Closer Look

MEMORANDUM

Executive Highlights

- Novo Nordisk is initiating a clinical proof-of-principle trial (ClinicalTrials.gov Identifier: NCT02443155) investigating the effect of its GLP-1 agonist Victoza (liraglutide 1.8 mg) and the anti-IL-21 antibody NNC00114-0006 on preservation of beta cell function in new onset type 1 diabetes.

We recently learned that Novo Nordisk is initiating a phase 2 proof-of-principle trial investigating the effect of its GLP-1 agonist Victoza (liraglutide 1.8 mg) and the anti-IL-21 antibody NNC0114-0006 on preservation of beta cell function in new onset type 1 diabetes. The double-blind trial (ClinicalTrials.gov Identifier: NCT02443155; not yet recruiting participants) aims to enroll 304 patients with recently diagnosed (within 12 weeks) type 1 diabetes who will be randomized to receive the two components together, either component with placebo, or double placebo. All groups will receive intravenous infusions of either NNC0114-0006 or placebo every six weeks and daily subcutaneous injections of either liraglutide or placebo in addition to their pre-trial insulin regimen. The primary endpoint will be stimulated C-peptide area under the curve (AUC) after a four-hour mixed meal tolerance test at 54 weeks; secondary endpoints include change in A1c, fasting plasma glucose, total daily insulin dose, hypoglycemia and other C-peptide parameters at 54 weeks and 80 weeks. The study is scheduled to begin in October, with primary completion expected in November 2018. This patient population will have the advantage of having been introduced to injections already, although liraglutide's GI side effects will be new.

We see this as a very intriguing approach that is consistent with the growing consensus that disease-modifying therapies for type 1 diabetes will likely require the use of multiple agents in combination. Both of these components have attracted interest in the type 1 diabetes field in the past. A group led by Dr. Matthias von Herrath (La Jolla Institute for Allergy and Immunology, La Jolla, CA and also head of Novo Nordisk's Type 1 Diabetes Research Center) published results in 2009 implicating IL-21 (a cytokine with key roles in the immune system) in the pathogenesis of type 1 diabetes in the NOD mouse model. To our knowledge, there have not been any clinical trials of anti-IL-21 therapies for type 1 diabetes to date, though some studies (including a paper by Ferreira et al. published in Diabetologia last month) have suggested that it also plays a role in the disease process in humans. For their part, GLP-1 agonists have been shown in preclinical studies to potentially have a positive impact on beta cell proliferation, although these findings have not yet been convincingly translated into human studies. In addition to potential effects on beta cell mass, GLP-1 agonists are well known for their ability to suppress glucagon and cause weight loss for type 1 diabetes patients, providing meaningful benefits for glucose control. Indeed, Novo Nordisk is currently conducting two phase 3 trials (ADJUNCT ONE and ADJUNCT TWO) investigating Victoza as an adjunct to insulin in this population; both are expected to report results within the next six months. While the frustrating history of type 1 diabetes cure research suggests that plenty of caution is warranted, we have a great deal of confidence in Novo Nordisk and are optimistic that this approach has the potential to slow the progression of type 1 diabetes or at least significantly reduce insulin requirements in the post-diagnosis period, even if it does not achieve the holy grail of complete insulin independence.

- **For thoughts on beta cell biology from Dr. von Herrath, including comments on the need for a combination approach, see our coverage of this year's GNF-JDRF Symposium in April.**

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