Evaluate Vantage

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Controversial disclosure will probably benefit Contrave in the long run

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Whatever stance one chooses to take on the ethics of Orexigen Therapeutics' data disclosure, one thing is clear. In the short term angering the FDA has paid off, and the subsequent 46% share price jump will almost certainly be used to fuel a fundraising.

Certain longer-term gains are less clear. The company has likely severely hampered its ability to ever confirm the apparent cardiac safety benefit of Contrave that it has controversially made public, and its relationship with the FDA and others in the medical community lies in tatters. Commercially, however, none of this might matter as the drug's approval is unlikely to be revoked, leaving Orexigen and its partner Takeda to reap the rewards in the market.

Those rewards have been clearly articulated by sellside analysts, who have already widely moved to raise sales forecasts and valuations. Leerink, for example, now assumes a steeper US launch and greater peak sales, and has lifted its price target on the stock from $8 to $11.

This is in spite of the fact that, as the bank's analysts clearly state, the 41% reduction in major cardiovascular adverse events detected at an interim analysis of the ongoing cardiac safety study Light might never be sustained.

What matters, however, is that the data are out there, and physicians and patients will see it. Key opinion leaders consulted by Leerink said their opinions of Contrave had "improved significantly" now that it appears almost certain the drug does no cardiac harm. Even if any benefit proves more modest as the data mature, physicians are likely to still hold a "meaningfully improved opinion of the drug", the analysts wrote.

Chain of events

Orexigen yesterday justified publishing actual data from an interim analysis of the Light trial – the heart safety study being run to meet the FDA's conditions of Contrave's 2014 approval – on grounds of preventing selective disclosure. Although this raised the FDA's ire it seems that the company had already soured its relationship with the regulator some months previously.

The original interim analysis ruled out the pre-specified doubling in the risk of heart attack or stroke, allowing the FDA to approve Contrave on the proviso that further characterisation of the drug's risk profile would emerge later. It also detected an apparent reduction in the risk of cardiac events, an "unexpected result" that prompted a patent claim, Orexigen says.

The data behind the interim analysis were supposed to remain blinded to only a select few individuals, yet Orexigen went on to share it with more than 100 people, including investment bankers and Takeda executives. On discovering this the FDA decided that Light could not reliably meet its ultimate aim – ruling out the possibility that Contrave increases the risk of major cardiac events by 40% or more.

So, although the agency granted approval, it specified at the time that Orexigen would have to conduct a second outcome study. Orexigen says in an emailed statement that at this point it decided to continue with the patent – it must have known this would make the full data public but perhaps it concluded it had little else to lose in terms of its relationship with the FDA.

Building hopes

What the company could also lose, however, is the ability to ascertain the real risk-benefit profile of Contrave. Because the drug is already on the market patients can chose to take the chance of gaining any benefit – real or not – by seeking a prescription, rather than joining a trial and maybe getting placebo. This has obvious implications for enrolment into the next safety study, demanded by the FDA as a condition of its approval.

Whether that ultimately matters depends on the FDA; having publicly stated that it is comfortable that Light ruled out a certain level of harm, its powers to act would appear to be restricted. And while it has urged Orexigen to continue the study to conclusion, the company could still decide to conserve cash and scrap it; this

would cause further reputation damage in some quarters.

The second study will still be costly – at the time of approval this was estimated at $150-200m, of which Takeda will fund a portion (*Orexigen joins the fight for small advantages, September 11, 2014*). Orexigen ended the year with access to $206m – a healthy balance, but with European approval and launch still to come, a chance to top up the coffers will not be missed.

Raised prospects of an ex-US deal on the back of all this will also contribute to growing enthusiasm for the drug and the company.

Ironically, Contrave's launch has looked the most promising of the three obesity drugs to debut in the past few years (*Contrave's unexpected late turn in battle of the bulge, March 2, 2015*). But building out this market was always going to be tough. And the company's management team also has its reputation with investors to consider, something that is unlikely to have been harmed by this turn of events.

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