CLOSER LOOK

MEMORANDUM

Sanofi/Lexicon receive CRL from FDA for sotagliflozin in type 1 diabetes - March 22, 2019

Executive Highlights

- **FDA today issued a CRL in response to Sanofi/Lexicon's NDA for Zynquista (sotagliflozin) in adult type 1 diabetes.** The news, disappointing but not necessarily surprising, follows a deadlocked 8-8 FDA Advisory Committee vote in January, where the discussion heavily focused on the issue of DKA. In the EU, however, a positive CHMP opinion for adults with a BMI ≥27 kg/m² means final EMA approval is likely in the coming weeks or months.
- **Few details were available in Sanofi's press release and during Lexicon's investor call.** The latter reiterated its commitment to pursuing sotagliflozin for type 1 stateside, and CEO Mr. Lonnel Coats pointed to the past frequency of diabetes CRLs (which we can attest to - Tresiba, Fiasp, Bydureon, Victoza, Farxiga (twice), Jardiance, saxa/dapa, Afrezza (twice), Itca 650, Nesina, obesity drugs Belviiq and Qnexa, and the list goes on ...). However, he could not provide any details regarding next steps with FDA, nor whether additional clinical studies (e.g., to validate DKA risk mitigation strategies) might be necessary to address FDA's concerns.
- **In May 2018, dQ&A surveyed people with type 1 in Europe and Canada for their opinion on SGLT-2 inhibitors** - finding that ~50% would be interested in taking the therapy if (i) cost was not a barrier; and (ii) it was recommended by their doctor. Patients want more options for treating their diabetes, and they will continue to take these drugs off-label. It's imperative that FDA and manufacturers work together to make this as safe as possible for type 1s - we believe they are on the right track and that much of the learning will be done beyond clinical trials.

In disappointing but not necessarily surprising news, Sanofi today announced that FDA has issued a CRL in response to its NDA for SGLT-1/2 dual inhibitor Zynquista (sotagliflozin) as an adjunct therapy for adults with type 1 diabetes.

Sanofi and Lexicon's press release was especially brief at 77 words, offering essentially zero detail on the nature of the CRL. Lexicon held an investor call (webcast replay here and transcribed Q&A below) soon after this news broke, also light on detail regarding the CRL, discussions with FDA, or additional studies regarding DKA management. According to CEO Mr. Lonnel Coats, Sanofi will lead discussions with FDA and these conversations "will start to push forward as soon as possible." It's unclear whether the sponsors will be required to conduct any additional clinical studies (e.g., testing a DKA risk mitigation strategy) for resubmission.

The CRL comes on the heels of a highly contentious FDA Advisory Committee meeting, where DKA risk dominated the conversation and underpinned a 8-8- vote. Given an apparent lack of satisfaction over the sponsors' proposed DKA risk minimization protocol, we imagine it is somewhat possible that the agency will require further work demonstrating that DKA risk mitigation strategies work, before approving sotagliflozin. On balance, however, real-world risk management will likely prove a very different challenge compared to a clinical trial, and we question how such a trial could be conducted ethically.

Meanwhile in Europe, EMA's CHMP issued a positive opinion earlier this month recommending Zynquista approval in type 1 adults with a BMI ≥27 kg/m², and we're curious whether such a limited approval was ever considered by FDA. At the very least, we expect tremendous learning if and when SGLTs for type 1 come to market in Europe.

Lexicon conveyed optimism and emphasized its continued committed to pursuing sotagliflozin in type 1. On the investor call, Mr. Coats said that Lexicon "remains confident in sotagliflozin in type 1 diabetes and committed to making this drug available to patients as soon as possible." We salute this persistence and hope to hear a similar commitment from partner Sanofi moving forward.

- **A CRL is by no means a death sentence for sotagliflozin in type 1 diabetes, and Mr. Coats was quick to point to past CRLs for AZ's SGLT-2 Farxiga and Novo Nordisk's GLP-1 Victoza.** Both received a CRL from FDA and were approved first in Europe. We also note that Novo Nordisk's Fiasp (next-gen insulin aspart) and Tresiba (insulin degludec) both received a CRL prior to FDA approval, along with several other drugs in the diabetes and obesity spaces. Nonetheless, sotagliflozin's situation is certainly unique in terms of the magnitutde of population-level DKA risk, novelty of the indication for type 1, and uncertainties surrounding the effectiveness of proposed risk mitigation strategies.
- **In May 2018, dQ&A surveyed people with type 1 in Europe and Canada for their opinion on SGLT-2 inhibitors.** Notably, assuming cost was not a barrier and the medication was recommended by their doctor, just over half of those in Europe (51%) and half of those in Canada (50%) expressed interest in taking the oral medication. This data underscores that patients want and need more options for treating their diabetes; as the profile of SGLTs in type 1 continues to rise, only more people will start taking them off-label. It's imperative that FDA and manufacturers find a way to make this as safe as possible for type 1s. To learn more about these findings, please contact Richard Wood.
- **AZ's Farxiga (dapagliflozin) for type 1 was submitted for FDA review via an sNDA in ~4Q18.** We can't be sure exactly when AZ submitted the sNDA (making it difficult to anticipate a decision). And while this FDA decision doesn't bode immediately well for AZ, it'll be interesting to see whether the company brings a more robust risk mitigation strategy to the table (Forxiga also holds a positive CHMP opinion in the EU). Lilly/BI have not yet submitted an sNDA for Jardiance (empagliflozin) in type 1 to FDA that we know of, but have mentioned plans of doing so sometime in 2019.
- **Reaction from the diabetes community was assuredly one of disappointment.** JDRF released a statement on the decision expressing its disappointment and highlighting the need for new treatment options for people with type 1. Dr. Dan Drucker tweeted the news, conveying the sentiment that innovation in the type 1 diabetes arena is especially challenging - while we hope that this news does not de-motivate other manufacturers from investing in the space, we believe that the FDA wants to assure safety above all and we feel very hopeful and optimistic that sotagliflozin will ultimately see an approval.

Quotes from Key Thought Leaders

"**I respect the decision of FDA, but do not agree.** As a clinician working with people with T1D, I realize every day the unmet needs with our current therapies: not reaching tight enough glycemic control because of increasing risk of hypoglycemia as HbA1c goes down, increasing weight and in particular instability of glucose values, with insufficient time in range. The class of SGLT inhibitors improves all of the above, with impressive increases in time in range of several hours a day! The increased risk of genital infections and the small, but real, increase in DKA is a problem we can overcome with the right education of both patients and medical teams. I am happy that the European Agency has seen this and has proposed a positive decision."

- Dr. Chantal Mathieu (KU Leuven, Leuven, Belgium)

"**People with type 1 diabetes desperately need another therapy, especially one that goes beyond glucose control.** Because of this, I hope that the risk/benefit ratio of sotagliflozin will become better understood. Of course, there is nothing that is risk free. Perhaps FDA is not yet used to evaluating type 1 diabetes therapies from a Beyond A1c viewpoint, but the fact of the matter is that 4% to 5% of people with type 1 diabetes have DKA with or without these therapies according to the most recent T1D Exchange data. Many

physicians will continue to SGLT inhibitors in type 1 off-label moving forward, and we must now work to help FDA better understand the risk mitigation strategies and beneficial profile of sotagliflozin."

- Dr. Satish Garg (Barbara Davis Center, Denver, CO)

"**I am disappointed.** That said, hopefully there is a clear path forward for Lexicon and Sanofi to pursue."

- Dr. John Buse (UNC, Chapel Hill, NC)

"**I am disheartened by the FDA's decision to not approve sotagliflozin for type 1 diabetes (T1D).** As data from the Type 1 Diabetes Exchange has demonstrated, the vast majority of those living with T1D are not achieving glycemic targets. With sotagliflozin, we had the possibility of an adjunctive therapy that is orally administered and that has been shown in clinical trials to lower hemoglobin A1c levels, increase time in target range, lower total daily insulin doses, and lead to weight loss. Although increased risk of diabetic ketoacidosis can be seen with these agents, I believe the focus of healthcare providers is to assist patients in tailoring therapies that best meet their individual needs. The medical community must recognize the importance of outcomes beyond hemoglobin A1c results and must also consider how therapies affect time in range. Until then, I believe we will be left with a limited tool set to help our patients attain more targeted glycemia."

- Dr. Jennifer Sherr (Yale, New Haven, CT)

Select Q&A from Lexicon Investor Call

Q: Can you comment on whether the FDA has requested additional clinical work in the CRL?

A: We cannot say until we have those conversations with the agency. The next step is to engage with the agency and we will have more specificity at that time.

Q: You received a positive opinion from CHMP, indicating that EU regulators are looking at this differently than US regulators. Do you have a sense of where the disconnect may be between the EU and US on this issue?

A: This is a great question, and I'll try my best not to speculate. It's not unusual when you look at this category of the FDA, there have been a number of major products that have gotten approved in Europe first. Dapagliflozin was approved in Europe first before it was in the US for type 2 diabetes. The same happened with Victoza. There is a consistent history with this division [of the FDA]. The good news is that ultimately these compounds got approved.

Q: You aren't the only ones filing an SGLT inhibitor in type 1 diabetes. Do you think these issues that FDA pinpointed are specific to sotagliflozin, or a larger class issue with SGLT inhibitors in type 1?

A: I think all SGLT inhibitor products are remarkable products. That being said, we do have some unique aspects with our compound. But still, they're all pretty remarkable compounds. I will not make any speculations on what will happen thereafter. You can always assume that those who will come after us are certainly upset right now [with the news of a CRL for sotagliflozin in type 1].

Q: When you meet with FDA, will you come prepared with a clear clinical trial strategy to do a prospective risk mitigation strategy for DKA?

A: Great question. I can't speculate on Sanofi's strategy with the FDA. They're capable of advancing these conversations. We're going to do whatever we think is important to advance this compound with the agency.

Q: How are you preparing for the launch of sotagliflozin in type 1 diabetes in Europe?

A: We are very confident in Sanofi to launch in Europe. Europe is their responsibility.

--by Martin Kurian, Ann Carracher, and Kelly Close