Good evening from Silver Spring, MD, where we are in between FDA Advisory Committee meetings for BMS/AZ's metreleptin and BMS/AZ's dapagliflozin (SGLT-2 Forxiga). The Advisory Committee meeting for metreleptin ended with an 11-1 vote to approve the agent for generalized lipodystrophy, and a 2-10 vote against approval for partial lipodystrophy. The door was certainly open for negotiation on a partial lipodystrophy indication and we hope FDA moves ahead on that front. Now, we are quickly returning our attention to the Ad Comm for BMS/AZ's Forxiga (dapagliflozin), which is to begin tomorrow morning at 8:00 am EST (watch the webcast here). Also on the regulatory front today was Orexigen's announcement that it has resubmitted Contrave to the FDA.

Diabetes Drugs

1. FDA Advisory Committee meeting for BMS-AZ's metreleptin Quick Take - Most moving patient testimonials we've heard at an EMDAC meeting
2. Reminder - FDA Advisory Committee meeting for BMS/AZ's Forxiga (dapagliflozin) is tomorrow

Obesity

3. Orexigen resubmits Contrave to the FDA (summary below; press release), just under four years after its initial submission and following an Ad Comm in December 2010 (despite positive vote, the FDA didn't approve it)

SUMMARIES

1. FDA Advisory Committee meeting for BMS-AZ's metreleptin Quick Take - An FDA Advisory Committee voted 11-1 today to approve BMS/AZ's leptin analog, metreleptin, for a generalized ("complete") lipodystrophy indication and 2-10 against approving it for metabolic disorders associated with partial lipodystrophy such as hypertriglyceridemia and/or diabetes inadequately controlled on existing therapy and/or evidence of hepatic steatosis (fatty liver). The decision to vote for approval in the generalized lipodystrophy population appeared to be nearly a formality for panelists, so in favor of it they seemed. By contrast, the decision to vote against approval of BMS' proposed partial lipodystrophy indication was more challenging and many appeared to have mixed feelings but just not believe the evidence was there. The orphan disease is clearly a devastating one with serious unmet need (the 72 patients in the pivotal NIH studies for the BLA required a median ~500 (!) daily units of insulin and some up to as much as 2,000 units/day). The sparse data showed dramatic improvements in metabolic abnormalities for generalized lipodystrophy patients but less clear benefits for the partial lipodystrophy subpopulation. Weighing this uncertainty against potential risks of immunogenicity and lymphoma, the panelists could not ultimately justify risking exposure for unknown benefit. We very much hope the FDA considers an option whereby metreleptin is approved for people with partial lipodystrophy with a rule to stop treatment if a certain amount of benefit is not achieved. Read our report for some of the most moving patient testimonials we have heard at an Advisory Committee meeting. We will be back later with a full report with more detail on each panelists' individual considerations.

2. As a reminder, this week's FDA Advisory Committee meetings continue tomorrow with BMS/AZ's SGLT-2 inhibitor Forxiga (dapagliflozin) - in case you missed it, you can

read our preview of the meeting here. See information on webcast here.

3. Earlier today, Orexigen announced that it had resubmitted the Contrave New Drug Application (NDA) to the FDA – read the press release here. This resubmission is occurring just under three years after Orexigen received the Complete Response Letter in January 2011 (see our Orexigen 4Q10 report that discusses management's perspective). Orexigen has previously stated that it expects the FDA to make a decision on Contrave by June 2014 – given all the complexity with this compound and the regulatory path, that doesn't sound too far away! As a reminder, FDA actually went against the Ad Comm in this case – the original vote was 13 to 7 in favor of approval back in December 2010. As further background, the complete response letter (CRL) noted only one application deficiency and stated that Orexigen must conduct a cardiovascular outcomes trial (CVOT) of Contrave pre-approval. Orexigen received interim results from this CVOT (now known as the Light Study) on November 25, about 18 months after the trial was initiated. The results enabled the agent's resubmission, because the 95% confidence interval of the hazard ratio for major adverse cardiovascular events (MACE) excluded 2.0, the threshold pre-specified by the FDA. It will be interesting to see opinions develop about these results; presumably the rest of the results won't be disclosed and there will not be an Ad Comm though that is challenging to project at this time.

Stay tuned for our updates from the Ad Comm for BMS/AZ's Forxiga (dapagliflozin); we will be there bright and early. Take good care ~

Very best, kelly

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