CLOSER LOOK

MEMORANDUM

US decision for Sanofi's iGlarLixi (lixisenatide/insulin glargine) pushed back three months to November 2016 - August 22, 2016

Executive Highlights

- The FDA has requested additional information regarding the pen delivery device for Sanofi's GLP-1 agonist/insulin glargine fixed-ratio combination iGlarLixi (lixisenatide/insulin glargine), also known as LixiLan.
- This request has resulted in a Major Amendment to the New Drug Application (NDA) for iGlarLixi and has delayed a final FDA decision by three months to November 2016.
- This setback stands in contrast to the strong patient endorsements of iGlarLixi that were shared at the May 2016 FDA Advisory Committee meeting. While several panelists expressed concerns about the device at the meeting, we felt the regimen was far simpler than many others already approved (particularly involving mealtime insulin).
- We continue to believe that FDA is extremely under-resourced and that the extended timing reflects this more than any meaningful problems with the device.

Sanofi announced last Friday that it has submitted a Major Amendment to the New Drug Application (NDA) for GLP-1 agonist/insulin glargine fixed-ratio combination iGlarLixi (lixisenatide/insulin glargine; also known as LixiLan) at the FDA's request. Specifically, the FDA requested that Sanofi submit additional information on the iGlarLixi pen delivery device, thus pushing back the expected date of a final decision by three months to late November 2016. Sanofi and Zealand (which licensed iGlarLixi to Sanofi) both indicated that because the NDA is still under review, the companies are unable to provide more specific details on what additional information was requested.

While disappointing for the company, this delay is not all that surprising following the discussion at the FDA Advisory Committee meeting for iGlarLixi in May and given how under-resources the FDA appears to be (we wish patient advocates could help change this!). Though the product received a 12-2 vote in favor of approval, with panelists expressing nearly unanimous confidence in its A1c-lowering ability and the importance of the reduced injection burden that comes with a combination drug, a number of concerns were raised surrounding Sanofi's proposed pen delivery device - a yellow pen providing medications in a 2:1 ratio (with 10-40 units of insulin glargine and 5-20 ug of lixisenatide) and a green pen providing medications in a 3:1 ratio (with 30-60 units of insulin glargine and 10-20 ug of lixisenatide). Panelists focused on (i) use of color as the primary point of differentiation between the 2:1 and 3:1 dose ratio pens (a challenge for patients who are colorblind or have poor eyesight); (ii) confusing pen labeling; and (iii) dosing nomenclature in "units" that describe the number of insulin glargine units without explicitly referring to the amount of lixisenatide. Overall, we were a bit surprised since there are so many products already approved in which pen colors signify a type of insulin, etc - we did not see the pen labeling and believe the units naming issue could have been resolved beforehand through patient and provider panels (this may have been tried).

Overall, this three-month setback is disappointing for the many patients with type 2 diabetes who would benefit tremendously from a GLP-1 agonist/basal insulin combination product though presumably this will get approval by year-end. Sanofi management emphasized that the company "remains confident" in its NDA submission despite this delay. Zealand management said it was encouraged that the request for additional information was related to the delivery device rather than the fixed-ratio combination itself. We agree and hope that this is an issue that will be easy to resolve with simple design improvements and/or nomenclature changes.

- **Standalone lixisenatide (which was the subject of the May AdComm meeting) was approved in the US in July under the trade name Adlyxin.** Lixisenatide was approved in Europe under the trade name Lyxumia in February 2013; Sanofi withdrew its original US NDA for the product in order to avoid issues surrounding disclosure of interim data from the ELIXA CVOT. Lixisenatide has also been approved in more than 60 other ex-US markets. As we noted at the time of the approval, this clever US proprietary name subtly alludes to the use of lixisenatide as an add-on or intensification option - Adlyxin to "add lixi." This is consistent with our impression that Sanofi aims to position Adlyxin primarily as an add-on to basal insulin and that its greatest potential lies in the iGlarLixi combination.
- **It is a testament to the patient demand for fixed-ratio GLP-1 agonist/insulin combinations that all patients, patient advocates, and providers who spoke at the Advisory Committee's Open Public Hearing argued unanimously for iGlarLixi's approval.** Leading diabetes nurse educator and type 2 diabetes patient Ms. Virginia Valentine (Northside Family Medicine, Albuquerque, NM) called GLP-1 agonist/basal insulin combinations the "next big thing" in diabetes management. In response to the panel's concerns, our very own Ms. Kelly Close reminded everyone that while we may perceive the proposed iGlarLixi delivery as complex, mealtime insulin therapy is much, much more complicated for patients. In perhaps the most powerful argument in favor of iGlarLixi's approval, three different participants from phase 3 trials traveled from across the country to speak in support of the product, emphasizing that they had never felt undue confusion or experienced any adverse events while taking the investigational drug. Despite the very real concerns surrounding the iGlarLixi pen device, we hope the FDA has not forgotten these compelling messages from people that know a great deal about it.
- **Novo Nordisk's fixed-ratio GLP-1 agonist/insulin combination Xultophy (insulin degludec/liraglutide) is already approved in Europe and is fast-approaching a US FDA decision in September 2016.** Although iGlarLixi was submitted in December 2015, compared to Xultophy's September 2015 submission, Sanofi's use of a Priority Review Voucher granted an expedited six-month review process for the candidate, putting it neck-and-neck with Xultophy to be the first GLP-1 agonist/basal insulin fixed-ratio combination to reach the US market. In an ironic twist, with a decision for iGlarLixi now delayed until November, Xultophy is now again slated to win the coveted first-to-market spot in the US if approved next month. Compared to iGlarLixi's 12-2 vote of approval, Xultophy received a unanimous 16-0 recommendation from its FDA Advisory Committee, boding well for its approval. We doubt that the timing will make much difference overall, but had Sanofi not used the voucher, of course, there would be a greater difference in likely launch dates (six months difference vs. potential three months). Presumably FDA has time to look into the various aspects of the uncertainty - we do think if FDA had more patient input on various components of diabetes therapy and equipment, this would help them.
- **iGlarLixi is also currently under review in the EU with a decision expected in 2017.** We are curious to see if it the European review board will have the same questions with iGlarLixi as the FDA.

-- by Abigail Dove, Payal Marathe, Emily Regier, and Kelly Close