Evaluate Vantage

August 24, 2017

Intra-Cellular bounces back in schizophrenia

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Intra-Cellular Therapies has overcome toxicity worries with its schizophrenia candidate lumateperone, but it still has work to do. The company plans to file the project in mid-2018, and then needs to persuade the FDA to accept mixed phase III data.

The FDA has been known to be flexible in CNS disorders, and there is a dearth of new options in schizophrenia – a problem when older antipsychotics are infamous for weight gain and metabolic side effects (see table below). Lumateperone does not appear to have these issues, a point that Intra-Cellular will no doubt press upon the FDA.

And worries about toxicity, raised after findings in a study in dogs, now appear to have been put to rest. The FDA has concluded that in this case the metabolic pathways in dogs and humans are different, meaning the safety signal is not relevant in humans.

Intra-Cellular still needs to monitor patients in an on-going safety study for the metabolite seen in dogs, but will be relieved to have got past an issue that threatened to scupper its only clinical project. The company's share price jumped 28% yesterday, but at $15 is still well off the $42 seen before the failure of its second phase III trial (*Intra-Cellular catatonic after schizophrenia fail, September 29, 2016*).

An earlier phase III study of lumateperone, also known as ITI-007, was a success and Intra-Cellular will hope that this, along with positive phase II data, will be enough to convince the FDA. Leerink analysts give it around a 50% chance of success.

Intra-Cellular has another shot on goal in bipolar disorder, with its first phase III data in this indication due in the second half of next year.

Next wave

If lumateperone does get the FDA nod in schizophrenia, it will be ahead of several rival products that are in the midst of or approaching phase III readouts.

The next most advanced is Alkermes' ALKS 3831, which has shown similar efficacy to olanzapine, but has so far not sidestepped the weight gain issue, a blow to its chances of commercial success (*Alkermes data don't Enlighten, June 30, 2017*).

ALKS 3831 contains olanzapine and samidorphan, a mu opioid antagonist that the company believes should reduce the weight and metabolic consequences of the antipsychotic by limiting the reward pathway effects of eating. More data, due next year, could ascertain whether this is indeed the case.

Like many existing antipsychotics, lumateperone and ALKS 3831 modulate both serotonin and dopamine – meanwhile, Acadia's Nuplazid avoids hitting dopamine receptors so could be used as an add-on therapy to dopamine-targeting drugs, the company believes.

The novel schizophrenia pipeline				
Product	**Company**	**Pharmacological class**	**Details**	**Data due**
Active phase III projects				
Lumateperone/ITI-007	Intra-Cellular Therapies	Serotonin antagonist & dopamine modulator	Two PIII trials completed vs placebo and Risperdal (NCT02282761; NCT02469155)	Completed
ALKS 3831	Alkermes	Serotonin, mu opioid, dopamine D1 & D2 antagonist	Enlighten-1 succeeded; Enlighten-2 to report next year (NCT02694328; NCT02634346)	Early 2018
Nuplazid	Acadia Pharmaceuticals	Serotonin inverse agonist	Being tested as an adjunctive therapy in Enhance 1 (NCT02970292)	2018/19
Lu AF35700	Lundbeck	Dopamine D1 modulator	Being tested in treatment-resistant schizophrenia in Daybreak (NCT02717195)	2019
SND-11	SyneuRx	DAAO inhibitor	Two PII/III trials ongoing as add-on and combination in refractory schizophrenia (NCT02261519; NCT03094429)	2019
Selected active phase II projects				
LY500307	Eli Lilly	Oestrogen receptor-beta agonist	NCT01874756	2017
MK-8189	Merck & Co	Atypical anti-psychotic	NCT03055338	2017
SEP-363856	Sumitomo Dainippon Pharma	Serotonin agonist	NCT02970929; NCT02969382	2018/19
Source: EvaluatePharma.				

Lundbeck is taking a different approach with Lu AF35700, a selective dopamine D1 modulator. The group says low dopamine D2 occupancy could result in a lower incidence of adverse events versus other antipsychotics, and this theory will be put to the test in a couple of years when results emerge from the Daybreak trial in treatment-resistant schizophrenia.

Most of these novel therapies are given daily, at a time when the antipsychotic market is moving towards monthly injections – as well as extending valuable franchises these could address the problem of compliance with schizophrenia therapies.

But these extended release formulations are still associated with weight gain, and any product that can avoid this side-effect has a chance to grab market share. The FDA will also care about this metabolic side effect, but with a mixed clinical package, Intra-Cellular will have to hope that the agency is in a lenient mood.

Trial	ID	Primary completion
Lumateperone monotherapy in bipolar depression	NCT02600494	Aug 2018
Lumateperone plus lithium or valproate in bipolar depression	NCT02600507	Feb 2019
Lumateperone monotherapy in bipolar depression	NCT03249376	Feb 2019

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