MEMORANDUM

Lexicon 2Q14 - Greater emphasis on LX4211's standalone potential for type 1 diabetes - August 14, 2014

Executive Highlights

- Following meetings with the FDA/EMA and the initiation of a new phase 2 trial for the SGLT-1/2 dual inhibitor LX4211 in type 1 diabetes patients; management could initiate a solo phase 3 program for LX4211 in type 1 diabetes at the beginning of 2015.
- Partnership discussions for LX4211 in type 2 diabetes draw on into their second year.

Late last week, Lexicon provided its 2Q14 financial update in a call led by new President and CEO Mr. Lonnel Coats. The company's main diabetes-related pipeline candidate is LX4211, an SGLT-1/SGLT-2 dual inhibitor currently in development for both type 1 diabetes and type 2 diabetes. The company's confidence in LX4211 is high - as Mr. Coats said during the call, he believes that LX4211 has the potential to be a "class-defining" compound in the way that Lipitor defined the statin class. Included below are our top five highlights from the call, followed by selected Q&A.

1. Following meetings with the FDA/EMA and the initiation of a new 12-week phase 2 trial with the JDRF, Lexicon is on track to initiate phase 3 for LX4211 in type 1 diabetes at the beginning of 2015.

2. Management dedicated an entire section of prepared remarks to highlight the clinical and commercial opportunities for LX4211 in type 1 diabetes, highlighting payers' desire for agents with greater efficacy and less hypoglycemia and weight loss.

3. The search for a partner for LX4211's phase 3 development for type 2 diabetes (which could also become a joint type 1/type 2 diabetes program) continues.

4. This was the first earnings presentation for new President and CEO Mr. Lonnel Coats, who replaced Dr. Arthur Sands.

5. It appears, from Lexicon's current finances, that its current store of cash and investments ($79 million at the end of 2Q14) may not be enough to finance a full type 1 diabetes phase 3 program (which management estimated at over $100 million for a standalone program).

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TOP FIVE HIGHLIGHTS

1. Lexicon is moving ahead with its plans initiate a solo phase 3 program for LX4211 in type 1 diabetes, although both the company (and the FDA) would have a preference for a joint type 1/type 2 diabetes program - management believes the company is in a position to launch a phase 3 program in type 1 diabetes at the beginning of 2015. This represents a slightly later timeline than was suggested during the company's 1Q14 update (phase 3 initiation in late 2014), but it is fairly impressive considering that the company only recently began a new phase 2 study in type 1 diabetes along with the JDRF (see below).

- **The phase 3 program for type 1 diabetes would involve two studies if the company finds a partner for a joint type 1/type 2 diabetes program.** These two pivotal studies would have reduction in A1c vs. placebo on optimized insulin treatment as the primary objective, with glycemic variability, daily insulin dose, weight loss, and some patient-reported outcomes as secondary objectives. If Lexicon conducts a standalone program, however, it would likely add a third phase 3 study to expand the safety numbers. These decisions are based on interactions with the FDA and EMA.
- **Both the FDA and Lexicon have a preference for a joint type 1/type 2 diabetes program, as it would be more cost efficient (from the company's perspective) and provide a characterization of the compound across the broader scope of diabetes.** During Q&A, management estimated the cost of a standalone phase 3 program for type 1 diabetes as over $100 million, but noted that the cost would be lower if it was part of an integrated program.
- **During prepared remarks, management commented on the new phase 2 trial that Lexicon is conducting on LX4211 in collaboration with the JDRF.** The trial will enroll up to 84 relatively young (< 30 yrs) and poorly controlled (A1c > 9%) type 1 diabetes patients, a patient with a high degree of unmet need. As compared to the initial phase 2 trial for type 1 diabetes, which involved a four-week treatment period, this second phase 2 study will randomize patients to LX4211 or placebo for 12 weeks.

2. Mr. John Northcott, Lexicon VP of Marketing, Commercial Strategy, and Operations, shared the company's perspective on the clinical and commercial opportunities that exist for LX4211 in type 1 diabetes. Drawing from IMS Healthcare data, he noted that there are over one million type 1 diabetes patients in the US, and that data from the T1D Exchange suggests that around 75% of adults type 1 diabetes patients have a 12-month A1c average above the ADA recommended goal of 7%, and more than 50% have an average above 8%. We were glad to hear management note that beyond A1c, intraday glucose variability is a major challenge in the management of type 1 diabetes. Management cited data that between 4% and 10% of the deaths of type 1 diabetes patients are due to hypoglycemia (Patterson et al., *Diabetologia* 2007), making that another major concern that is not easily addressable with insulin alone. T1D Exchange data also indicates that a quarter of type 1 diabetes patients over the age of 26 are obese. LX4211 shows promise in concurrently decreasing glycemic variability, improving glycemic control, and leading to weight loss (or at least reduced weight gain).

- **Based on feedback from providers, Lexicon believes that LX4211 could be incorporated into type 1 diabetes patients' treatment within the first few months post-diagnosis.** To capture the full range of patients shortly after diagnosis a pediatric indication will be necessary, but given that Lexicon (now along with the JDRF) is studying LX4211 in younger and younger adult patients, we have reason to hope that the company would be reasonably proactive in pursuing this indication at some point.
- **Lexicon is confident that it can commercialize LX4211 for type 1 diabetes with a reasonably sized infrastructure.** Management noted that type 1 diabetes care is concentrated around endocrinologists and select primary care physicians, a relatively small body of providers.
- **From primary research with large payers in the US, Lexicon has learned that payers' priorities for the management of type 1 diabetes align well with LX4211's clinical profile.** The company surveyed ten large payers about key areas of unmet need in adult type 1 diabetes: all ten listed achieving optimal A1c targets, eight listed weight loss, and six listed reduction of severe hypoglycemia. While these are well understood areas of need within the diabetes clinical and patient community, having data on hand regarding payer receptiveness to agents like LX4211 could help demonstrate the agent's potential to possible partners that might be interested in a joint type 1/type 2 diabetes program.
- **might see value in new agents for type 1 diabetes that address weight loss, hypoglycemia, the need for greater efficacy, and other factors that LX4211 is well-positioned to target.**

3. Once again, there were no concrete updates on Lexicon's ongoing efforts to seek a partner for LX4211's phase 3 development for type 2 diabetes. However, management did comment broadly about the opportunity during Q&A, perhaps sounding slightly less confident than in the past. Lexicon is "not going to give up on the hope to develop this compound for type 2 diabetes," but the company has had to make unspecified "tweaks" in the way it is approaching partners and is not planning on waiting for a partnership to pursue the more attainable type 1 diabetes indication - a caller during Q&A noted that Lexicon's advantage and bargaining power with LX4211 diminishes as time goes on.

- **There are a number of factors that could explain Lexicon's challenges in finding a partner, which has taken a long time given the compound's differentiation against SGLT-2 inhibitors.** The SGLT-2 inhibitor competitive landscape is slowly but steadily growing more crowded, with Lilly/BI's Jardiance (empagliflozin) recently having joined J&J's Invokana (canagliflozin) and AZ's Farxiga (dapagliflozin) in the US and EU. Additionally, as more SGLT-2 inhibitors progress through development and onto the market, there are fewer companies that do not have an SGLT-2 inhibitor of their own, and the chances that a company would look to market both an SGLT-2 inhibitor and an SGLT-1/2 dual inhibitor are fairly slim. Finally, the FDA's requirement for long-term cardiovascular outcomes data for new agents for type 2 diabetes makes the proposition of moving a new compound like LX4211 through phase 3 much more expensive.
- **The ideal partner for LX4211 would fit the following criteria:**
    - **The company does not have an SGLT-2 inhibitor on the market or late-stage development** - This eliminates J&J, AZ, Lilly/BI, and Merck/Pfizer, among others.
    - **The company has a DPP-4 inhibitor on the market** - During the 2Q14 call, as with previous calls, Lexicon management emphasized that LX4211 has the potential for synergy with DPP-4 inhibitors. The only DPP-4 inhibitors that are on the market and not associated with an SGLT inhibitor include Takeda's Nesina (alogliptin) and Novartis' Galvus (vildagliptin), the latter of which is a twice-daily agent at the highest dose.

4. This was the first Lexicon earnings call led by new President and CEO Mr. Lonnel Coats, who assumed the role just a month ago. He took over from Dr. Arthur Sands - the change is reflective of the company's broader move away from early-stage research and its refocusing towards the late-stage development and commercialization of LX4211 and its other major candidate, telotristat etiprate (a drug for carcinoid syndrome). Before taking the helm at Lexicon, Mr. Coats was President and CEO of Eisai Inc. (Eisai's US subsidiary), and before that he worked for eight years at J&J.

5. On the financial front: Lexicon's R&D spend in 2Q14 totaled $21 million, down from $24 million in 2Q13 and $24 million in 1Q14. The company ended 2Q14 with $79 million in cash and investments, down from $98 million at the end of 1Q14 and $129 million at the end of 4Q13. During Q&A, management estimated the cost of a standalone type 1 diabetes phase 3 program at over $100 million, meaning that the company will not have sufficient runway with its current cash and investments to make it to the product's regulatory submission and commercialization.

QUESTIONS AND ANSWERS

Q: It has been over two years now since the phase 2b results were first announced on LX4211 in type 2 diabetes. There has obviously been a lot of positive regulatory validation for the SGLT-2 inhibitor pathway over the intervening period. You guys have been talking about making progress on the partnership front for some time now, going back into 2013. At what point do you need to turn the page to plan B and what point do investors need to look beyond the partnership and focus on type 1?

A: We're continuing those partnership discussions, and having that partnership around the full diabetes program is one of our priorities, but the timing is not totally within our control. We feel that one of the things we have to do is move forward in type 1 diabetes, and we're planning on doing that whether we have a

partnership in place or not. We feel very confident in the value of LX4211 in that indication, and that is something that we need to proceed with, partnership or no partnership.

Comment: To be clear, though, I'm not really concerned about moving forward with type 1 diabetes. I understand and realize the opportunity there and that the company can handle that on its own. It's just that, going on roughly a year now, you guys have been talking about making good progress on the partnership front and that you're close to a deal and expect to have something in place. It's the same message on every quarterly conference call. At what point do you think that the partnership is just not realistic? Or are you just as confident as you've been?

A: This is Lonnel. This is my fourth week here, and I've been involved in this process. I will simply say this: we should never give up on the opportunity to develop this compound for type 2 diabetes. Companies will come in, and companies will go out. But at the end of the day, we know this compound has efficacy. We know that there is extraordinary value that can be yielded for patients in the marketplace. Therefore, we will use all of our efforts and energies to ensure that we find a way to advance this compound for type 2 diabetes as well, and more than likely, that would be in a partnership. My confidence is growing every day as we have had these discussions - the question will be less about if, and more a matter of when.

The challenge here is that we shouldn't wait for the partnership. We know that the compound has value for type 1 diabetes, and we need to start that work. Secondarily to that, I do believe eventually a partner will come onboard because I believe the opportunity is so great and the number of opportunities that remain to participate in the type 2 diabetes marketplace are few and far in between. Regarding my confidence just being here for the month, we would ask you to continue being patient. But ultimately, we are not going to give up on the hope to develop this compound for type 2 diabetes.

Q: What is it that gives you confidence that the prior gating factors to finding a partner will be resolved going forward? Surely as time passes, the attractiveness of this asset and your bargaining power diminishes?

A: The type 2 diabetes marketplace, for unfortunate reasons, will continue to grow. All you have to do is look at the growth rate in the obesity marketplace, which is feeding the type 2 diabetes marketplace. Therefore, the number of assets with a mechanism such as what we have, which is a differentiated agent, are few and far in between for many players, who will be losing exclusivity in the near term. Therefore, I have every confidence that there are few opportunities such as the one that exists for LX4211, and that we will consummate a partnership. Now we've made some tweaks to how we are approaching the situation, but nonetheless, I believe that those tweaks will yield value for the company eventually in the future.

Q: Can you clarify what you meant when you said the agency would prefer to see a program in type 1 and type 2 diabetes? Are you saying that you have not yet had confirmation that a phase 3 program in type 1 diabetes would be sufficient for approval?

A: The FDA's preference is our preference. The preference is to develop this compound in both type 1 and type 2 diabetes so that you have the proper population exposure across the entire diabetes scope. That being the case, that does not preclude us from moving forward with the type 1 diabetes program for regulatory filing.

A: We believe that our meetings with the FDA and other agencies were sufficient to ensure that, from a regulatory standpoint, the type 1 standalone program is feasible.

Q: I'm a little uncertain about what is is that the FDA would object to in a type 1 diabetes pivotal program that you do on your own. Is the concern that if it is approved for type 1 diabetes, it might be used off-label in type 2 diabetes patients?

A: It's not a question of whether the drug will work in type 1 versus type 2. If you do a full-blown diabetes program, then the characterization of the drug will go across both. However, my felling is that it's less of a review question and more a labeling question relative to the indication we're seeking. I ultimately believe that we will end up in a full development program across type 1 and type 2 diabetes, and that we will achieve what

the FDA will ultimately want. But in the absence of having that program at this moment, if we proceed alone with type 1, I think there is a clear pathway for us to do so.

Q: On the type 1 diabetes program, what was the feedback from the FDA regarding CV requirements for approval in type 1 diabetes?

A: We do not believe at this time that a cardiovascular outcome study is required for approval of LX4211 exclusively in type 1 diabetes. We are not currently planning a specific meeting on cardiovascular outcomes studies in this area. We shared with the agency and others our plans for a type 2 diabetes program, so we do feel like we have a general understanding of what is required for type 2 diabetes. We did mention in our program that if we do a standalone type 1 diabetes program, we will do a third study to enhance our safety exposure. So the opportunity for other regulatory interactions will be at the time that we finalize those plans.

Q: Can you give us more detail about the scope and cost of the two studies in the phase 3 program for type 1 diabetes if you go the standalone route?

A: We're continuing to work on developing the plan, and we'll be able to provide more color once those plans are more fully developed. Obviously, a standalone program will end up being more expensive than an integrated program. Our expectation would be that the cost of phase 3 in type 1 diabetes, if it was a standalone program, would be more than $100 million. It would be less than that if we are able to do it as part of an integrated type 1 and type 2 program.

Q: If you do a third phase 2 study to increase the size of the database, would a potential strategy be to do a safety trial in both type 1 and type 2 diabetes patients?

A: I think you're correct that we're thinking that a third trial would really be for safety purposes to expand the size of the safety database. But in terms of the specifics of who is enrolled and the endpoints, that is something we'll be determining in the weeks ahead.

-- by Manu Venkat and Kelly Close