Evaluate Vantage

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One out of two is not enough for Intra-Cellular

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Hopes for lumateperone rest on schizophrenia as bipolar data raise questions.

A hit in only one of Intra-Cellular Therapies' two phase III monotherapy trials of lumateperone in bipolar depression has come as a bitter disappointment to the group's shareholders, with a 22% drop in the stock so far today.

The fact that the unsuccessful trial, study 401, was conducted solely in the US whereas the one that hit its endpoint, study 404, drew more than two-thirds of its patients from sites in countries including Colombia and Russia has done little to reassure.

First, the good news. Study 404, which was conducted in 381 patients with major depressive episodes associated with either bipolar I or II disorder at in 57 sites around the world, met its primary and one of its secondary endpoints.

Patients treated with 42mg of lumateperone once daily for six weeks showed a statistically significant placebo-adjusted improvement from baseline on MADRS total score. In the intent-to-treat population, the least squares mean reduction from baseline for the drug was 16.7 points, versus 12.1 points for placebo, giving a 4.6 point placebo-adjusted benefit, with an effect size of 0.56 and a p value of less than 0.001.

The atypical antipsychotic hit the secondary endpoint of statistically significant improvement in total score on the clinical global impression scale, bipolar version, but the company made no mention of its performance on the other secondary endpoint listed on clinicaltrials.gov – its performance on a quality of life questionnaire.

No illumination

The failed trial, Study 401, used a different design. This was conducted at 58 US sites and randomized 554 patients 1:1:1 to 42mg or 28mg doses of luma or placebo. Intra-Cellular Therapies put the failure of this trial down to an unusually high response to placebo, and indeed the placebo group's 19.7 point MADRS improvement was higher than the 12.1 point seen in 404's placebo recipients.

But the response among drug-treated patients was higher too. In the failed 401 study a 20.7 point MADRS improvement was seen among patients given the higher dose of lumateperone, four points greater than in study 404. Remarkably, patients taking 28mg of the drug in 401 responded more strongly than those given 42mg in 404 – an 18.9-point vs a 16.7-point improvement.

Even more worryingly for Intra-Cellular, patients given the 28mg dose actually performed worse than those given placebo.

Data from Intra-Cellular's phase III monotherapy trials in bipolar disorder		
Study 404		
	Change from baseline in MADRS total score	**Placebo-adjusted change**
Lumateperone 42mg	16.7 points	
Placebo	12.1 points	4.6 points
Study 401		
	Change from baseline in MADRS total score	**Placebo-adjusted change**
Lumateperone 42mg	20.7 points	
Placebo	19.7 points	1.0 point
Lumateperone 28mg	18.9 points	
Placebo	19.7 points	-0.8 points
Source: company press release.		

The differences in placebo response between the two trials may be explained by differences in standard care in the US and other countries. This effect would be easier to assess if Intra-Cellular broke out the response rates from study 404 by country. On a conference call this afternoon executives said it would provide these data at a later date, along with other, unspecified, subgroup analyses.

All that is known at the moment is that the US patients made up about 30% of the population in study 404, and it was the most prevalent nationality in the trial.

Yes or no?

Intra-Cellular has not been deterred from its plan to go to the FDA with these results, saying that it would not wait for data from its other phase III trial of luma in bipolar, study 402, which is testing the drug as an adjunct to the mood stabilisers lithium or valproate. These are due next year.

Lumateperone is already filed in schizophrenia – an advisory committee will review the product on July 31, ahead of a September 27 PDUFA date – so the FDA's opinion of this product will soon become clear.

But the mixed data do not bode well for the biopolar indication. The product’s current sellside forecast for bipolar, as compiled by *EvaluatePharma*, is $396m in 2024; this will surely be revised downwards in the coming weeks.

Study	Design	Trial ID	Result
401	381 patients; US only; lumateperone monotherapy 42mg & 28mg vs placebo	NCT02600494	Failure
404	554 patients; global; lumateperone monotherapy 42mg vs placebo	NCT03249376	Success
402	550 patients; lumateperone 60mg & 40mg adjunctive to lithium or valproate vs placebo	NCT02600507	Data expected 2020

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