

Therapeutic focus - Addex could be leading the mGluR pack



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Addex Pharmaceutical might have only released one set of phase IIb results from its lead programme in GERD, but it was enough for investors to get very excited yesterday. Shares in the company hit a high for the year in anticipation of further positive data and a tasty licensing deal.

The product in question is ADX10059, which acts on metabotropic glutamate receptor 5 (mGluR5); one of a family of receptors that holds much promise, but has yet to be successfully targeted by drug developers (see tables). Because its candidate is an allosteric modulator, which work in a different way to conventional small molecules, Addex believes '059 could succeed where others have failed. Assuming that the remaining data are positive and a partner is found to push on with later stage trials, '059 could be the first drug targeting mGluR5 to enter pivotal trials, although a couple of other candidates are not too far behind.

Encouraging monotherapy

Yesterday, Addex released encouraging data from a monotherapy trial, which tested '059 in patients known to respond to proton pump inhibitors. The number of symptom free days increased by five-fold, and importantly the tolerability profile was clean enough to warrant larger studies in this setting, the company believes.

Results from a bigger trial in patients who only partially respond to PPIs is now the big event on the horizon, due in January. This will allow a more complete picture of the drug's efficacy in this indication to be drawn ([Event - Addex hoping for top marks in GERD trial November 13, 2009](#)).

The excitement around '059 is down to the fact that it promises to treat the underlying cause of the disease - abnormally functioning lower esophageal sphincter muscles, that allow stomach contents to pass back into the esophagus too easily - rather than just the symptoms.

This novel mechanism of action and innovative approach is exactly the sort of opportunity that big pharma is looking for at the moment, and many observers hope that Addex will negotiate lucrative terms. Many are expecting a deal to emerge next year.

Distant potential

The variety of functions that metabotropic glutamate receptors play in the central nervous system means they hold great potential for therapeutic agents, however, the industry's history of targeting them with traditional small molecules has not been great.

Because allosteric modulator binding sites offer the potential for greater selectivity, Addex believes it has found a solution. Of course, it is not alone, and Novartis and AstraZeneca also have candidates, also targeting mGluR5 and also believed to be allosteric modulators, in phase II studies. Addex appears to be the most advanced in GERD, however.

Clinical candidates targeting metabotropic glutamate receptor 5 (mGluR5)

	Product	Company	Indication Summary
Phase II	AFQ056	Novartis	Fragile X syndrome [Phase II]; Parkinson's disease [Phase II]
	NPL-2009	Neuropharm	Fragile X syndrome [Phase II]
	AZD2066	AstraZeneca	Pain [Phase II]; Gastro-oesophageal reflux disease (GORD/GERD) [Phase I]
	ADX10059	Addex Pharmaceuticals	Gastro-oesophageal reflux disease (GORD/GERD) [Phase II]; Migraine [Phase II]; Generalised anxiety [Phase II]; Parkinson's disease [Pre-clinical]
Phase I	AZD2516	AstraZeneca	Pain, chronic [Phase I]
	ADX48621	Addex Pharmaceuticals	Parkinson's disease [Phase I];
	STX107	Seaside Therapeutics	Fragile X syndrome [Phase I]; Autism [Pre-clinical]

In terms of drugs targeting mGluRs more widely, Eli Lilly appears to have done the most work in this area, and has got the furthest in the clinic. Two candidates, against mGluR2/3, made it into phase III trials in anxiety, but both were terminated in 2004 when a risk of seizure was noted in animal tests; neither were allosteric modulators.

The company also took an mGluR3 into phase II migraine studies, but this was suspended in 2007. It currently has another mGluR2/3, LY2140023, in a phase II schizophrenia study.

The larger table below highlights Addex's dominant presence in this field; it should be noted that not all of the candidates below work through allosteric modulation. As well as a schizophrenia deal with Johnson & Johnson, Merck & Co has a couple of the Swiss company's compounds in preclinical development for schizophrenia and Parkinson's disease.

Addex and its platform still has some way to go; the company may be going after primarily clinically validated targets with a novel mechanism but historically these targets have been very challenging, even for some of the biggest names in the business. The full phase IIb data due in the coming months will no doubt be watched with great interest. But if the results are as positive as some are anticipating, the company should have no trouble attracting a partner.

Metabotropic glutamate receptor modulators in development					
	Pharmacological Class	Product	Company	Originator	Indication Summary
Phase II	Metabotropic glutamate receptor 2/3 (mGluR2/3) agonist	LY2140023	Eli Lilly	Eli Lilly	Schizophrenia [Phase II]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	AFQ056	Novartis	Novartis	Fragile X syndrome [Phase II]; Parkinson's disease [Phase II]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	NPL-2009	Neuropharm	McNeil Laboratories	Fragile X syndrome [Phase II]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	AZD2066	AstraZeneca	AstraZeneca	Pain [Phase II]; Gastro-oesophageal reflux disease (GORD/GERD) [Phase II]

	Target	Drug	Company	Company	Phase I
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	ADX10059	Addex Pharmaceuticals	Addex Pharmaceuticals	Gastro-oesophageal reflux disease (GORD/GERD) [Phase II]; Migraine [Phase II]; Generalised anxiety [Phase II]; Parkinson's disease [Pre-clinical]
Phase I	Metabotropic glutamate receptor 2/3 (mGluR2/3) agonist	ADX71149	Johnson & Johnson	Addex Pharmaceuticals	Generalised anxiety [Phase I]; Schizophrenia [Phase I]; Depression [Phase I]; Alzheimer's disease [Phase I]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	AZD2516	AstraZeneca	AstraZeneca	Pain, chronic [Phase I]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	ADX48621	Addex Pharmaceuticals	Addex Pharmaceuticals	Parkinson's disease [Phase I];
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	STX107	Seaside Therapeutics	Merck & Co	Fragile X syndrome [Phase I]; Autism [Pre-clinical]
Pre-clinical	Metabotropic glutamate receptor 1/5 (mGluR1/5) antagonist	mGLUR1/5 Antagonist	Forest Laboratories	Gedeon Richter	Generalised anxiety [Pre-clinical]; Depression [Pre-clinical]
	Metabotropic glutamate receptor 4 (mGluR4) modulator	PD PAM Research Program	Merck & Co	Addex Pharmaceuticals	Parkinson's disease [Pre-clinical]
	Metabotropic glutamate receptor 5 (mGluR5) antagonist	ADX63365	Merck & Co	Addex Pharmaceuticals	Schizophrenia [Pre-clinical]; Alzheimer's disease [Pre-clinical]
	Metabotropic glutamate receptor 2 (mGluR2) agonist	TS-032	Pfizer	Taisho Pharmaceutical	Schizophrenia [Pre-clinical - possibly phase I]
	Metabotropic glutamate receptor 1 (mGluR1) agonist	SYN-119	Synosia Therapeutics	Roche	Cocaine addiction [Pre-clinical]; Opioid addiction [Pre-clinical]

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