Closer Look

MEMORANDUM

Intarcia releases positive topline phase 3 FREEDOM-2 results for ITCA 650 vs. Merck's Januvia (sitagliptin) - August 18, 2015

Executive Highlights

- Intarcia just announced impressive topline results from the phase 3 FREEDOM-2 study demonstrating significantly greater A1c reductions (1.5% vs. 0.8%; p<0.001) and weight loss (4 kg vs. 1.3 kg; p<0.001) with its implantable exenatide mini-pump ITCA 650 vs. Merck's Januvia (sitagliptin).
- ITCA 650 was also superior to Januvia in terms of the percentage of patients achieving a secondary composite efficacy endpoint (>0.5% A1c reduction and ≥2 kg weight loss) and the percentage of patients achieving an A1c <7%.

Just a couple of hours ago, Intarcia announced impressive topline results from the phase 3 FREEDOM-2 study investigating its implantable exenatide mini-pump ITCA 650 (60 mcg/day) vs. Merck's Januvia (sitagliptin) in 535 patients with type 2 diabetes on background metformin. Results demonstrated significantly greater A1c reductions (1.5% vs. 0.8%) and weight loss (4 kg vs. 1.3 kg) with ITCA 650 vs. Januvia after 52 weeks (p<0.001 for both; baseline A1c = 8.5% in the ITCA 650 group and 8.7% in the Januvia group). ITCA 650 was also superior in terms of the percentage of patients achieving a secondary composite efficacy endpoint (>0.5% A1c reduction and ≥2 kg weight loss) and the percentage of patients achieving an A1c <7%. While full details were not disclosed, Intarcia CEO Mr. Kurt Graves indicated to us that the number was well over 50% in the ITCA 650 arm for both secondary endpoints. The safety/ tolerability profile was similar to that seen in previous phase 3 studies, with low-single-digit discontinuation rates due to nausea, no cases of major hypoglycemia, and a <1% application site infection rate. The press release noted that these positive results will trigger a $100 million milestone payment to Intarcia from investors in the $300 million financing executed earlier this year.

The glucose-lowering results are largely in line with the company's (high) expectations - management had previously forecasted A1c reductions in the 1.8% range for ITCA-650 in the head-to-head sitagliptin trial (compared to the 0.8-0.9% reductions typically observed with sitagliptin). Mr. Graves suggested that the weight loss results (particularly combined with the similar 3-4 kg weight loss seen in the FREEDOM-1 study) had even exceeded the company's expectations. He also noted that in FREEDOM-1, weight loss with ITCA-650 had not begun to plateau at the end of nine months; we are very eager to see the full FREEDOM-2 results to see if that holds true at one year as well as beyond that mark. We see the results for the composite endpoint as especially compelling and expect that payers will agree. Overall, we expect these results to further expand the growing GLP-1 market.

As Intarcia has previously indicated, this trial is critical to the company's plans to position ITCA 650 as the optimal second-line therapy after metformin. If the CVOT results are positive, some may even position this as first line (as well as the entire GLP-1 class - we are curious about the potential long term impact of better adherence). The growing body of impressive clinical trial data and the enormous adherence advantage over existing options certainly give the product significant disruptive potential, and Intarcia's longstanding emphasis on soliciting payer input bodes well in terms of access. As the very highly regarded Ms. Nancy Thornberry (inventor of Januvia who now serves on Intarcia's board) put it, "the magnitude of the glycemic control and weight loss…together with the innovative delivery system…suggest that this approach has the potential to be transformational" for patients. Dr. John Buse offered a similarly positive endorsement, emphasizing the product's advantages for patients who struggle with "daily self-care." The main challenges

for the company will likely be convincing patients and non-specialist HCPs of the procedure's simplicity and managing expectations given the enormous hype surrounding ITCA 650 over the past year. As well, we will look forward to seeing if early forecasts on reimbursement for the procedure will hold over time. There's some room for it to fall and still be seen as an attractive element by HCPs in our view - ultimately we expect nurses and other allied health officials to be doing most of these procedures.

- **As a reminder, ITCA-650 is a small (matchstick-sized) implantable exenatide osmotic mini-pump that is placed under the skin and releases a steady stream of exenatide for up to one year.** Once the mini-pump is implanted, a small stream of body fluid diffuses into the device, pushing the exenatide suspension out in a controlled fashion, leading to continuous delivery without the peaks commonly seen with injectable drugs. Intarcia plans to market both 40 mcg/day and 60 mcg/day doses of ITCA 650, and both six-month and one-year mini-pumps (in addition to a three-month mini-pump with a 20 mcg/day "starter" dose that will be used to begin treatment in all patients).
- **Intarcia released positive topline results from the FREEDOM-1 and FREEDOM-1 HBL phase 3 trials in October 2014, with full results for both trials presented at ADA this past June.** FREEDOM-1 results demonstrated a statistically superior 1.4% A1c reduction (we estimated 1.1% placebo-adjusted, based on the graph from the presentation) from a baseline of 8.4% with ITCA 650 compared to placebo in patients with type 2 diabetes (n=460) on up to three oral medications. Furthermore, a pre-specified secondary analysis of efficacy by concomitant therapy found that patients not on a sulfonylurea did far better in terms of A1c reduction from baseline to week 39 (1.7% from baseline; we estimate ~1.4% placebo-adjusted) than those on a sulfonylurea (1.2% from baseline; we estimate ~0.9% placebo-adjusted). FREEDOM-1 HBL was an open-label study of ITCA-650 in patients with high baseline A1cs (>10%) and found an impressive mean A1c reduction of 3.4% from a mean baseline of 10.8% at 48 weeks.
- **A CVOT (FREEDOM-CVO) for ITCA-650 is ongoing, with an estimated completion date of July 2018 according to ClinicalTrials.gov.** The trial intends to enroll 4000 patients with a history of cardiovascular disease. Initial funding for the CVOT, as was the case for the phase 3 trials, comes entirely from independent Intarcia funding, without a Big Pharma partner. Given the beneficial effects of the GLP-1 agonist class as a whole on multiple CV risk factors, and the adherence advantage with ITCA 650 in particular, we imagine that this trial is one of the most likely ongoing CVOTs to demonstrate cardioprotection. However, several key limitations (relatively short duration, high-risk patients) still apply.
- **Intarcia is planning a number of exciting future studies for ITCA 650.** We are particularly excited by what the company characterized as a potentially "guideline-changing study" to determine the optimal drug to add to metformin: ITCA 650 vs. a sulfonylurea vs. a DPP-4 inhibitor vs. an SGLT-2 inhibitor. Intarcia also plans to conduct studies investigating combination therapy with ITCA 650 and an SGLT-2 inhibitor (which could potentially be co-administered through the same osmotic mini-pump technology in the future).
- **Intarcia still plans to submit ITCA 650 to the FDA in the first half of 2016, consistent with previous guidance.** As a reminder, Intarcia retains full development and commercialization rights for ITCA-650 in the US and is partnered with French pharmaceutical company Servier for development and commercialization outside of the US and Japan. The company plans to seek another partner in Japan.

-- by Helen Gao, Emily Regier, and Kelly Close