CLOSER LOOK

MEMORANDUM

Lexicon 1Q17 - Timeline for key secondary endpoint readouts from phase 3 trials of sotagliflozin in type 1 diabetes; FDA meeting on type 1 submission scheduled for end of 2Q17 - May 2, 2017

Executive Highlights

- Lexicon provided its 1Q17 update this afternoon in a call led by CEO Mr. Lonnel Coats. The company shared that key secondary endpoint (body weight and blood pressure) data from the phase 3 inTandem1 trial of Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin is expected to report in May 2017. Data from secondary endpoints from inTandem2 will report in 3Q17, as well as - notably - pooled CGM data from the two studies.
- Lexicon management confirmed that a meeting with the FDA has been scheduled for the end of 2Q17 to discuss filing sotagliflozin for type 1 diabetes.

Lexicon provided its 1Q17 update this afternoon in a call led by CEO Mr. Lonnel Coats. The company provided more detail on its phase 3 data readout and filing plans for Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin in type 1 diabetes. We also heard continued enthusiasm for the company's early-stage, diabetes-related pipeline. Below, we include our top five highlights from the update, followed by a transcript of relevant Q&A.

Top Five Highlights

1. Lexicon provided the most specific timeline to-date of the remainder of phase 3 data readouts for the type 1 diabetes program for Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin. Key secondary endpoints from the inTandem1 trial, including body weight and blood pressure data, will be available this month (May). Body weight and blood pressure results from inTandem2 will be available in 3Q17, as will pooled CGM data from inTandem1 and inTandem2. inTandem3 will read out mid-year.

2. Lexicon management shared that a meeting with the FDA has been scheduled for the end of 2Q17. Lexicon will present primary endpoint efficacy and safety data to the agency and discuss next steps in preparation for the planned 1Q18 filing.

3. Lexicon characterized its early-stage pipeline as "fantastic," including phase 1 SGLT-1 inhibitor LX2761 (phase 1 data expected by the end of 2017) and phase 1 neuropathic pain candidate LX9211 (expected to enter clinical trials by end of 2017).

4. There were no updates on the progress of the Sanofi-led type 2 diabetes program for sotagliflozin. This was disappointing as we did not hear any updates during Sanofi's 1Q17 update either.

5. On the financial front, Lexicon's R&D spend in 1Q17 totaled $44 million, up 18% year-over-year (YOY) from $37 million in 1Q16. Management shared that the bulk of Lexicon's financial responsibility for the phase 3 type 2 diabetes program will be incurred throughout 2017. As of March 31, 2017, Lexicon had $260 million in cash and investments, down from $347 million at the end of 2016.

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Top Five Highlights

1. PHASE 3 SOTAGLIFLOZIN DATA READOUTS TIMELINE

Lexicon provided the most specific timeline to-date of the remainder of phase 3 data readouts for the type 1 diabetes program for Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin. Key secondary endpoint data such as body weight and blood pressure, from the inTandem1 and inTandem2 trials will be available this month (May) and 3Q17, respectively, as will pooled CGM data from inTandem1 and inTandem2 in 3Q17. inTandem1 and inTandem2 reported positive topline efficacy and safety results in September and December 2016, respectively. The trials demonstrated placebo-adjusted mean A1c reductions of 0.35%-0.41% for patients treated with the 200 mg and 400 mg doses of sotagliflozin. Notably, these reductions occurred on top of optimized insulin therapy without increasing hypoglycemia and relatively low rates of DKA (though there was still a significant signal for DKA that we hope is manageable with appropriate patient and provider education on this front). In our view, however, sotagliflozin's potential outcomes beyond A1c may be more exciting than its significant, but modest, A1c efficacy. We're particularly excited for the time-in-range data from the CGM sub-studies of inTandem1 and inTandem2 - we've seen impressive data from the JDRF-sponsored phase 2 study of sotagliflozin in young adults with poorly-managed type 1 diabetes, which found an impressive one-third increase in time spent in range of 70-180 mg/dl. Further, Dr. Anne Peters and her patients with type 1 diabetes have raved about the effect of selective SGLT-2 inhibitors in reducing glycemic variability - Lexicon management has speculated that sotagliflozin may have an even stronger effect on postprandial glucose due to the GI site of action of the SGLT-1 inhibition. The impact of SGLT-2 inhibitors on body weight is also a major draw for patients and providers and we're eager to see how sotagliflozin's impact on body weight compares to marketed SGLT-2 inhibitors. Finally, Lexicon has consistently expressed immense confidence in the blood pressure-lowering potential of sotagliflozin in type 1 diabetes patients with hypertension. Certainly, phase 2 blood pressure data for sotagliflozin is impressive, with double-digit reductions that are 3-4 times that of marketed SGLT-2 inhibitors. We're very eager to see how this data plays out in the larger phase 3 population.

- **Management reiterated that the phase 3 inTandem3 trial will report topline results in mid-2017.** inTandem3 is a larger, 1,400-participant exposure study that, notably, includes a 2-week placebo run-in rather than the intensive 6-week optimization effort prior to randomization that was incorporated in the design of inTandem1 and inTandem2. In addition, all types of insulin are allowed in this study. Thus, the company intends to help define drug in the type 1 patient population by demonstrating efficacy in the reduction of blood glucose in the absence of the two main risks of severe hypoglycemia and diabetic ketoacidosis, or DKA.
- **Lexicon plans to present a substantial amount of data for sotagliflozin in type 1 diabetes at ADA 2017.** In Q&A, management shared that data from inTandem1, inTandem2, the inTandem4 phase 2 dose-ranging study, and the JDRF-sponsored trial will all be presented at ADA. While inTandem3 probably won't be presented at ADA 2017 or EASD 2017 due to timing (and the fact that EASD does not have late-breaking abstracts), management confirmed that topline data from the trial will be publicly available. We can't wait!

2. MEETING WITH FDA ON SOTAGLIFLOZIN FILING SCHEDULED

Lexicon management shared that a meeting with the FDA has been scheduled for the end of 2Q17. Lexicon will present primary endpoint efficacy and safety data to the agency and will discuss next steps in preparation for the planned 1Q18 filing. Notably, management shared that CGM and inTandem3 data will not be available in time for this meeting. Nonetheless, the company continued to express strong optimism

that it will be able to move ahead with filing in both the US and EU by 1Q18 as planned and characterized this meeting as a opportunity to ensure that all of the major pieces required by the FDA for filing were in place. Lexicon has been very optimistic about the ability to file for type 1 diabetes substantially earlier than type 2 diabetes for some time now. That said, prior to the start of phase 3 for sotagliflozin, the FDA had signaled a preference for a joint type 1 and type 2 diabetes program and submission and it's unclear of the agency maintains this view. Due to partnering challenges, Lexicon had initially decided to move forward with a solo type 1 diabetes program, while the partnership with Sanofi and the decision to also pursue a type 2 diabetes indication came later. As a result, the progress of the type 2 diabetes program is significantly delayed compared to the type 1 diabetes program.

3. CONTINUED ENTHUSIASM FOR EARLY-STAGE PIPELINE

Lexicon characterized its early-stage pipeline as "fantastic" - candidates include phase 1 SGLT-1 inhibitor LX2761 and preclinical AAK1 kinase inhibitor LX9211 for neuropathic pain (including diabetic neuropathy). Management reiterated that the first phase 1 data readout for LX2761 is expected by the end of this year and Sanofi currently holds the rights of first negotiation for future development of LX2761. Lexicon management has previously emphasized that, ideally, Sanofi would decide to pursue this option and LX2761 will be added to the existing partnership between Lexicon and Sanofi for sotagliflozin. LX9211 is expected to enter a phase 1 clinical trial by the end of this year. The candidate was discovered in collaboration with BMS - BMS declined to move forward with the candidate and the rights reverted back to Lexicon in early 2017. That said, Lexicon management has emphasized that Lexicon played a significant role in the discovery of LX9211 and the company feels that candidate fits in well with diabetes expertise area that Lexicon is building. It's unclear whether or not the company will eventually seek a new clinical development partner for LX9211 - phase 2 and 3 trials for diabetic neuropathy are notoriously long and expensive and we expect Lexicon may pursue a partnership to defray the costs unless sotagliflozin is very, very successful. That said, we're extremely pleased that Lexicon is investigating this challenging area of immense unmet need.

4. NO UPDATES ON PROGRESS OF SANOFI-LED TYPE 2 DIABETES PROGRAM FOR SOTAGLIFLOZIN

There were no updates on the progress of the Sanofi-led type 2 diabetes program for sotagliflozin. This was disappointing as we did not hear any updates during Sanofi's 1Q17 update either. We're particularly curious as to how many trials will be involved in the program and their design - Sanofi has previously emphasized that the phase 3 program is designed to demonstrate a potential benefit for sotagliflozin in three specific use cases: (i) as a monotherapy; (ii) as an add-on to oral diabetes medications; and (iii) as an add-on to basal insulin. Additionally, the program will attempt to demonstrate differentiation in two specific ways: (i) greater A1c and blood pressure efficacy compared to Lilly/BI's SGLT-2 inhibitor Jardiance (which is indicated for the reduction of cardiovascular death) and (ii) efficacy in renal-impaired patients. As such, we expect a very robust phase 3 program with several head-to-head trials. Even more ambitiously, Sanofi management has implied that it intends to conduct a pre-approval CVOT for sotagliflozin designed to demonstrate superiority. Currently, only three trials from the program are posted on ClinicalTrials.gov: (i) in drug-naïve patients (n=240, expected completion September 2018); (ii) as an add-on to metformin (n=500, expected completion March 2019); and (iii) as an add-on to sulfonylureas (n=500, expected completion May 2019). We did notice that the expected completion of the trial in drug-naïve patients has been pushed back about six months, from March 2018 previously - this trial is still enrolling patients and we're curious if the delay may be due to slower-than-expected recruitment.

5. FINANCIAL POSITION

On the financial front, Lexicon's R&D spend in 1Q17 totaled $44 million, up 18% year-over-year (YOY) from $37 million in 1Q16. Management shared that the bulk of Lexicon's financial responsibility for the phase 3 type 2 diabetes program will be incurred throughout 2017. Overall, Lexicon is responsible for a proportional amount of R&D expenses for the type 2 diabetes program, up to a maximum of $100 million. The remainder

of this amount will be incurred in 2018, according to management. As of March 31, 2017, Lexicon had $260 million in cash and investments, down from $347 million at the end of 2016. We expect Lexicon's cash reserves may increase soon, now that it's very first product has launched (Xermelo [telotristat ethyl] for carcinoid syndrome diarrhea).

Questions and Answers

Q: In addition to primary endpoint for inTandem3, are we going to see the rates of hypos and DKA separately broken out when you report the topline data?

A: The answer is yes. We'll provide the safety information consistent with inTandem1 and inTandem2. We provided those numbers for those trials.

Q: Given that you're not doing the optimized insulin run-in, what is your expectation for the placebo rate of events, particularly with DKA?

A: The placebo rate of events may be higher in inTandem3 for DKA than in inTandem1 or inTandem2 because very aggressive treatment with insulin will increase severe hypoglycemia while decreasing DKA. It's one of the reasons why we have this endpoint, that balance and the effects of having too much insulin, too little insulin, and A1c control. We think it's an important way to develop our vision for the net benefit of the drug.

Q: What's the latest on your plans and discussions with the FDA for submission of sotagliflozin?

A: We requested a meeting with the agency. That meeting has been granted and will be toward the end of the second quarter. We have every intent to provide FDA with data we have, and every intent to come out of that meeting moving forward with filing.

Q: You are responsible for sharing some of the R&D costs with Sanofi on the type 2 diabetes program. Can you give us a sense of where you stand on that in terms of that?

A: We're sharing a proportion of the cost of the development program in type 2 diabetes, up to a maximum of $100 million in aggregate. We incurred a fair amount of that cost last year. The bulk of the cost will be this year, and then we have a remainder that we expect next year. This year is the heaviest proportion of our cost in terms of our contribution. That's included in all of our expense numbers - we've incurred meaningful expenses in the first quarter and we will be incurring those expenses over the course of this year. By the end of this year, there will be a relatively limited portion of that $100 million left to be incurred.

Q: InTandem3 was a global study - can you give us a breakdown of what proportion of sites were US vs. ex-US? As far as efficacy endpoints, you have discussed in the past the notion of time in range. Today you highlighted blood pressure data that we should anticipate - when can we learn more about time in range as a component of helping us understand the profile?

A: The time in range data will be pooled analysis that we would disclosed in the early part of the summer, in the third quarter in connection with the inTandem2 study. We think that data is extremely important and therefore we will extract it out that way.

I don't have an exact or proportion for you of US to ex-US sites, but I would say the majority of sites are ex-US. We're recruiting in Western Europe, Eastern Europe, and Latin America, in addition to US.

We'll learn about blood pressure data from inTandem1 in the month of May.

Q: The US regulatory update is appreciated. I believe in Europe you had talked about 2018 as well - should we be thinking about a similar part of 2018 for that?

A: Yes. We're always trying to move as fast as we can, but we expect to be able to file in both US and Europe by 1Q18. One may come before the other if we can move even faster, but right now our plan is to file them in the first quarter next year.

Q: Is the reason that you're giving us the pooled CGM data in 3Q as opposed to sooner is because there just aren't that many patients with CGM data in each study so you want to pool

it? Also, the May update that we're getting for inTandem1 - is that at a medical meeting and if not, should we also expect any data at ADA? And that 3Q timing for inTandem2 and the pooled analysis - does that mean EASD?

A: On the pooled analysis, you're correct, because we moved very quickly with inTandem1 and inTandem2, these were sub-studies in both of those and we enrolled fairly quickly. So what we decided to do was pool the analysis from both of those studies and then present that later in the year.

At ADA, we plan to have presentations with results from our dose-ranging study, our JDRF collaboration, and inTandem1 and inTandem2. Look forward to a good update at ADA with information on our program in type 1 diabetes. As far as EASD, the meeting does not have late-breaking clinical trials, so having the data available over the summer does not mean that we will be presenting it at EASD. But important data will be made publicly available in very high-level summary form anyway.

Q: Regarding the geographic breakdown of the 1,400-patient safety study, you said the majority is going to be ex-US - do you know the breakdown of that? I'm just thinking about the pump usage as it relates to US and outside of the US.

A: I don't have an exact percentage for you for inTandem3. One thing to note is that we do expect generally less pump use than we had in inTandem1 because it's being ex-US but also because we allowed patients on pre-mixed insulins. Some patients are still receiving mixtures of 70/30 NPH/regular - that also means that pump use will be lower.

Q: With respect to the end of 2Q meeting that you've been granted with the FDA, is it safe to assume that you're going to have all the CGM and inTandem3 data available for that meeting?

A: No, we would not have that data in time for that meeting, but we will have a complete assessment of all of our efficacy and safety data on the two pivotal studies.

Q: Given the importance of the CGM data, both from a patient and physician perspective, why schedule the meeting ahead of having that data available to discuss with the agency?

A: What we will be discussing with the agency is the primary endpoint, and that's what's going to be important. We're also making sure from the agency whether there is anything else we would need to get ready for our filing. That's the primary nature of that meeting. We'll have many other opportunities to engage the agency, particularly as we have our end of phase 3 meeting with them, which will be different from what we're having right now, and we'll have other opportunities beyond that to engage with them. Right now is really to lay out our case and to make sure we have everything locked and loaded to prepare to file - we're planning to file in the first quarter which gives us very little time to prepare so we want to make sure we have everything ready before then.

Q: There's been a competitive dual inhibitor announced by a Big Pharma and they're advertising it as part of their NASH portfolio and maybe looking at it as a weight loss drug. Just curious if there's any kind of additional freedom to operate on the Sanofi side outside of diabetes?

A: I'll just say imitation is the greatest form of flattery. But no, we continue to do work to figure out what additional things we want to do, but right now our focus in the alliance is getting our phase 3 programs fully up and loaded for type 2 diabetes and getting ready to file in Europe and the US for type 1. We always will have lifecycle management discussions and we think we have appropriate opportunities to do that beyond the work we're doing right now as priorities.

-- by Helen Gao and Kelly Close