



MEMORANDUM

Lexicon and JDRF announce collaboration for phase 2 trial of SGLT-1/SGLT-2 dual inhibitor in young adults with type 1 diabetes - July 13, 2014

Executive Highlights

- JDRF and Lexicon will collaborate on a phase 2 trial of the SGLT-1/SGLT-2 dual inhibitor LX4211 in relatively young type 1 diabetes patients (<30 yrs) with relatively high A1cs (>9%).
- We are optimistic about this partnership; the degree of unmet need in the younger type 1 diabetes patient population remains high and JDRF should give Lexicon a "halo" effect through the partnership.

Lexicon [announced](#) a collaboration with the JDRF late last week for a phase 2 trial of its SGLT-1/SGLT-2 dual inhibitor LX4211 in a relatively young population with type 1 diabetes. The 12-week randomized, double-blind, placebo-controlled study will enroll up to 76 patients with type 1 diabetes between ages 18 and 30 and with a baseline A1c >9%. The study's primary endpoint will be reduction in A1c, with blood glucose variability and change in insulin dose as secondary endpoints. We applaud the company for including changes in "time in zone" to convey the impact of the drug. In a recent interview with us, JDRF Assistant Vice President of Translational Development Dr. Sanjoy Dutta stressed the importance of composite endpoints for trials of non-insulin agents in type 1 diabetes, especially as it is unlikely that adding another agent to insulin will lead to a significant enough difference in A1c in his view that will augment patient use and/or facilitate reimbursement. Rather, the benefits of an added agent could manifest through beneficial effects on hypoglycemia, weight, insulin dosage, or other parameters. These benefits certainly have significant value for patients, and we believe they will be increasingly recognized by both regulatory agencies and (equally importantly) by payers now that a much better way to measure them is available.

The collaboration decision follows Lexicon's [announcement](#) earlier this year of topline results from a proof-of-concept phase 2 trial of LX4211 in adults with type 1 diabetes, which enrolled (on average) an older and better-controlled patient population. The results showed that treatment with LX4211 led to a ~26% placebo-adjusted reduction in bolus insulin use, a 0.49% placebo-adjusted decrease in A1c, a significant 12% increase in time-in-zone, and a ~2 kg (~5 lb) weight benefit over just four weeks. The company expects to present full results from that trial at a meeting in 2015. During the topline data presentation, management suggested that phase 3 for type 1 diabetes could begin by the end of 2014 - we do not know if the company would wait for the new trial to end before entering phase 3, or if phase 3 initiation could begin as per the previous timeline. The new proposed trial is expected to begin soon, and it lays the groundwork for the phase 3 program to involve a wider variety of patients who could benefit from the drug. Dr. Dutta indicated that JDRF would be open to supporting future clinical trials of this compound in specific populations, though he did not feel that JDRF is best equipped to support a pivotal trial. On the type 2 diabetes front, phase 3 initiation continues to depend on the long-ongoing search for a partner, which is necessary due to the immense cost of phase 3 development and cardiovascular outcomes trials for that indication.

We applaud Lexicon and JDRF for attempting to address the high degree of unmet need for new non-insulin pharmacotherapy in the type 1 diabetes patient population. We are especially pleased to see the focus on younger patients, who we think could see a particular benefit in outcomes given that they have much longer to live than those diagnosed with type 1 at much older ages. Quality of life and ease of management could also really improve with this therapy, especially for school age children who do not dose lunchtime insulin themselves. Dr. Dutta does not expect this compound to be approved for pediatrics "anytime soon," but he

believes people of "all ages...will improve with this therapy" and feels it is JDRF's role to test this and other drugs' potential in type 1 diabetes patients.

- **For more details on LX4211, read our [Lexicon 1Q14 Report](#)**, which discusses Lexicon's plans to meet with the FDA regarding phase 3 development for type 1 diabetes as well as the ongoing search for a partner for phase 3 trials for type 2 diabetes.
- **LX4211 is likely to be a first-in-class drug** - the closest competition is Novartis' phase 2 SGLT-1/2 dual inhibitor LIK066, which faces an uncertain future after a phase 2 dose-finding trial was withdrawn in April (see our [Novartis 1Q14 Report](#) for details), though the candidate still appears on the company's pipeline.
- **The choice of the younger, more poorly controlled patient population was largely driven by the JDRF, according to Dr. Dutta.** He pointed out that pharmaceutical companies often lack the incentives to investigate drugs in younger type 1 diabetes patients (especially pediatric patients), but that the younger population has a high level of unmet need and can have a harder time achieving tight glycemic control due to transitions from pediatric to adult caregivers. Dr. Dutta underscored that one of the JDRF's key missions is to move research forward in areas like this, filling gaps that the pharmaceutical industry might be slower to fill when working alone. He also noted that the JDRF is interested in investigating LX4211 in even younger patients, including individuals under 18, but is waiting to hear from the FDA before proposing those sorts of trials.
- **Although it currently appears likely that Lexicon will pursue phase 3 for type 1 diabetes solo and phase 3 for type 2 diabetes separately with a partner, we believe that an all-encompassing partnership is still a possibility.** More specifically, the very positive proof-of-concept phase 2 data in type 1 diabetes, as well as the halo effect of JDRF support for the second phase 2 trial in type 1 diabetes, could be added draws for a partner interested in LX4211 for both type 1 and type 2 diabetes.
- **This development is part of a larger trend of exploration of type 2 diabetes drug classes in type 1 diabetes.** SGLT-2 inhibitors in particular have generated excitement because of their insulin-independent mechanism of action. The much-respected Dr. Anne Peters (USC, Los Angeles, CA) discussed the off-label application of J&J's SGLT-2 inhibitor Invokana (canagliflozin) in type 1 diabetes at this year's [Clinical Diabetes Technology Meeting](#) as well [as at the recent Children with Diabetes Friends for Life 2014 meeting](#), and AZ recently [announced](#) plans to initiate a phase 3 trial of its SGLT-2 inhibitor Forxiga/Farxiga (dapagliflozin) in type 1 diabetes patients by the end of the year. Dr. Dutta stated that he has been pleasantly surprised that pharmaceutical companies have begun focusing on the use of SGLT-2 inhibitors in type 1 diabetes relatively early in the game, given that other type 2 diabetes drugs like GLP-1 agonists have been around for much longer without a broad groundswell in interest in their potential application to type 1 diabetes. We believe this is due in part to advocacy by JDRF, the Helmsley Charitable Trust, and patient advocates working faster to make sure the needs are known; **we also note that some major companies like J&J, who had the first SGLT-2 inhibitor approved on the market in the US has made no visible moves toward type 1 research. Close Concerns hope this changes going forward.**

-- by Emily Regier, Manu Venkat, and Kelly Close