CLOSER LOOK

FDA Advisory Committee Meeting for Sanofi's LixiLan

May 25, 2016; Silver Spring, MD - Draft

Executive Highlights

The FDA Advisory Committee meeting for Sanofi's LixiLan (lixisenatide/insulin glargine) wrapped up several hours ago with a 12-2 vote in favor of approval (one panelist did not vote due to travel). The final verdict would be perhaps more accurately described as a unanimous vote of "yes, YES, but": nearly to a person, the panel agreed that the benefits of the combination itself outweighed the risks but expressed concerns about the proposed delivery devices. Standalone lixisenatide was also a topic of discussion during the meeting but did not receive a separate voting question - we felt there was full confidence for this compound. On the positive side, the panel agreed that lixisenatide and LixiLan demonstrated sufficient A1c-lowering efficacy to support approval and that there were no serious safety concerns. Many also seemed to grasp the enormous difference the reduced injection burden could make for patients, a message communicated loud and clear during the Open Public Hearing. There was some difference of opinion on how to interpret the weight results for LixiLan (1.4 kg benefit vs. Lantus). Some panelists echoed the FDA's opinion that the weight benefit was not clinically meaningful, but others argued (correctly in our view) that modest weight loss or even prevention of weight gain can be very meaningful for patients. As at yesterday's meeting for Novo Nordisk's Xultophy (insulin degludec/liraglutide), the panel agreed that patients already on insulin or a GLP-1 agonist would be a clearer target population for LixiLan than patients on oral medications.

Most of the panelists' concerns about LixiLan surrounded its packaging and delivery. MedStar Georgetown University Hospital's highly respected Dr. Kenneth Burman cited flaws with the design of the two delivery pens for LixiLan as the main factor leading to his negative vote, noting that one of the 15 pharmacists and one of the 45 patients and diabetes educators made errors selecting the correct pen in a human factors study for LixiLan. Other members suggested that the use of color as the primary point of differentiation between the two pens could pose challenges for patients who are colorblind or have poor eyesight (see below for an image of the two proposed pens). The majority of panelists also raised concerns about the nomenclature used to dose the combination. LixiLan is dosed in terms of "units" that refer to the number of insulin glargine units in a particular dose of the combination. The proposed dosing nomenclature does not explicitly refer to the amount of lixisenatide in the combination dose, which panelists felt would be confusing for non-diabetes-focused healthcare providers and patients. This echoes concerns raised yesterday about the lack of units altogether for dosages of Xultophy. Fairview Health Services' Dr. Steve Meisel cited two main additional concerns with his vote against approval: (i) the lack of clinical data investigating LixiLan as an intensification option for patients already on a GLP-1 agonist and (ii) the signal for increased serious allergic reactions with lixisenatide and LixiLan. Many other panelists also voiced similar concerns and suggested that both could be addressed with post-marketing studies.

- **All 11 patients, patient advocates, and physicians who spoke in the Open Public Hearing passionately implored the Advisory Committee to approve LixiLan.** Leading diabetes nurse educator and type 2 diabetes patient Ms. Virginia Valentine called GLP-1 agonist/basal insulin combinations the "next big thing" in diabetes management. Three different participants from the phase 3 trials for LixiLan 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 study drug. Furthermore, several patients anecdotally shared that they had even lost weight on LixiLan (though the phase 3 results for LixiLan suggested a weight neutral effect overall). Type 2 diabetes blogger Ms. Lizmari Collazo powerfully underscored that patients need more choices and better management tools - hear hear! Addressing some of the panelists' concerns, our very own Ms. Kelly Close reminded the panel that, while they might perceive the proposed LixiLan delivery as complex, mealtime insulin therapy is much, much more complicated for

patients. The clear need for additional treatment options such as LixiLan from the Open Public Hearing overall provided an extremely persuasive argument in favor of approval.

- **Overall, we were encouraged by the favorable verdict and hope that Sanofi and the FDA can work together to resolve the dosing and device concerns.** The question of the combination's efficacy in patients on a GLP-1 agonist should be easily resolved by a post-approval study, and Sanofi indicated during the meeting that it does intend to conduct such a trial. We assume the issue of the pen colors can also be easily resolved - perhaps brighter, more distinctive colors and/or clearer labeling could make the pens more easily distinguishable. As mentioned above, we also do not believe confusion between pens should be too much of a concern for most patients, as they will only have one pen in the home at a given time - it would likely be most relevant during transitions of care into hospitals, nursing homes, etc. The questions around dose nomenclature suggests that it would be useful for the FDA or other authorities to devise a standardized unit for such fixed-ratio combinations, as they will likely be a substantial part of diabetes care for the foreseeable future. Ultimately, we assume these issues can be addressed before the product launches and applaud the committee's decision to support its approval overall. We strongly feel that it's important to give patients and providers as many efficacious options for diabetes management as possible and are glad that this product will likely be made available to the many patients for whom it might be a terrific therapeutic option

Detailed Discussion and Commentary

Open Public Hearing

- **LixiLan trial participant Ms. Gloria Cunningham (travel paid for by Sanofi) shared her very positive experience with the drug.** She stated that before the trial, she was "ready to try anything" to get her glucose under control, particularly given her cousin's experience losing a leg to diabetes complications. She was impressed with LixiLan's efficacy - her A1c dropped from 8.1% to 7% or lower - and experienced no side effects other than decreased appetite and weight loss (which she said was more like an added bonus). Ms. Cunningham stated that she would much prefer to take only one injection instead of her current MDI regimen and that she plans to be one of the first to use the product if it is approved.
- **Diabetes nurse educator and type 2 diabetes patient Ms. Virginia Valentine characterized GLP-1 agonist/basal insulin combination as "the next big thing" in diabetes management.** Drawing on her personal experience living with diabetes for 35 years and caring for 18,000 patients with diabetes, Ms. Valentine especially highlighted the weight benefits of adding a GLP-1 agonist to insulin. She called GLP-1 agonists a "lifesaver" for her personally and "one of the greatest classes of drugs we've come up with." She pointed out that patients with type 2 diabetes and obesity are often blamed for their condition and told to just lose weight ("we treat type 2 diabetes as a character flaw") and advocated for the need for better, more effective therapies that don't cause weight gain. From a clinician's perspective, she also noted that primary care physicians are often overwhelmed by the complexity of diabetes and need a therapy that's simple to titrate.
- **Dr. Stanley Schwartz, representing AACE, spoke positively about the ability of GLP-1 agonist/basal insulin combinations to treat more aspects of diabetes pathophysiology with fewer medications compared to other therapies.** He highlighted lixisenatide's positive effects on glycemia, weight, and postprandial glucose and the benefits of avoiding bolus insulin with the combination. He suggested that lixisenatide should be considered among the many second- and third-line options for type 2 diabetes and that LixiLan could be appropriate for patients not at goal on oral drugs or on one of its components. He also suggested that for patients already on one injectable agent, providers could first add the second agent separately and then switch to the combination once the right dose is determined.
- **Study participant Ms. Maria Barino discussed how LixiLan eased her concerns about initiating an injectable therapy.** She emphasized that taking LixiLan was not confusing, it was

just different from the pills she was used to. She also noted that she had few side effects and better glycemic control, and even lost about 10-12 lbs (though she noted that may have also been due to walking her new German Shepherd for 45 minutes a day during this time period). Ms. Barino concluded with a strong endorsement of the product, emphasizing that she hopes it reaches the market because she would take it again.

- **Dr. Glen Sussman (travel paid for by Sanofi) spoke about his experiences as an investigator in clinical trials of lixisenatide/LixiLan.** He repeatedly emphasized the potential adherence benefits of a single daily injection with an easy-to-use pen - "if it's done in a single pen, the compliance rate will go through the roof." He highlighted a number of advantages of lixisenatide and other GLP-1 agonists, particularly the weight loss and low risk of hypoglycemia, and noted that he has personally encountered very few problems with adverse events or device issues.
- **Type 2 diabetes blogger Ms. Lizmari Callazo powerfully underscored the need for more choices and better management tools for patients with diabetes.** She noted that while many patients may initially feel some anxiety about starting new insulin, she has personally faced far more resistance from physicians reluctant to prescribe insulin. Ms. Callazo shared a shocking story in which she experienced blood sugars over 300 mg/dl in an ER and was refused insulin. She suggested that this reluctance stems from concerns about dosing errors (leading to hypoglycemia for the patient and potential liability for the physician), weight gain, and added cost to patients. Ms. Callazo suggested that GLP-1 agonist/basal insulin combinations could alleviate some of those concerns, increasing patient access to the therapies that are so sorely needed.
- **Our own Ms. Kelly Close argued that the simplicity of GLP-1 agonist/basal insulin combinations makes them a perfect fit for our imperfect healthcare system.** She expressed concern about the enormous stress facing providers caring for patients with diabetes, noting that she can't remember a time when HCPs seemed more exhausted and overwhelmed. She argued that many providers simply do not have time to handle the complexity of prescribing mealtime insulin and that there is a real need for easy-to-use alternatives like LixiLan that can help improve outcomes without adding more burden for patients and providers.
- **Dr. Robert Ratner (ADA, Alexandria, VA) addressed some of the panel's questions around how GLP-1 agonist/basal insulin combinations might fit into the type 2 diabetes treatment paradigm.** This topic had been a fairly significant point of discussion in the previous day's Advisory Committee meeting for Xultophy. He pointed out that the ADA 2016 Standards of Care already include guidelines for combination therapy involving insulin. The recommendations suggest an initial dual therapy with insulin if the patient's A1c is greater than 9% and the addition of a GLP-1 agonist (or mealtime insulin) on top of basal insulin for patients who need additional postprandial glucose lowering. Confronting the panel's concerns about the lack of clinical trial data on the intensification of therapy from GLP-1 agonists to LixiLan in the phase 3 development program, Dr. Ratner pointed out that there is published data on the addition of insulin to GLP-1 agonists and vice versa in a non-fixed dose regimen.
- **Our own Ms. Helen Gao shared survey data illustrating LixiLan's ability to address many of the key barriers to basal insulin intensification.** A survey conducted by diabetes market research company dQ&A of approximately 5,000 people with type 2 diabetes found that only 12% of patients on basal insulin, and only 22% of those with an A1c >9%, have had a conversation with their physician about adding mealtime insulin. The most frequently cited barriers to intensification were more hassle, difficulty dosing/calculating carbs, cost, hypoglycemia, and weight gain. Ms. Gao argued that LixiLan can address all of these concerns: it is "one pen, one injection, one prescription" that does not require carb counting, cause weight gain, or carry additional hypoglycemia risk on top of basal insulin. Ms. Gao also highlighted lixisenatide's distinct effects on postprandial glucose that make it an ideal alternative to mealtime insulin.
- **Our very own Ms. Emily Regier took to the podium to convey the enthusiasm and praise GLP-1 agonist/basal insulin fixed-ratio combinations have generated on the**

conference circuit. She shared that Close Concerns has reported on around 50 talks at 17 different scientific meetings on the topic of these combination products and emphasized the compelling nature of the phase 3 data supporting them. She quoted several key opinion leaders praising these combinations and their versatility ("the modern equivalent of basal-plus therapy," "the most effective way to treat type 2 diabetes, bar none," "if I only get one shot on goal, I do think this is the single best shot we have. Pun not intended"). Ms. Regier's talk offered an opportunity for the panel to consider opinions from experts who were not able to speak at the Advisory Committee meeting themselves.

- **LixiLan trial participant Mr. David Garcia (travel paid for by Sanofi) delivered a compelling presentation about his experience with the drug.** He explained that when he entered the study, his A1c was 9%, he weighed 240 pounds, and he felt terrible physically and mentally. After beginning treatment with LixiLan, his energy returned, his fasting glucose dropped from 180-190 mg/dl to 90 mg/dl and he lost 50 pounds - he joked that the only disadvantage was that he had to buy new clothing. He highlighted how well the drug's simple administration fit into his life as a high school teacher - he could just take one injection between first and second period - and how fantastic he felt at the end of the trial. Mr. Garcia said he would go back on LixiLan now if he could and expressed hope for a speedy approval and an affordable price.

Commentary from Voting Committee Members

Following the final panel vote, each panelist was allowed a few minutes to explain his or her decision. Included below are summaries of each statement, arranged in alphabetical order by speakers' last names. The panel voted 12-2 in favor of approval (with one member not voting due to travel) and the comments revealed ambiguity from both panelists who voted in favor and those who voted against approval.

- **Patient representative Ms. Barbara Berney voted yes, saying "this is another weapon in the fight, and it is a fight."** She concurred with the concerns raised about packaging and delivery and stressed that the field will need to figure out the "units" question soon, as these combination products are the wave of the future. Ms. Berney also emphasized the enormous difference the convenience of a single injection makes for patients, especially people who work full-time with no place to store insulin. As at the previous day's meeting, she recounted her story of quitting insulin therapy after gaining 30 pounds in two months to highlight the appeal of agents that are weight neutral or produce weight loss.
- **Dr. Daniel Budnitz (CDC, Atlanta, GA) voted yes, "but it could have been no."** His only reservation with the combination itself was the possibility of starting two drugs at once in some patients who might have done well on a single agent. He also strongly encouraged the development of a standard vocabulary for the dose units. He was optimistic that his concerns could be addressed but stressed that they do need to be addressed for him to feel confident supporting approval.
- **Dr. Kenneth Burman (MedStar Georgetown University Hospital, Washington, DC) cited flaws with the design of the two delivery pens for LixiLan as the main factor leading to his negative vote.** He pointed to the results of the human factors study for LixiLan, in which one of the 15 pharmacists and one of the 45 patients and diabetes educators in the study made errors selecting the correct pen. He also took issue with the inflexible fixed ratio, the less than maximally effective dose of lixisenatide at most doses of insulin glargine, the maximum 60 unit dose of insulin, the fact that the clinical trials may not correlate with real life practice, and the allergy data. He did emphasize that he felt that these issues could be worked out and that he was very close to voting yes. Overall, he felt the advantages of the product outweighed the disadvantages and that the evidence supported approval and use in patients already on basal insulin or a GLP-1 agonist.
- **Dr. Brendan Everett (Harvard Medical School, Boston, MA) voted yes, with one of the more positive sets of comments we heard.** He emphasized that phase 3 trials had demonstrated efficacy for LixiLan both in patients on basal insulin and those on oral drugs. While he sees patients on insulin as the main target population, for the combination, he believes it could be a good choice earlier in the disease course if it is clear that the patient will eventually need a number

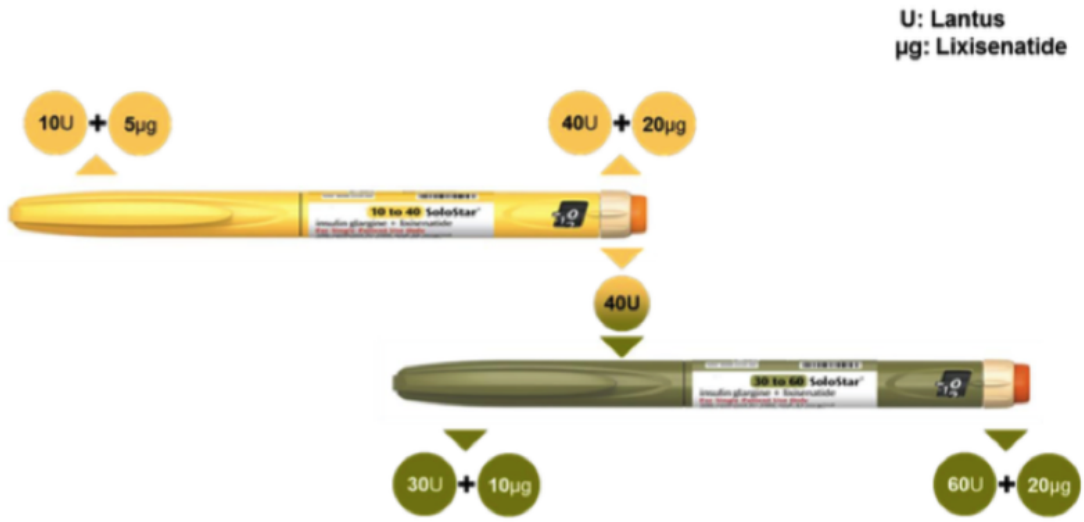
of medications to reach their goal. He also argued that the combination is likely effective at lower doses of lixisenatide than those tested in phase 3 trials as a standalone product. Dr. Everett shared the other panelists' concerns about the delivery device but expressed confidence that the FDA and the company could address the problems.

- **Consumer Representative Ms. Diana Hallare (Visalia, CA) voted in favor of approval, due to the clinical trial evidence indicating the product is relatively safe and not too difficult to use.** She also noted that the product demonstrated little to no increase in hypoglycemia. She did feel that the most appropriate patient population for the combination would be those already on basal insulin or a GLP-1 agonist.
- **Dr. Timothy Lesar (Albany Medical Center, Albany, NY) felt that LixiLan's A1c-lowering efficacy and reduced GI side effects justified a vote in favor of approval.** He did raise concerns around the dosing nomenclature and the allergy signal.
- **Dr. Steven Meisel (Fairview Health Services, Minneapolis, MN) voted no due to the delivery/dosing issues but emphasized that the combination is "clearly medically safe and effective."** He also raised a few additional concerns: (i) the lack of data in people on a GLP-1 agonist; (ii) the product's utility in people with high insulin requirements; (iii) the potential risk of allergic reactions; and (iv) the possibility of overdosing if patients switch to the combination from a twice-daily lixisenatide regimen (which he believes may be necessary for a sustained effect).
- **Dr. Martha Nason (NIH, Bethesda, MD) voted yes but raised concerns about allergic reactions and immunogenicity in addition to the dosing/delivery issues.** She argued that LixiLan had successfully demonstrated efficacy in phase 3 and suggested that it would be a very convenient and possibly cost-effective option to have on the table. She did express some hesitation about the issue of allergic reactions and the potential for anti-drug antibodies that could cross-react with endogenous GLP-1 or glucagon, saying she did not have a good sense of how to assess this. She also called for post-approval studies in patients on a GLP-1 agonist and more information on the product's effects in nonwhite people, especially African-Americans (~90% of phase 3 trial participants were white).
- **Dr. Michael Reed (Rainbow Babies and Children's Hospital, Cleveland, OH) struggled with his decision, ultimately voting yes but raising a number of issues.** He feels that the combination is rational from a pathophysiological perspective and even went so far to suggest that GLP-1 agonist/basal insulin combinations could be paradigm-shifting. He highlighted improved choice, cost, and convenience as the main factors that led to his yes vote. That said, Dr. Reed expressed significant concern over the "units" dosing nomenclature. He called on the FDA to create a standardized description for the dose - this would probably benefit Xultophy (with its lack of units altogether) as well. Dr. Reed also expressed significant anxiety over potential confusion between the two pens based on their color or proprietary names but emphasized that he didn't have a problem with the concept of two pens itself. Like others, he would like to see a post-marketing study on the allergy signal.
- **Dr. Ellen Seely (Harvard Medical School, Boston, MA) voted yes for a broad population but expressed strong concerns about the dosing measurements.** She explained that she voted yes because it was clear that an effective combination delivered in one injection would be very helpful for patients and clinicians. However, she felt very strongly that LixiLan should not be marketed in the proposed pen, saying that dosing a non-insulin product in units is "asking for trouble" during transitions of care. She suggested that the drug will be most useful for people on insulin but that there is enough variability in the patient population that there should not be limitations on the indication. She did urge the company to collect data for LixiLan in patients already on a GLP-1 agonist and recommended post-marketing surveillance to monitor the risk of allergic reactions.
- **Chairperson Dr. Robert Smith (Brown University, Providence, RI) voted in favor of approval due to his belief that LixiLan meets a clinical need with "adequate efficacy."**

In general, he felt that the safety issues were not very concerning though he would like to see a post-marketing study investigating the incidence of allergic reactions to the combination. He would also like to see a post-marketing study examining intensification to LixiLan from GLP-1 agonists. Like other panelists, he also felt that the distinction between the two pens needed to be made clearer through more differentiated pen body colors and very clear labeling and instruction materials.

- **Dr. Charles Stanley (University of Pennsylvania, Philadelphia, PA) voted yes, describing the possibility of a single injection that addresses fasting and postprandial glucose as very attractive.** As a solution to the dosing/pen issues, he suggested that it could be useful to think of the two pens as two different drugs, both dosed in units of volume - i.e., patients would be instructed to take X microliters of the yellow pen.
- **Dr. Peter Wilson's (Emory University, Atlanta, GA) "yes" vote was partially influenced by the passionate patient advocates who spoke about the need for additional therapeutic options and the benefits of having more than one GLP-1 agonist/basal insulin combination available.** He felt that the combination could be a boon to both endocrinologists and primary care physicians by making initiation of insulin therapy easier. He also expressed confidence that Sanofi will improve the delivery system.
- **Dr. Susan Yanovski (NIDDK, Bethesda, MD) noted that her vote in favor of approval came with "less than complete enthusiasm."** She felt that LixiLan met the targets for efficacy and that the safety was generally consistent with other products in the two classes. Like other panelists, she indicated that she would like to see allergic reactions closely tracked post-approval. She also noted that she is not completely confident in the combination's efficacy since the maximum comparator insulin dose was capped in the phase 3 trials. She also would have preferred to see data for LixiLan as an intensification of GLP-1 agonist therapy and data on the combination's efficacy in patients with a BMI over 35 (who might have higher insulin requirements). Like others, she felt that the combination should primarily be used in patients who were already on a basal insulin or GLP-1 agonist.

Figure 1: Proposed LixiLan Pens



--by Helen Gao, Emily Regier, and Kelly Close