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Obseva needs more to beat Abbvie in endometriosis

Madeleine Armstrong

Obseva, lagging behind its bigger rival Abbvie in the oral gonadotrophin-releasing hormone antagonist space, has a clear mission. The smaller company's candidate, linzagolix, will need to show best-in-class efficacy if it is to have a chance of competing with Abbvie's elagolix, which could hit the market this year in its first indication, endometriosis-associated pain.

Obseva believes that it has gone some way to proving linzagolix's superiority with data from the small phase IIb Edelweiss trial in the same disorder, and investors sent the group's stock up 23% yesterday in response. But a look at how the results stack up against data from elagolix's pivotal trials suggests some cause for concern (see table below).

Of course, cross-trial comparisons should always be treated with caution, and this one is particularly fraught with difficulty, as the studies used different endpoints. But on the most similar measure, response on non-menstrual pain, linzagolix appears to fall short, particularly at the highest dose used, 200mg.

Cross-trial comparison of linzagolix and elagolix

	Placebo	50mg	75mg	100mg	150mg	200mg
Linzagolix/OBE2109: Edelweiss (phase IIb, NCT02778399)						
Response rate (primary endpoint)*	35%	49%	62%	56%	-	56%
P value	-	0.155	0.003	0.039	-	0.034
Response rate, nonmenstrual pain	37%	46%	59%	62%	-	48%
P value	-	0.38	0.017	0.022	-	0.297
Elagolix: Elaris EM-I, Elaris EM-II (phase III, NCT01620528, NCT01931670)						
Response rate, nonmenstrual pain	37%	-	-	-	50%**	55-58%**

**Response defined as reduction of ≥30% in combined menstrual and non-menstrual pelvic pain at week 12; **p<0.003; Source: Company presentations; NEJM paper.*

Even this is not an apples-to-apples comparison, however. Obseva's chief executive, Ernest Loumaye, said on a conference call that while, in Edelweiss, a responder was defined as a patient with a 30% or greater reduction in pain, in Abbvie's trials "we don't know if the definition of a responder is a 30% reduction, or lower, or higher".

Phase III data might go some way towards clarifying how the two agents compare – and will also put to the test Mr Loumaye's assertion that the disappointing performance of the 200mg dose in non-menstrual pain is "an artefact relating to the rather small sample size" that should be ironed out in larger studies.

Avoiding add-back

At least results with the 75mg dose were more consistent, and here Obseva reckons it has the edge, as this dose could be given without concomitant oestrogen therapy, the addition of which has led to safety and tolerability concerns with other GnRH antagonists.

Obseva will also have to replicate its findings with the lower dose in phase III – it looks like it has already selected the 75mg and 200mg doses for pivotal trials, which could start in the first half of next year if all goes well.

Mr Loumaye envisions the 75mg dose of linzagolix, which only partially suppresses estradiol, being used as a first-line option, while the 200mg dose, which would need to be given alongside “add-back” oestrogen therapy, would be reserved for patients whose symptoms remain uncontrolled.

Add-back therapy is needed to counteract the menopause-like symptoms that result from full suppression with GnRH agonists, and is expected to be required for both elagolix and Myovant’s rival GnRH antagonist relugolix, which is in phase III for endometriosis-associated pain.

Elagolix is due an FDA approval decision in the third quarter, after its original PDUFA date in April was pushed back, so its exact dosing schedule could soon become clear. It is expected to be the biggest endometriosis drug in 2024, according to *EvaluatePharma* sellside consensus.

Top five endometriosis products in 2024

			Annual indication sales ($m)			
Product	**Company**	**Mechanism**	**2018e**	**2020e**	**2022e**	**2024e**
Elagolix	Abbvie	GnRH antagonist	39	336	660	1,040
Visanne	Bayer	Progestogen agonist	151	181	212	242
Linzagolix/OBE2109	Obseva	GnRH antagonist	-	-	35	221
Leuplin	Abbvie	LHRH analogue	181	169	160	150
BAY 1128688	Bayer	AKR1C3 inhibitor	-	-	19	56

Source: EvaluatePharma.

Still, linzagolix has become Obseva’s biggest hope, ahead of the more advanced fertility project nolasiban, which posted mixed data in February (*Obseva still faces hard labour with fertility therapy, February 26, 2018*).

Linzagolix is also in two phase III trials in uterine fibroids, and these could yield data in 2019. Obseva has a chance to upset the status quo, but it will need more than data from a small phase II trial to have a real impact on the market.

This story has been updated to reflect the correct dosing of linzagolix and elagolix in their respective trials.

To contact the writer of this story email Madeleine Armstrong in London at madeleinea@epvantage.com or follow @ByMadeleineA on Twitter