Closer Look

MEMORANDUM

Executive Highlights

- Orexigen and Takeda have announced their acceptance of a steering committee recommendation to terminate Contrave's (naltrexone/bupropion) CVOT, the Light Study - a decision that Orexigen is "pleased" about.
- The Cleveland Clinic released 50% interim data yesterday showing a non-statistically-significant 0.88 hazard ratio - a regression to the mean from previous interim results, though still with a favorable point estimate.
- Later, Orexigen released a second statement clarifying its position and defending against media accusations of misleading patients and investors.
- Orexigen also announced that Takeda has initiated a formal dispute claiming material breach against Orexigen, which includes Takeda seeking Orexigen to pay the entire cost of the new CVOT.

Orexigen and Takeda announced yesterday that they have accepted the steering committee recommendation to terminate the Light Study, the CVOT for Contrave (naltrexone/bupropion). According to Orexigen's press release, this decision was not due to a finding of superiority or harm and final data will be presented in an unspecified "scientific forum" after the collection and adjudication of all CV events. Providing a clearer answer on specifically why the study was discontinued, the Cleveland Clinic (home of Light Study steering committee chair Dr. Steve Nissen) released its own statement criticizing Orexigen's initial data disclosure and emphasizing the risks of over-interpreting interim data. Reading between the lines, it appears that, following the disclosure of interim data, the steering committee deemed the integrity of the Light Study as compromised, making any of the study's further results of little to no use for regulatory or safety purposes. Notably, the Cleveland Clinic press release included interim data based on 50% of events accrued. These showed neither benefit nor harm: out of a total of 192 MACE events, 102 occurred in the placebo group vs. 90 in the Contrave group (HR = 0.88, 95% CI 0.66-1.17). This represents a regression to the mean compared with the first controversial interim data disclosure back in March, which trended towards benefit (based on very few events).

Continuing the back-and-forth and laying bare the underlying tension in the situation between the companies and investigators involved, Orexigen released a subsequent statement. Orexigen firmly stated that it was not planning to release data without access to the full data set, which the company reported it still does not have. Additionally, the statement clarified the company's rationale behind its interim data disclosure in defending against some of the media's accusations of Orexigen "misleading" patients and investors - read more on this in our coverage of the controversy. The company highlighted that it has long advocated for terminating the Light Study since it is not a post-marketing requirement and most of its participants are no longer on blinded study drug (this may be due to the issue with non-responders with obesity drugs). The statement noted that Orexigen is "pleased" with the termination of the study - CVOTs are indeed a lot for a small company to bear, though the means of ending the trial were certainly unconventional and would have been surprising to patients. During Q&A in the company's 1Q15 call, Orexigen CEO Mr. Mike Narachi also characterized the decision "to terminate the trial early and focus resources on the next CVOT" as "what we have been advocating," although nobody knew at that time whether trial discontinuation was a possibility. As Orexigen is a smaller company, this early termination is an optimal business decision from its perspective since the company's continued spending on the Light Study would not have much of a purpose and reallocation of resources to Contrave's post-marketing requirement of a second CVOT (which has more potential for superiority) would give the most bang for the buck. That said - a great deal of time and effort by investigators and patients had gone into the trial and we

wouldn't term the decision (based on input from the company, steering committee, and likely the FDA) to terminate the trial as a shining example of regulatory effort. As a reminder, the FDA required a new CVOT at the time of Contrave's approval - that decision itself had been surprising and disappointing to us, since expecting a small company (even with help of a partner) to take on two CVOTs seems excessive. This trial reportedly remains on track to begin later this year with its study design recently finalized in April. However, adding on to the drama-filled day, Orexigen also provided an update that Takeda has initiated a formal dispute process claiming material breach against Orexigen, which would require Orexigen to pay the entire cost of the new CVOT; the two companies are thus set to enter into a dispute resolution process. So, in this case - is Takeda even still a partner? That is hard to assess and there would likely be repercussions for the trial - so we don't really know that the design "finalized in April" is really final. Orexigen argued that the dispute should not impact Contrave's commercialization - obviously if a major partner is backing out of funding a required very expensive trial, it is hard to see how that could be the case. Obviously even in the best case scenario, Orexigen's share of the costs is still a major burden. One major question, of course, is what does the design look like - this is a classic case of companies not having an incentive to design to show benefit since designing to show safety is already incredibly challenging. As a reminder, in a previously disclosed non-binding term sheet, the costs of this study were agreed to be split between the two companies. Takeda is likely (and understandably) displeased to lose out on potential safety or efficacy data that would have come from the Light Study years before it will come from the second CVOT (this is a factor for Orexigen too, but of course Orexigen was bearing the costs of the Light Study solo).

Ultimately, we see the day's developments as a clear sign of the complexity and lack of clarity surrounding interim data disclosure, as these have seemed to manifest into heated disagreements in many forms. While the FDA held a public hearing on this issue last August, there still appears to be little consensus and we hope that the conversations can be moved forward to reach more explicit guidance not only on this but on CVOTs more broadly speaking.

-- by Melissa An, Manu Venkat, and Kelly Close