inhibitors have been recognized as potentially being the next generation GERD therapy because they address the cause of the disease and are complementary to marketed acid suppression therapies. Inhibition of mGluR5 has therapeutic potential in multiple other indications because, as with other glutamate receptors, mGluR5 is involved in a variety of functions in the central and peripheral nervous systems\*. In addition to GERD, mGluR5 inhibitors have achieved clinical proof of concept in separate studies in patients with migraine headache, Parkinson's disease levodopa induced dyskinesia (PD-LID) and generalized anxiety disorder (GAD).

\*mGluR5 antagonists: Discovery, characterization and drug development, Current Opinion in Drug Discovery & Development 2008 11(5):655-665

**GERD** is a chronic condition caused by stomach contents flowing back into the esophagus on a regular basis. The underlying cause of this is an abnormally functioning lower esophageal sphincter (LES) muscle that allows stomach contents to pass too easily back into the esophagus. GERD leads to painful symptoms like heartburn and can also damage the lining of the esophagus. It is a common disorder with prevalence at about 15 percent in the U.S. and between 10 percent and 25 percent in EU. Marketed GERD products work by reducing the acidity of the stomach contents but do nothing to reduce reflux events, so that in many patients symptoms of GERD persist because the cause of the disease is left untreated.

**Addex Pharmaceuticals** ([www.addexpharma.com](http://www.addexpharma.com)) discovers and develops allosteric modulators for human health. Allosteric modulators are a different kind of orally available small molecule therapeutic agent, which we believe will offer patients better results than classical drugs. Our lead allosteric modulator product, ADX10059, has achieved clinical proof of concept and is in Phase IIb testing for the treatment of GERD and, separately, migraine headache. Both are important diseases for which existing products have established multi-billion dollar markets despite sub-optimal efficacy. ADX10059 is a first-in-class mGluR5 inhibitor, a therapeutic strategy that also is being pursued to treat multiple indications by large pharma competitors.

Our product pipeline and technology already have proven their value through our relationships with four of the top 10 pharmaceutical companies in the world. Specifically, in two separate license agreements with Merck & Co., Inc., we are developing positive allosteric modulators of mGluR4 and mGluR5 as drugs to treat Parkinson's disease and schizophrenia, respectively. A third agreement, with Ortho-McNeil-Janssen Pharmaceuticals Inc., a Johnson & Johnson company, is focused on development of positive allosteric modulators of mGluR2 to treat anxiety and schizophrenia. Separately, investment funds from Roche and GlaxoSmithKline have extended their validation of our technology, products and management by making significant investments in Addex.

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