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Esketamine floats past adcom vote

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Johnson & Johnson's esketamine should get approved in depression, but a safety plan requiring supervision raises questions about its commercial promise.

Any worries that safety issues and questionable efficacy with Johnson & Johnson's depression project esketamine might put paid to its chances of US approval appear to be unfounded. A combined psychiatry and drug safety advisory committee was yesterday largely satisfied that the nasal spray could be administered safely under the supervision of healthcare practitioners, and that it offered an effective treatment for patients who have failed oral antidepressants.

The 14-2 vote in favour of esketamine is also good news for Allergan, which has a similarly acting project, rapastinel, nearing phase III readouts in treatment-resistant disease. The expert advisers were willing to look past the risk of esketamine's abuse, something that has the potential to derail both projects (*Ketamine finding raises the risks for J&J and Allergan projects, August 30, 2018*).

Two out of four ain't bad

Esketamine, which now bears the trade name Spravato, is the S-enantiomer of ketamine, an anaesthetic that has become a "club drug" because of its dissociative side effects. Thus the FDA had been sensitive to the potential for abuse, even as the project showed signs of efficacy – albeit in only two of four pivotal trials.

The two successful studies were Transform-2 and Sustain-1. The former had a randomised controlled design, in which patients taking Spravato plus an oral antidepressant saw their scores on the Montgomery-Asberg depression rating scale (MADRS) fall from baseline by 19.8 at four weeks, compared with a placebo-plus antidepressant arm in which MADRS fell by 15.8. The four-point difference was significant at a p value of 0.01, bettering a one-sided p value threshold of 0.025.

Sustain-1, a randomised withdrawal study, randomised patients classified as remitters or responders to a maintenance phase in which they received either Spravato plus oral antidepressant or placebo plus antidepressant. The primary endpoint was time to relapse in the group of patients in remission, and this was significantly longer in the Spravato versus the control group, with a p value of 0.003.

As a secondary endpoint, the study also tested time to relapse in those classified as responders to Spravato but who had not met the bar for remission. These patients, when given Spravato, also had a significantly longer time to relapse than the control group, with a p value of less than 0.001.

Since the studies had a different design there was some concern that Sustain-1 was not technically

confirmatory of Transform-2, particularly given the former's enriched patient population. In addition, the Transform-1 and Transform-3 trials, which had a similar design to Transform-2, did not show a significant reduction in MADRS.

This was not an issue for the advisory committee, which viewed Spravato's efficacy as sufficient in a 14-2 vote. The agency has proposed a risk-evaluation and mitigation strategy that requires self-administration in a healthcare facility that can monitor patients for two hours, until dissociative and sedation side effects have subsided, as well as a patient registry that could help characterise the project's risk.

Another drug

The supervised dosing would limit the commercial promise of Spravato but, on the other hand, treatment options for patients who have failed on conventional antidepressants largely consist of devices and more invasive procedures, so a new drug option would probably be welcomed. The only drug approved in this indication is Symbyax, which is associated with weight gain.

And even if Spravato's closest competitor, rapastinel, yields positive results, it is unlikely to prove more convenient as it is given intravenously. Ketamine, meanwhile, is already used off-label in this indication, and it is not a stretch to believe specialists might be able to get a generic intranasal version from a compounding pharmacy. Thus, J&J will need to be conscious of its price when it launches Spravato.

The positive adcom vote for esketamine has to be taken as a good sign for rapastinel. The Allergan project is a partial agonist of the NMDA receptor, while esketamine is an inhibitor, so the former might be a safer alternative. This will be put to the test when rapastinel yields phase III data in the first half (*Upcoming events – Allergan and Lundbeck await depression and mania data, January 24, 2018*).

In any case, the two projects would not necessarily be in direct competition as Allergan is targeting patients with a partial response to oral antidepressants.

These two projects are similar in more ways than one. Both are their respective sponsor's biggest pipeline hopes, with Spravato forecast to sell $1.3bn and rapastinel $505m in 2024, according to *EvaluatePharma*'s consensus of sellside analysts.

The chances of either project getting a no from the FDA went down yesterday, but this cannot be ruled out entirely. Still, the vote should be taken as good news at J&J and Allergan's respective headquarters today. The former's stock rose 2% yesterday, while the latter climbed 3%.

Outlook for depression drugs

		Annual sales ($m)			
Product	**Company**	**2019e**	**2020e**	**2022e**	**2024e**
SAGE-217	Sage Therapeutics	-	-	661	1,913
Spravato/esketamine	Johnson & Johnson	74	362	858	1,299
Rexulti	Otsuka Holdings	460	590	814	1,022
Trintellix	Takeda/Lundbeck	841	1,034	1,256	856
Rapastinel	Allergan	-	9	204	505
Zoloft	Pfizer	287	281	270	261
Total		**5,110**	**5,611**	**7,268**	**9,463**

Source: EvaluatePharma.