CLOSER LOOK

MEMORANDUM

FREEDOM-CVO demonstrates CV non-inferiority for Intarcia's implantable GLP-1 agonist ITCA 650 - May 6, 2016

Executive Highlights

- This morning, Intarcia announced topline results from the FREEDOM-CVO cardiovascular outcomes trial (n=~4,000) demonstrating non-inferiority for the primary endpoint of four-point MACE (cardiovascular death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina) with implantable exenatide mini-pump ITCA 650 vs. placebo.
- Intarcia plans to submit ITCA 650 to the FDA at the end of 3Q16.
- Intarcia CEO Mr. Kurt Graves stressed that FREEDOM-CVO was not designed to demonstrate superiority in cardiovascular outcomes.

This morning, Intarcia released topline results from its FREEDOM-CVO cardiovascular outcomes trial (n=~4,000) demonstrating non-inferiority for the primary endpoint of four-point MACE (cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) with implantable GLP-1 agonist ITCA 650 (exenatide mini-pump) vs. placebo. The trial had a total duration of just under three years and accrued a total of 150 MACE events; average treatment duration was 1.2 years. Secondary endpoints were not disclosed, though we'll be curious to see if heart failure was included as a secondary endpoint and whether the drug had any effect on that front. Heart failure is emerging as an increasingly important endpoint in cardiovascular outcomes trials of diabetes drugs - it was a main driver of the cardioprotective benefit for Lilly/BI's Jardiance (empagliflozin) in EMPA-REG OUTCOME and a source of concern in the CVOTs for AZ's Onglyza (saxagliptin) and Takeda's Nesina (alogliptin). The full results of the trial will be presented at a future scientific meeting. We assume it is too late for the results to be included in the ADA agenda, though EASD in September could be a possible forum. FREEDOM-CVO concludes the pivotal phase 3 development program for ITCA 650 (FREEDOM-1, FREEDOM-1 HBL, and FREEDOM-2 results were released in 2014 and 2015). Intarcia expects to submit the product to the FDA at the end of 3Q16. Based on a standard FDA review, we'd expect to see the product launch in the second half of 2017.

- **In a call, Intarcia CEO Mr. Kurt Graves emphasized that FREEDOM-CVO was not designed to demonstrate superiority.** He suggested that much larger and longer trials - such as the LEADER trial that demonstrated superiority for Novo Nordisk's market-leading GLP-1 agonist Victoza (liraglutide) - are necessary to draw out a potential cardiovascular benefit. In contrast, he emphasized that the FREEDOM-CVO was designed to be small and short to meet the cardiovascular safety requirements for FDA approval as quickly as possible. In addition, he shared that Intarcia simply did not have the funds to conduct a larger trial designed specifically for superiority (FREEDOM-CVO already cost ~$250 million) and that a larger, longer trial would have delayed the launch of the ITCA 650 by two to three years - we certainly understand the math here and are glad that Intarcia prioritized getting this potentially disruptive product into the hands of patients earlier. For comparison, the LEADER trial enrolled 9,340 patients and conducted 3.5-5 years of follow-up. Although the SUSTAIN 6 pre-approval trial that demonstrated a cardiovascular benefit for Novo Nordisk's once-weekly GLP-1 agonist semaglutide enrolled only ~3,300 participants, which suggests that it is at least possible to demonstrate a cardioprotective benefit in a shorter, smaller trial, the logic would certainly suggest that getting to approval as fast as possible would make the most sense. Granted, SUSTAIN 6 did have a longer average treatment duration (2 years vs. 1.2 years) and more total events (250 vs. 150) than FREEDOM-CVO. Mr. Graves also suggested that the SUSTAIN 6

results may not be sufficient to support a cardioprotective benefit in semaglutide's label due to the lack of statistical power, though we have not heard any comments to this effect from Novo Nordisk.

- **Intarcia raised the intriguing possibility of conducting a larger, longer cardiovascular outcomes trial for ITCA 650 post-approval.** The positive LEADER and SUSTAIN 6 results have raised optimism for a cardioprotective class effect for GLP-1 agonists. With the recent series of positive cardiovascular outcomes trials, we've heard several pharmaceutical company executives suggest that the bar for diabetes drugs has been raised even higher and that new drugs will be expected to demonstrate a cardioprotective benefit or some other benefit beyond glucose-lowering to be successful. We imagine Intarcia would be eager to definitively demonstrate a cardioprotective benefit with ITCA 650, especially since the GLP-1 agonist class is looking to be fairly heterogeneous in terms of cardiovascular results (Sanofi's GLP-1 agonist Lyxumia [lixisenatide] demonstrated a neutral effect on cardiovascular outcomes in the ELIXA trial).
    - **Intarcia also shared that it plans to initiate additional head-to-head studies against "market-leading oral and injectable medicines."** The FREEDOM-2 phase 3 trial for ITCA 650 already demonstrated superiority against Merck's DPP-4 inhibitor Januvia (sitagliptin). We'd imagine Intarcia might be interested in conducting trials against Lilly/BI's cardioprotective SGLT-2 inhibitor Jardiance (empagliflozin) and/or another GLP-1 agonist such as Novo Nordisk's Victoza (liraglutide). Some of these trials are expected to begin in 2016. The company also plans to initiate real-world trials for ITCA 650 after it is approved.
- **ITCA 650 will join a crowded competitive landscape with multiple diabetes drugs that have demonstrated cardioprotective benefits.** Victoza's leading position within the GLP-1 agonist market will likely be further strengthened by the positive LEADER results. In addition, injectable semaglutide will likely be approved just after ITCA 650, offering another GLP-1 agonist option with strong efficacy and a demonstrated cardioprotective benefit. On the other hand, Intarcia has previously suggested that it may price ITCA 650 at a point closer to oral diabetes medications than existing injectable GLP-1 agonists, which could be a promising point of differentiation. Intarcia's promise of day-to-day convenience and guaranteed adherence should also be attractive to many patients, providers, and especially payers.
    - **It is possible that ITCA 650 and Victoza/semaglutide could end up occupying distinct niches within the market**. We could imagine the injectable products being used primarily for patients with longstanding diabetes and high CV risk and ITCA 650 appealing to an earlier-stage population. Indeed, Intarcia has stated that it hopes to position ITCA 650 as a potential second-line option and push GLP-1 agonists earlier in the diabetes treatment algorithm. That said, the product would have to compete with Lilly/BI's Jardiance (and potentially other SGLT-2 inhibitors) as a second-line therapy. Jardiance demonstrated a cardioprotective benefit in the EMPA-REG OUTCOME trial and also has an impressive weight reduction benefit, though ITCA 650 would likely have the edge in terms of adherence and A1c-lowering efficacy. Intarcia is exploring a GLP-1 agonist/ SGLT-2 inhibitor combination delivered through its mini-pump device, which could be a winning combination in terms of A1c, body weight, and cardiovascular outcomes.
- **Intarcia concurrently announced a $75 million round of debt financing.** The funding is meant to facilitate manufacturing scale-up to produce the product inventory needed for a global launch. Intarcia will be bringing ITCA 650 to market entirely on its own, without a larger pharmaceutical company partner. This expensive strategy is not without its risks, but the company has demonstrated impressive fundraising prowess and clearly believes that its innovative delivery method will translate to success within the diabetes marketplace.

Close Concerns Questions

Q: Was there a signal toward cardioprotection for the composite endpoint or any of the components of the composite endpoint?

Q: Did the use of a four-point MACE composite endpoint rather than a three-point MACE affect the results at all?

Q: What were the secondary endpoints? Were any of them positive?

Q: How does the patient population of FREEDOM-CVO compare to that of LEADER or SUSTAIN 6? To that of EMPA-REG OUTCOME?

Q: Will Intarcia commit to a larger cardiovascular outcome study designed to demonstrate superiority for ITCA 650?

Q: How might the formulary positioning for ITCA 650 look compared to that of semaglutide or Victoza?

Q: How will guideline-writing committees consider the heterogeneity in cardiovascular outcome results for the GLP-1 agonist class?

Q: Will these results alter Intarcia's strategy for promoting ITCA 650?

Q: Will these results impact sales of AZ's Byetta (exenatide twice-daily) or Bydureon (exenatide once-weekly)?

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