Evaluate Vantage

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Upcoming events – Sage and Biohaven await pivotal data

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Sage Therapeutics will report the first pivotal data with its oral postpartum depression candidate, while Biohaven Pharma transfers its hopes to a faster-acting migraine formulation.

Welcome to your weekly digest of approaching regulatory and clinical readouts. The first phase III data with Sage Therapeutics' biggest growth driver, the oral depression project Sage-217, are due next quarter.

Previous positive phase II results with the compound in major depressive disorder (MDD) helped push the company's market cap up to a peak of over $8bn. The shares have come down recently, but a positive result in the smaller postpartum depression (PPD) indication could see the stock receive another boost.

Some analysts already see success in PPD since the phase III study has a similar design to the phase II MDD trial. The phase III study has enrolled 140 women with severe PPD and will compare the changes in the Hamilton Depression rating scale seen after two weeks' treatment with 30mg of Sage-217 versus placebo.

Those getting excited about the outcome might want to remind themselves of the notoriously tricky transition from phase II in neurology to phase III, where the placebo effect tends to become more pronounced. Given the target patient population Sage cannot afford serious adverse events or safety issues.

The company, however, hopes that as a first-in-class neuroactive steroid GABA modulator Sage-217 might avoid problems that have bedevilled other depression drugs. It also has the advantage of a rapid onset of action, working within two weeks compared with six to eight weeks for traditional antidepressants like SSRIs. This makes a compelling argument for Sage-217's use in PPD, where relieving depressive symptoms quickly could be essential to protecting the health of mothers and infants.

Sage has a more advanced PPD project, Zulresso, which is due to receive a US FDA approval decision by December 19, after an advisory committee meeting on November 2. But Zulresso requires a 60-hour infusion, which will relegate its use to inpatients and could limit uptake given that physicians might prefer mothers to stay with their children.

Such are the expectations around Sage-217 that the sellside's 2024 forecasts for it have hit $2bn. Most of these sales are pencilled in for MDD, but the PPD results are bound to be used to handicap the results of any pivotal MDD study, so missteps here will be punished severely.

Faster formulation

Also in the fourth quarter, Biohaven will report phase III data with an orally disintegrating tablet (ODT) formulation of its acute migraine candidate rimegepant, an oral CGRP inhibitor.

The company has promising pivotal data with a traditional pill version of the project, but hopes to launch the faster-acting ODT formulation. Showing similar or better efficacy to the pill in the upcoming 1,800-patient study will be key if Biohaven is to file for approval by the end of the year, as planned.

The co-primary endpoints of the ODT trial are the proportion of patients free from pain and most bothersome symptoms at two hours – the same as those used in the phase III trials of the traditional tablet that were reported earlier this year.

Although those studies, known as 301 and 302, read out positively, Biohaven faces questions about rimegepant's efficacy versus rival oral projects like ubrogepant and lasmiditan, which have the respective might of Allergan and Lilly behind them (*Biohaven hopes to give Allergan a headache, 9 July 2018*).

Cross-trial comparison of ubrogepant, lasmiditan and rimegepant in phase III			
	% of patients pain-free at 2hr, placebo-adjusted		
Allergan	**Ubrogepant 25mg**	**Ubrogepant 50mg**	**Ubrogepant 100mg**
Achieve 1	-	7.4 (p=0.0023)	9.3 (p=0.0003)
Achieve 2	6.4 (p=0.0285)	7.5 (p=0.0129)	
Lilly	**Lasmiditan 50mg**	**Lasmiditan 100mg**	**Lasmiditan 200mg**
Samurai	-	12.9 (p<0.001)	16.9 (p<0.001)
Spartan	7.3 (p=0.003)	10.1 (p<0.001)	17.5 (p<0.001)
Biohaven	**Rimegepant 75mg**		
BHV3000-301	5.0 (p<0.03)		
BHV3000-302	7.6 (p<0.001)		
Source: Company press releases.			

The ODT formulation might boost Biohaven's chance of competing, because the tablet version of rimegepant does not appear to reach its maximum blood concentration until 2.5 hours after dosing, which could explain its apparently worse performance on the two-hour endpoints. The ODT version, which can be taken without water, is thought to start working in 45-90 minutes.

Biohaven is also developing an intranasal anti-CGRP project, BHV-3500, with an even faster onset of action – 10-15 minutes – for which it filed an IND earlier this month.

The oral CGRPs will be targeted at the four million or so US patients who either do not respond to or cannot take triptans, an old drug class that is contraindicated in patients with cardiovascular disease. They will not initially be competing with injectable anti-CGRPs like Amgen/Novartis's Aimovig and Lilly's recently approved Emgality, which are used for migraine prevention.

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