CLOSER LOOK

MEMORANDUM

Lexicon 4Q16 - Additional phase 3 data readouts for sotagliflozin in type 1 diabetes expected throughout 2017; Continued confidence in 1Q18 type 1 submission; Commentary on early-stage pipeline - March 13, 2017

Executive Highlights

- Lexicon provided its 4Q16 update recently in a call led by CEO Mr. Lonnel Coats. The company provided additional granularity on when additional data readouts are expected from the phase 3 program for sotagliflozin in type 1 diabetes. In particular, management was extremely optimistic about sotagliflozin's potential impact on a number of secondary endpoints, including blood pressure and time in range. Lexicon hopes to submit the drug for type 1 diabetes in 1Q18.
- Management provided additional color on its early-stage pipeline. In particular, the company confirmed that it hopes to develop preclinical neuropathic pain candidate LX9211 for diabetic neuropathy specifically.

Lexicon provided its 4Q16 update recently in a call led by CEO Mr. Lonnel Coats. We continue to be extremely enthusiastic about this therapy for type 1 patients in particular. Below, we include our top five highlights from the call, followed by a full transcript of relevant Q&A.

Top Five Highlights

1. Lexicon management provided additional clarity on when additional data readouts are expected from its phase 3 type 1 diabetes program for Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin. Full results from inTandem1 and inTandem2, as well as topline inTandem3 results, are expected in mid-2017.

2. Lexicon management was extremely optimistic about sotagliflozin's potential impact on a number of secondary endpoints, including time in range and blood pressure.

3. Management reaffirmed its confidence that Lexicon will be able to submit sotagliflozin to the FDA for type 1 diabetes in 1Q18, ahead of a type 2 diabetes submission.

4. Lexicon provided big picture commentary on how it views its pipeline. Management reiterated that initial phase 1 data for selective SGLT-1 inhibitor LX2761 are expected in 2017. Additionally, the company expects to file an IND for neuropathic pain candidate LX9211 in mid-2017 and initiate phase 1 studies by the end of the year. Notably, management specified its interest in investigating LX9211 in diabetic neuropathy.

5. On the financial front, Lexicon's R&D spend in 4Q16 totaled $40 million, up 33% year-over-year (YOY) from $30 million in 4Q15, unsurprising in light of all the trial activity. Full year 2016 R&D spend nearly doubled to $178 million from $95 million in 2015. As of December 31, 2016, Lexicon had $347 million in total cash and investments, down from $396 million at the end of 3Q16 and from $521 million at the end of 2015 - but still a heck of a lot of funds.

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Top Five Highlights

1. SOTAGLIFLOZIN TYPE 1 DIABETES PHASE 3 DATA READOUTS

Lexicon management provided additional clarity on when additional data readouts are expected from its phase 3 type 1 diabetes program for Sanofi-partnered SGLT-1/2 dual inhibitor sotagliflozin. Full 52-week safety and efficacy data, as well as data on some of the secondary endpoints, from inTandem1 will be available in the first half of 2017. Topline results from the third pivotal trial, inTandem3, will be available in mid-2017 - ClinicalTrials.gov currently lists an expected primary completion date of March 2017. "Shortly after," Lexicon expects to have full 52-week results from inTandem2. Additionally, time in range results from inTandem1 and inTandem2 will be pooled for the pre-specified CGM sub-study - Lexicon expects these data will be available around the same time as the full inTandem2 results, in the second half of 2017. We were pleased to hear more granularity in when we may expect further results from this very exciting candidate. Among the secondary endpoints of inTandem1 and inTandem2, we're particularly interested in the time in range, body weight, and blood pressure results as we expect these will make the biggest difference for many patients with type 1 diabetes. Also, positive results on these parameters - time in zone and body weight, especially - likely bode well for the Sanofi-led phase 3 program for sotagliflozin in type 1 diabetes. We're also looking forward to inTandem3 results - importantly, unlike in inTandem1 and 2, treatment in inTandem3 is not administered on top of optimized insulin therapy, suggesting that the inTandem3 population is closer to a "real-world" patient population and we may see even greater glucose reductions and associated time in range than in the first two trials.

2. OPTIMISM FOR SECONDARY ENDPOINT RESULTS

Lexicon management was extremely optimistic about sotagliflozin's potential impact on a number of secondary endpoints, including blood pressure and time in range. Management particularly expressed enthusiasm for sotagliflozin's blood pressure data to date, noting that candidate produced double-digit reductions in systolic blood pressure in patients with hypertension in phase 2 trials in both type 1 and type 2 diabetes, on top of standard-of-care hypertension treatment. Lexicon noted blood pressure change in the subgroup of patients with hypertension is a pre-specified secondary endpoint inTandem1 and inTandem2. The company hopes that these data will be able to define sotagliflozin's potential to treat hypertension as well as diabetes and stated that it was "cautiously excited" about having the data unblinded. Furthermore, Lexicon suggested that it's possible that Sanofi may eventually seek a blood pressure-lowering label for sotagliflozin in type 2 diabetes, though management was careful to emphasize that it does not speak directly for Sanofi or know its partner's exact plans. That said, Lexicon management shared that Sanofi is similarly excited about the blood pressure-lowering potential of sotagliflozin and expects the blood pressure data to translate into a cardiovascular benefit for patients with type 2 diabetes. Furthermore, management emphasized that both Lexicon and Sanofi would like to develop sotagliflozin to give it as many strategic advantages as possible - we assume this means that the partnership will certainly pursue a blood pressure-reduction if the data supports it.

- **Management pointed to time in range benefits as a point of differentiation for sotagliflozin compared to SGLT-2 inhibitors on the market.** Indeed, the JDRF-partnered phase 2 study of sotagliflozin in young adults with poorly-managed type 1 diabetes found an impressive one-third increase in time spent in range of 70-180 mg/dl, as measured by CGM. Lexicon attributed the time in range to the SGLT-1 inhibition aspect of sotagliflozin, which blunts postprandial glucose spikes more than selective SGLT-2 inhibition. We're certainly very, very interested in the upcoming pooled CGM data from inTandem1 and inTandem2. We expect that (i)

sotagliflozin is able to produce a marked improvement in time in range; and (ii) the FDA and payers begin to recognize the importance of outcomes beyond A1c such as time in range. Among patients surveyed by diabetes market research firm dQ&A, patients across the board (with type 1 diabetes and with type 2 diabetes taking and not taking insulin) ranked time in range as the factor with the largest impact on daily life. Thus, it would be a major win for both sotagliflozin's type 1 and type 2 diabetes program if it is able to demonstrate an increase in time in range (particularly a reduction in hypoglycemia and glycemic variability) and we eagerly await our first look at this data in a large participant population in the latter half of this year.

- **Regarding body weight, Lexicon noted that it expects sotagliflozin to produce comparable but not superior weight reductions to currently-available SGLT-2 inhibitors.** Management pointed out that, due to its dual inhibition mechanism, urinary glucose excretion - the main mechanism of caloric loss with SGLT-2 inhibitors - is relatively modest with sotagliflozin. Thus, Lexicon doesn't necessarily view weight loss as a point of differentiation for sotagliflozin from other SGLT-2 inhibitors. As long as it isn't considerably worse, that's probably fine. Management did note that sotagliflozin therapy could lead to reduced prandial insulin doses in particular, which may translate into a more favorable weight profile for sotagliflozin+insulin therapy compared to regular basal-bolus therapy though we think most SGLT-2s do prompt less insulin use among those taking it who are already taking insulin.

3. TYPE 1 DIABETES FDA SUBMISSION EXPECTED IN 1Q18 AHEAD OF TYPE 2 SUBMISSION

Management reaffirmed its confidence that Lexicon will be able to submit sotagliflozin to the FDA for type 1 diabetes in 1Q18, ahead of a type 2 diabetes submission. Lexicon and partner Sanofi have an upcoming meeting with the FDA in which the company hopes to gain more clarity on the expectations for sotagliflozin's submission. The company emphasized that both Lexicon and Sanofi are planning for a separate 1Q18 type 1 diabetes submission and reiterated its position that the current phase 3 program for sotagliflozin in type 1 diabetes will sufficiently support approval. In particular, management suggested that inTandem1 and inTandem2 have already cleared the most challenging clinical hurdle by demonstrating an A1c benefit on top of optimized insulin therapy. Furthermore, management believes that, due to the size of the phase 3 program, any additional information that the FDA might require can be gathered from the data in the current trials, without the need for additional trials. From Lexicon's point of view, the largest remaining question for the FDA is how the DKA risk associated with sotagliflozin may be managed, which management suggested could be addressed through careful care instructions on the drug's label. 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.

- **Lexicon management reiterated that the first trials in the Sanofi-led phase 3 program for sotagliflozin in type 2 diabetes initiated in 4Q16 and the balance of trials are expected to begin in 2017.** The third trial in the program was recently added to ClinicalTrials.gov - the trial (n=500) will evaluate sotagliflozin as an add-on to a sulfonylurea or as an add-on to sulfonylurea+metformin therapy. The trial has an expected completion date of May 2019. The other two trials listed on ClinicalTrials.gov will evaluation sotagliflozin (i) in drug-naïve patients (n=240, expected completion March 2018) and (ii) as an add-on to metformin (n=500, expected completion March 2019). Given the timeline of these trials, we expect that sotagliflozin will not be submitted for type 2 diabetes for over a year following its type 1 diabetes submission, if all goes according to plan. We've also yet to receive any details on the remaining trials in the program. We anticipate a cardiovascular outcomes trial, possibly designed for superiority, will also be part of the phase 3 program for type 2 diabetes - this trial would likely delay the type 2 diabetes submission even further though we don't necessarily think the results would need to be pre-approval, though we

aren't sure. After all the SGLT-2 trials are out, we would be very surprised if it did! If the FDA allows for a solo type 1 diabetes submission and approval, sotagliflozin could very well be on the market while the type 2 diabetes program is still progressing, opening up the possibility for off-label prescription for patients with type 2 diabetes. We would certainly be very interested in a CVOT having a type 1 arm.

4. ENTHUSIASM FOR EARLY-STAGE PIPELINE

Lexicon management provided big picture commentary on its clinical development pipeline, expressing its view of its two early-stage candidates as extensions of the company's efforts in diabetes. In particular, management specified that Lexicon is interested in developing its preclinical neuropathic pain candidate LX9211 for diabetic neuropathy specifically. The company expects to file an Investigational New Drug (IND) application for the candidate in mid-2017 and plans to initiate phase 1 studies by the end of the year. The drug is an AAK1 kinase inhibitor 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 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.

- **Lexicon reiterated that initial phase 1 data for selective SGLT-1 inhibitor LX2761 are expected in 2017.** Sanofi currently holds the rights of first negotiation for future development of LX2761. Lexicon management 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.
- **Overall, management is focused on bringing its existing pipeline products to the market, rather than adding to Lexicon's early-**stage pipeline. Management noted that Lexicon has quite a few pipeline projects and other priorities already for a company of its size - the company's very first product (telostristat ethyl for carcinoid syndrome diarrhea) was just approved by the FDA and we expect much of the company's resources are devoted to establishing that product as well completing the phase 3 program for sotagliflozin. That said, Lexicon emphasized that it is a "science-based" company, and thus the team is looking at the company's candidates in discovery to see which ones may fit into the company's two focus areas: diabetes and neuroendocrine tumors. We're certainly pleased to hear Lexicon's continued commitment to innovation within diabetes and are looking forward to see what may be added to the company's burgeoning pipeline in the coming years.

5. FINANCIAL POSITION

On the financial front, Lexicon's R&D spend in 4Q16 totaled $40 million, up 33% year-over-year (YOY) from $30 million in 4Q15 due to more trial activity presumably. Full year 2016 R&D spend nearly doubled to $178 million from $95 million in 2015. Much of this increased spend is attributable to Lexicon's phase 3 program for sotagliflozin in type 1 diabetes and its contribution to the Sanofi-led phase 3 program in type 2 diabetes. As of December 31, 2016, Lexicon had $347 million in total cash and investments, down from $396 million at the end of 3Q16 and from $521 million at the end of 2015. Although cash goes quickly in such an aggressive development program, it's great for Lexicon that cash is not its major worry. We believe the company continues to be very good stewards of its funds.

Questions and Answers

SOTAGLIFLOZIN

Q: You've previously mentioned a plan to meet formally with the FDA in the first half of 2017 to get an initial read with existing data on their thoughts on potentially reviewing an NDA in

2018 for type 1 diabetes separately from type 2 diabetes. Presuming you're not able to publicly disclose this information after meeting with them, what kind of activities would change if the FDA tells you they're leaning toward a solo type 1 review in 2018?

A: We are absolutely preparing for success. To be frank, we think we have remarkably good data. We have overcome the biggest hurdle the agency has put in front of us, which was to show that you can provide a patient benefit - specifically an A1c reduction - on top of optimized insulin. We haven't done that just once, but we have done it twice now in two well-controlled pivotal trials. So, we're very confident about that data.

I think the question we have to answer for the agency going forward is what care instructions should we change in order to manage the DKA risk that we have with this drug. I think once we're able to answer those questions, we'll remain very confident we can file this drug in the first quarter of 2018.

So, I don't see much changing other than that preparation and putting together an aggregate package that we can get some feedback on from the agency. If they ask us for some additional information, I think we have such a large program with the inTandem trials that we should be in a position to answer any question for the agency within the total breadth of that program. So, the meeting is really to make sure that there's not something we're missing and don't understand that we'll need clarification on in that meeting. From an aligned point of view with both us and Sanofi, it remains our intent to file the compound based on what we see in our data already in the first quarter of 2018.

Q: What could the label for sotagliflozin look like in type 1 diabetes? You've done the juvenile study with JDRF, obviously and about a sixth of the patients in the United States that have type 1 diabetes are pediatric. So are you going to get the pediatric indication through the JDRF study or is that going to come later because obviously the phase 3 studies were conducted in adults?

A: The study that we did with JDRF was actually in young adults. We're looking at a population of adults with type 1 diabetes as the initial target population for sotagliflozin in type 1 diabetes. There are approximately 1.1 million adults with type 1 diabetes in the US. We will be doing pediatric studies with the objective of extending this to people who are younger, but that's something that will take place after we complete the phase 3 program in adults, which is consistent with the way that the FDA would want us to proceed.

I think that we will keep our relationship with the JDRF. It is an opportunity for us to continue to do work in collaboration with JDRF in designing and developing studies for pediatric use.

Q: When you meet with the FDA in the first half of this year, do you expect to ask them how they are thinking about the two doses of sotagliflozin? Will they perhaps want to see an inTandem3-like study with the 200 mg dose?

A: Certainly, we're hoping to present to the FDA our pivotal program. As you know, we have completed that and we hope to get feedback from the agency both on what they believe remains for us to do in preparation for our submission. Included in that will be the 200 mg and 400 mg dose, as they both were contained in our pivotal phase 3 program. So we should have full information from them, and if there is something remaining for us to do we'll be in a good position to try to get that done in preparation for our intent to file by the first quarter of 2018.

Q: Should we think about the 52-week safety and efficacy data updates for sotagliflozin in type 1 diabetes in inTandem1 and inTandem2 as separate readouts? Are the secondary endpoint data from these studies - including the CGM - going to be presented as a pooled analysis or should we expect separate readouts from each of the two pivotal trials?

A: The 52-week data are very important for safety, in particular. One of the things we will be examining is the time course of safety events. Among the secondary endpoints, the blood pressure data will be particularly important. We've talked about very large blood pressure reductions in the past, observed in three phase 2 studies (two in type 2 diabetes and one in type 1 diabetes). The CGM data is also very important because we've believed from our first phase 2 study in type 1 diabetes that sotagliflozin can significant reduce glycemic

variability and improve time in range, and patients value that. The CGM will be pooled in order to provide a robust analysis from inTandem1 and inTandem2.

There will be differences in timing. We'll have the longer-term data and some of the secondary endpoints from inTandem1 a little bit before the middle of the year. We will have inTandem3 data in the middle of the year, and then shortly after that we will have inTandem2 data and the CGM pooled data.

Q: For inTandem3, is it correct that the duration of the study will be complete at the 24-week endpoint and that you're not going to have a 52-week endpoint? So when you share the results at midyear, that would be the final results?

A: Yes. We will have the data - it will be top line data, but it will be data complete from the complete duration of the study around the middle of this year for inTandem3 because the duration is basically a six months.

Q: What are the secondary endpoint expectations? What magnitude of weight change can we expect? What can we expect from the 52-week data and to what extent would experiences with other SGLT-2 inhibitors be a good proxy? How might subtle differences in mechanism between sotagliflozin and other SGLT-2 inhibitors influence secondary endpoints such as body weight, blood pressure, and time in range?

A: From what we've seen in our type 2 diabetes population and in our first studies of type 1 diabetes at 24-weeks, the weight change observed with sotagliflozin has been significant and similar to that seen with other SGLT-2 inhibitors in type 2 and type 1 studies.

Sotagliflozin has relatively modest urinary glucose excretion and we think that's an important part of its profile and may have important safety implications. With that modest urinary glucose excretion, we do not expect more caloric loss than with selective SGLT-2 inhibitors. Thus, we have not projected a profile of superiority in weight loss. What we've seen in terms of body weight has been similar to SGLT-2 inhibitors so far.

In terms of type 1 diabetes, there are a few factors at play. Obesity is common - we've seen a mean body mass index of 29 to 30 in inTandem1, and patients are often on very high doses of insulin and have a lot of issues with severe hypoglycemia from those high doses of insulin. Thus, weight change could be related to patients looking for way to manage their type 1 diabetes safely. Some patients may decrease their bolus insulin dose and that may have an impact on weight.

So, overall for weight change, we've generally seen a similar profile, although, with 52-week data and patients on optimized insulin, we have the potential for some good results.

In terms of blood pressure, we've seen in type 2 diabetes, among patients with hypertension (meaning patients whose baseline systolic blood pressure was greater than 130 mmHg) we saw a 14 mmHg placebo-subtracted reduction in systolic blood pressure with the 400 mg dose of sotagliflozin. That was quite striking to us and we have not seen that with selective SGLT-2 inhibitors. Additionally, in a renal impairment study, we saw an 11 mmHg drop in systolic blood pressure compared to placebo, in just seven days. In our phase 2 type 1 diabetes study, in the subgroup of patients with hypertension, we again saw a 14 mmHg drop in systolic blood pressure. We have to be a bit cautious, because these were small studies, with analysis on the order of 30 to 40 patients. We really look forward to seeing these data in a much larger study where we pre-specified blood pressure analysis in this subgroup of patients with systolic blood pressure of at least 130 mmHg. We feel that we'll have enough patients in inTandem1 and inTandem2 to have meaningful readouts and define well the potential for sotagliflozin to treat patients with hypertension and type 1 diabetes and we're cautiously excited about having those data unblinded.

In terms of time in range, there could also be differentiation from selective SGLT-2 inhibitors. We have not seen good data in terms of time in range from selective SGLT-2 inhibitors. That said, we are encouraged with that experience that we had in our 203 study in type 1 diabetes where we saw time in range improved on the order of one to two hours over the course of 24 hours. We do believe that this relates to the SGLT-1 inhibition, not the SGLT-2 inhibition, because we've reduced the peaks of glucose after meals. So, that could be

differentiating factor and I think will be an important readout with the inTandem1 and inTandem2 CGM pooled data.

Q: Might Sanofi's phase 3 development program for sotagliflozin in type 2 diabetes actually intend to seek a blood pressure-lowering label?

A: That's a challenging questions. I would say that they were as excited about the blood pressure data as we are. We're always cautiously optimistic about the direction we're take once we have blood pressure data in a larger trial, like inTandem1 and inTandem2. We'll want to develop the compound to give it a strategic advantage. That said, we never speak directly on behalf of Sanofi.

One of the key areas that we and Sanofi both view as the value of sotagliflozin is the expectation that the blood pressure data will provide a benefit in terms of cardiovascular risk to patients with diabetes.

This optimism is driven by the huge systolic blood pressure drop we saw for sotagliflozin therapy in patients with type 1 and type 2 diabetes. For us, that's quite extraordinary, which led us to make sure to pre-specify that secondary endpoint in our phase 3 program so that we can get clear on just what exactly this means. Once we have that clarity, I think it informs us on how we want to continue to develop this compound to ensure that we have all of the advantages that we think we can have as we come to market.

Q: Can you clarify whether those reductions in blood pressure were observed on the background of maximal anti-hypertensive therapy?

A: I wouldn't say maximal, in the sense that we didn't have a formal program to review everybody's anti-hypertensive therapy. I would say it was on top of standard-of-care. That's the best description of our program, standard of care rather than maximal, per se.

OTHER PIPELINE PRODUCTS

Q: Did Sanofi have right of first refusal on the SGLT-1 inhibitor and what happened there that you're seem to be developing the candidate independently?

A: With LX2761, the arrangement that we have with Sanofi is a right of first negotiation and we have a framework for us to consider adding LX2761 into the partnership. That said, that's something that would require an agreement between us and Sanofi. The hope as we develop this asset is we add to the relationship that we have with them.

Q: You're bringing this neuropathic pain compound forward with or formerly with BMS. Can you comment on what that means bigger picture for Lexicon, in terms of where you intend to take the company?

A: The compound was out of an alliance that we established some time ago with BMS in which we jointly discovered and developed targets in neuroscience. LX9211 for neuropathic pain is an extremely promising program that we're really excited about, and it is something that we also had a very significant part in creating.

There is some interesting overlap between areas and LX9211 could be used in the areas that we're already working in. For example, one of the most significant areas in neuropathic pain is diabetic neuropathy. We've contributed to this program and we're very enthusiastic about it.

Q: Can we expect more compounds to be added to the pipeline? How do your pipeline candidates fit into the specialty organization that you're building?

A: Our team is looking at all of our science and doing a thorough review to try and figure what has good chemistry to put into one of the two areas we're focused on, either the neuroendocrine tumor area or certainly the diabetes space.

Based on the remarkable success we've had with sotagliflozin, we certainly expect that we will have some success as well with the LX2761 selective SGLT-1 inhibitor, and Sanofi already has the opt-in opportunity to participate in its development.

Additionally, now that we have the rights to LX9211, we have the possibility to explore not just neuropathic pain in general but, more specifically, diabetic neuropathy, which fits into our diabetes focus.

Q: How high a priority is it to add to the pipeline behind LX9211 and LX2761. Do you feel like you have enough to keep you busy as it is?

A: I think we have been very cautious of that. I try not to get myself too terribly excited everyday on finding new things because, for a company of our size, I think we have quite a few priorities already. That said, we are a science-based company, so we do have a team that's continuing to look at our early science and the implications that may have on the areas that we now consider most important to us - the metastatic neuroendocrine tumor market and the diabetes market. So we're looking at adding to our pipeline but it's not our biggest priority. Our biggest priority is to continue moving assets we have toward commercialization.

-- by Helen Gao and Kelly Close