Heart benefit now a baseline for Invokana and all diabetes drugs

Jonathan Gardner

Invokana looking for good showing at American College of Cardiology meeting to improve prospects.

Johnson & Johnson's struggling diabetes drug, Invokana, has been dogged by safety concerns and battered by pricing pressure. More cardiovascular analyses to be delivered at the American College of Cardiology meeting this weekend could help steady the ship.

The Canvas outcomes trial showed that Invokana can prevent major adverse cardiovascular events (MACE), though specific results on non-fatal myocardial infarctions and strokes were equivocal. With the US FDA to decide whether to permit Johnson & Johnson to begin marketing on these data this summer, a new analysis of the heart failure benefit should lend confidence that the regulator will give it the green light.

Invokana also needs to show that that the lower-limb amputation risk that emerged last year is minimal, a safety scare that has already dented sales. The ACC analysis should include an update, although it seems unlikely that the FDA will withdraw the black box warning it has placed on the SGLT-2 inhibitor.

Deeper cut

J&J released data from the primary endpoints of Canvas and Canvas-R at the 2017 American Diabetes Association conference. The two trials in 10,000 diabetics revealed that Invokana was superior to placebo in preventing MACE, a composite of cardiovascular death or non-fatal myocardial infarction or stroke.

However, when calculating each of these events independently, the trials did not detect a statistically significant difference, raising questions over the importance of the main finding (ADA - Canvas paints a mixed picture for J&J's Invokana, June 12, 2017).

Thus on March 11 at ACC the New Jersey-based group will release an analysis of heart failure among patients enrolled in Canvas, which could help explain why the composite endpoint met significance when each of the individual components did not.

The SGLT-2 class works by increasing glucose excretion in urine, and a mild diuretic action might help prevent worsening of heart failure. Lilly and Boehringer Ingelheim's Jardiance has also shown a benefit on cardiovascular outcomes; yesterday the companies expanded a new trial, Emperial, in chronic heart failure regardless of diabetes status.
Showing a cardiovascular benefit is increasingly important for diabetes drugs since patients often develop heart disease because excess glucose damages blood vessels; most diabetics die from cardiovascular causes.

Of the two main oral antidiabetic classes, SGLT-2s and DPP-IVs, only the former have shown a cardiovascular benefit. DPP-IVs like Januvia and Tradjenta have been unable to match SGLT-2s here, and in Tecos the best showing Januvia could muster was that it did not increase cardiovascular risk. Januvia, by far the most dominant DPP-IV, loses patent protection in mid-2022.

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<td><strong>Drug class</strong></td>
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*Source: EvaluatePharma.*

Real-world data have begun to support the notion that the impact on cardiovascular outcomes is a class effect, with more data from the CVD-Real study of the SGLT-2s to be released at ACC (*ACC – Jardiance heart benefit looks like a class effect*, March 20, 2017).

Among the other non-insulin diabetes agents, the GLP-1 agonist Victoza from Novo Nordisk has shown a cardiovascular benefit and can be marketed on this basis. The class leader, Lilly’s Trulicity, is expected to have cardiovascular data later this year. Novo’s follow-up Ozempic has passed a cardiovascular safety test, but will need to follow up with data indicating that it can prevent heart attacks and strokes.

The marketed GLP-1s are injectable and thus are not competing as directly with SGLT-2s as are DPP-IVs, but this could change very soon. An oral version of semaglutide, the active ingredient of Ozempic, has passed an initial phase III exam, and as it will likely go toe to toe with Januvia and Invokana prevention of cardiovascular events will be crucial (*Novo Nordisk prepares to swallow its rivals for breakfast*, February 22, 2018).

Diabetes drugs are increasingly seen as heart disease medications. J&J needs to shore up Invokana’s position with convincing heart failure data along with persuading the FDA to allow marketing on a cardiovascular benefit.

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