Evaluate Vantage

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Obseva shows why red flags are worth heeding

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A crucial second pivotal trial in uterine fibroids fails to dispel concerns about the company's linzagolix.

Obseva trailed the results from its second pivotal uterine fibroid study a week ago, and then failed to include crucial data in the press release, forcing investors to wait for a conference call for the big reveal. Those cynical about such tactics were proved correct: linzagolix's profile versus the competition now looks even more questionable than before.

This is despite two ostensibly successful phase III trials in uterine fibroids, with primary and most secondary endpoints met; executives this afternoon continued to insist that the project has a "best-in-class profile". This is a matter of interpretation, however, and the 40% plunge in Obseva stock this morning suggests that a different conclusion is possible.

While Obseva is focused on a comparison of absolute measures, investors are more concerned with placebo-adjusted figures. On a call this afternoon executives insisted that patients and physicians were more interested in the former, which has more relevance in clinical practice – but a look at competing data from Abbvie and Myovant shows why Obseva wants the spotlight to fall on this comparison.

Without head-to-head data it is placebo-controlled results that more typically provide a cross-trial analysis, albeit with the normal caveats. A much higher placebo response was recorded in Obseva's trials, with executives claiming that this was actually more typical than the rates seen in the control arms of its rivals' studies.

Cross-trial comparison of GnRH inhibitors in uterine fibroids								
	Linzagolix (Obseva)				**Oriahnn (Abbvie)**		**Relugolix (Myovant)**	
	Primrose 1	**Primose 2**	**Primrose 1**	**Primrose 2**	**Elaris UF-1**	**Elaris UF-2**	**Liberty 1**	**Liberty 2**
	100mg daily w/o ABT	**100mg daily w/o ABT**	**200mg daily***	**200mg daily***	**300mg bid***	**300mg bid***	**40mg daily***	**40mg daily***
Responder rate	56%	57%	76%	94%	69%	77%	73%	71%
Placebo-adjusted responder rate	21%	27%	40%	65%	60%	66%	55%	57%
**Doses with ABT (add-back hormone therapy); bid=twice daily. Source: company press releases, SVB Leerink.*								
Responders were defined as patients with menstrual blood loss volume of less than 80ml and ≥ 50% reduction from baseline in menstrual blood loss volume at 24 weeks.								

However it is not only the efficacy data that has investors worried. In Primrose 2, which was toplined last December, bone density loss was much greater than in trials of elagolix and relugolix, the Abbvie and Myovant GnHR products. At the time, Obseva management argued that different demographics and prohibition of vitamin D/calcium use in its studies were to blame, but Primrose 1 seems to rule out that theory.

In terms of patient characteristics, Primrose 1 looked a lot more like the Elaris-UF and Liberty trials of elagolix and relugolix – yet bone mineral density loss was still greater for linzagolix. This level of bone loss is not particularly concerning, Professor Eugene McCloskey, from Sheffield University, said on the Obseva call this afternoon. However, it remains to be seen what regulators make of this signal.

At the very least it could provide Obseva's rivals a stick with which to beat linzagolix, when it comes to persuading physicians which of these GnHR agonists to pick. At worst, it could force the hands of regulators, which are already very mindful of safety in this setting.

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Change in bone mineral density	-2.0%	-2.1%	-0.84	-1.31%	-0.76%	-0.61%	-0.36%	-0.13%
Placebo-adjusted bone mineral density change	-2.3%	-2.6%	-1.1%	-1.8%	-0.55%	-0.55%	-0.41%	-0.45%
**Doses with ABT (add-back hormone therapy); bid=twice daily. Source: company press releases, SVB Leerink research.*								

Abbvie snared the first GnRH approval for elagolix, branded Oriahnn, in fibroids last month, but the FDA insisted on much stronger warnings and exclusions than expected. A black box warning related to clotting associated with the hormone add-back therapy (ABT) that these agents require was expected – however, contraindicated groups extended much further, to women with increased risk of blood clots, including those over 35 who smoke or have high blood pressure.

This safety aspect leads to what Obseva seems to be turning to as a key opportunity. Only linzagolix was

investigated as a low-dose option, 100mg, with no hormone add-back. Many women are unwilling to take hormones to ameliorate the menopause-like side effects of GnHR antagonism, which could make linzagolix an attractive option, the company maintains.

Of course for this to be proven linzagolix must first gain approval; despite the disappointment around the data this is still widely expected. But then the game really begins, and in reality Obseva is simply not big enough to compete.

Investors certainly are not buying it: the company's market cap was already tiny compared with Myovant, which is considered to have a very strong contender in relugolix, and today's plunge takes Obseva's valuation below $200m (*Myovant socks it to Orilissa, June 24, 2020*).

Efforts to bring on a larger player are under way, and for now Obseva probably has enough cash to see linzagolix across the regulatory finish line. Unless a partner or deep well of capital can be found, arguments around who owns the “better” drug might not matter much.