Evaluate Vantage

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JP Morgan 2019 – development shortcuts pay off for Sage

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Despite several changes of direction SAGE-217 comes out positive in postpartum depression, setting Sage Therapeutics up as a takeover target.

Biotech-sponsored clinical development often fails because naivety or financial constraints force the companies involved to cut corners. Not so for Sage Therapeutics, which today reported an important pivotal study success for its oral GABA-A modulator SAGE-217 in severe postpartum depression.

This came despite several changes of direction that had called for cross-trial comparisons and nerves of steel to handicap the chances of today's phase III success. But SAGE-217 has emerged from the risky plan smelling of roses, and Sage celebrated the first day of the JP Morgan conference with a 40% share price surge.

Of course, negative data would have spelled the worst-case scenario. But Sage also risked a situation whereby a delay to the results would have seen it go into JP Morgan, where it presents on Tuesday, having said nothing about the data; given what was already being priced into the group's multi-billion dollar valuation, investors would not have responded well.

Any such worries have now been allayed, and the development of SAGE-217 has worked out to perfection. This makes Sage a possible takeover target, and Biogen, now worryingly dependent on aducanumab in Alzheimer's disease, looks the most logical potential CNS-focused acquirer.

The recent days' takeouts of Celgene and Loxo have shown that biotech M&A is firmly back on the cards.

Follow-up

For Sage, development of SAGE-217 came as a sort of follow-up to brexanolone, a molecule with a similar chemical structure that is expected to receive US approval, under the trade name Zulresso, for postpartum depression by its March 19 PDUFA date.

On top of a short patent life Zulresso, however, has another major drawback: it is delivered intravenously via a 60-hour infusion, necessitating a hospital stay. The orally dosed SAGE-217 offers the prospect of outpatient treatment, and this is how the phase III Robin trial, toplined today, was run.

In efficacy terms the data seemed pretty clear: 14 days' treatment yielded a statistically significant effect on the primary endpoint, the HAMD-17 score, with a p value of 0.0029, despite placebo recipients doing better than expected.

However, safety was at least as important as efficacy; this is because brexanolone had seen rare reports of fainting, a side effect that would be particularly worrying in the outpatient setting. Hence Sage's robust statement today: "There were no reports of loss of consciousness or syncope in either arm of the [Robin] trial."

Of course, the data need to be picked apart further, and less severe adverse events such as dizziness or nausea could still cause concern. And Robin's small size (151 subjects were enrolled) means that data from larger safety trials might be needed to assuage any regulatory concerns over what is a relatively rare, albeit serious, side effect.

Shortcut to success

But given SAGE-217's development path, and the biotech sector's infamous history of coming unstuck because of development shortcuts, it cannot be denied that the Robin data are an amazing result.

Sage had started off developing the project in major depressive disorder, using a liquid formulation. When the first part of a phase II trial yielded an unacceptable level of loss of consciousness-type adverse events the group switched to the current capsule form – without going back to test this fully in phase I.

And running the first phase III trial in postpartum depression was a late decision, there having been no earlier SAGE-217 trials specifically in this indication. Thus any investor buying the stock into today's readout simply had to believe that the capsule gave the right pharmacokinetics, and that pivotal brexanolone postpartum depression data provided a sufficient read-across.

It is still not known whether postpartum use truly represents an indication separate from major depressive disorder, but what is clear is that there are no drugs approved specifically for it. The thinking on pharmacokinetics was that the liquid form's sharp plasma concentration spike had to be reduced while maintaining sufficient mean concentration for activity.

SAGE-217 is also in a pivotal study in major depressive disorder, but this only got under way late last year. For now Sage has the luxury of a $6.5bn market cap and absolutely no need to hurry. Over to bidders hungry for late-stage CNS assets and willing to provide the icing on the cake.