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Now what for Intarcia with clinical work done?

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Intarcia Therapeutics' rise from fund-raiser nonpareil to clinical-stage graduate is now complete with results of the cardiovascular outcomes trial of the glucose-lowering implant ITCA 650.

The private Massachusetts-based group used the positive data to secure the cash for commercial scale-up, this time in the form of a $75m credit facility. This is where the Intarcia story becomes more risky, as the real-world commercial promise of using an implant to secrete a known diabetes drug slowly for a year will need to be proven in a space where once-weekly injections are becoming the norm.

Non-inferior

ITCA 650, a matchstick-sized implant that releases the active ingredient in Bydureon, met the primary objective of its Freedom-CVO trial of 4,000 diabetics, Intarcia said. The study aimed to show that when used in addition to other glucose-lowering medications ITCA 650 presented no greater cardiovascular risk than the other medications alone.

This is a pre-approval requirement for glucose-lowering drugs, because diabetics are at higher risk of cardiovascular disease and because so many patients take them. The data consisted of a meta-analysis of major adverse cardiovascular events taken from the Freedom-CVO study along with two other efficacy trials used for approval, Freedom-1 against placebo and Freedom-2 against Januvia.

In the combined analysis there were 160 cardiovascular events, although the company did not disclose the numbers of events in ITCA 650 and comparative arms. It was sufficient to rule out an increased risk of cardiovascular events for the implant versus the other treatments – average treatment time was 1.2 years.

Speaking to *EP Vantage*, Intarcia's chief executive, Kurt Graves, said detailed cardiovascular safety data from the Freedom programme would be released at medical meetings later this year, although it was too late for the American Diabetes Association meeting in New Orleans next month. The European Association for the Study of Diabetes meeting in September is a more likely forum.

ITCA 650's data package is now sufficiently complete for an FDA submission in the third quarter. While the exenatide delivery is in the form of an implant, the product will be regulated as a drug. However, its commercial strategy is expected to need to use practices developed by device makers (*Interview – Intarcia looks for partnership money after trial win, October 3, 2014*).

An implant, but …

Assuming a launch 10 months after submission, ITCA 650 would premiere sometime in mid-2017, a time when there could be as many as four once-weekly agents in the glucagon-like peptide 1 (GLP-1) agonist class on the market. The commercial test for ITCA 650 will be persuading patients and physicians of the medication adherence benefits of an implant over an injection that now can occur as seldom as once a week.

Mr Graves also points to a better side-effect profile with ITCA 650. Without injections there are no site reactions, for example, while the well-known nausea side effects of the GLP-1 class are attenuated by a steadier release of exenatide than the twice-daily or once-weekly injections of Byetta and Bydureon, which cause spikes in patient exposure.

What the implant will probably not have on its side is a claim of cardiovascular benefit. Novo Nordisk's once-daily GLP-1 Victoza recently released data that would support such a claim, and the very similar molecule semaglutide on a standard-of-care treatment backbone showed superiority to standard-of-care treatments alone in its own pre-approval trial (*Semaglutide heart data spice up once-weekly GLP-1 race, April 28, 2016*).

With its own phase III programme complete, semaglutide looks on track to reach the market on a similar timeframe as ITCA 650 if both projects are successful with regulators, although a post-approval trial to confirm the cardiovascular benefit of both will be expected.

So far, exenatide has not passed a post-approval cardiovascular outcomes trial, with Bydureon due to report from its own 14,000-patient study in 2018. Whatever the result, Mr Graves believes that ITCA 650 should

perform at least as well if not better than Bydureon because the chronic daily exposure of 60mcg a day is three times that of Bydureon.

Intarcia appears to have done everything right in the run-up to its regulatory milestones. It will only be after that, as the commercial plan plays out, that the sector knows if its financiers were equally correct in creating a multi-billion-dollar valuation.

Study	Trial ID
Freedom-CVO	NCT01455896

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