

Entresto Facing Pressure From Diabetes Drugs

► By Lucie Ellis



WITH DIABETES THERAPEUTICS ADDING CARDIOVASCULAR RISK reduction claims, Novartis's heart failure drug Entresto could face pressure from new fronts – just as sales start to take off.

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The demonstration of reduced heart failure, death and other cardiovascular benefits with major classes of diabetes drugs means cardiovascular products like **Novartis AG's** congestive heart failure therapy *Entresto* must deal with imminent – and unexpected – competition from marketed metabolic drugs broadening their reach.

Entresto (valsartan/sacubitril) has finally started to make its mark on the CHF market, but there are other products moving up the pipeline (see *chart*). While a few early- to mid-stage pipeline compounds are revealing innovative mechanisms, these drugs are several years from market entry. However, Entresto will feel the heat sooner from already approved sodium-glucose cotransporter-2 (SGLT-2) inhibitors, which are currently used to treat type 2 diabetes.

Analysis of **AstraZeneca PLC's** CVD-REAL study, presented in March at the American College of Cardiology (ACC) annual meeting, did not break out patient outcomes for individual SGLT-2 inhibitors, but did present compelling evidence that the rates of hospitalizations for heart failure and death were cut by half by use of the three currently marketed SGLT-2 drugs in type 2 diabetes patients, compared with other types of diabetes therapies.

Meanwhile, **Boehringer Ingelheim GMBH** and partner **Eli Lilly & Co.'s** *Jardiance* (empagliflozin) became the first diabetes therapy to have a claim for cardiovascular mortality risk reduction in diabetics approved by the FDA at the end of 2016, based on the results of the EMPA-REG CV OUTCOME trial. As such, the two companies have launched two other CV outcome studies for the drug, enrolling around 7,000 patients, which will include both diabetics and non-diabetics with heart failure.

Lilly told *Scrip* it is carrying out these CV outcome studies to better understand *Jardiance's* potential in CHF. However, the firm has not yet confirmed whether it will pursue regulatory approval for the drug as a heart failure therapy, a move described as a “logical next step” by Datamonitor Healthcare when the companies announced the two trials in April 2016.

“Pressure from diabetes therapies on the heart failure market is not competition Novartis would have expected when starting to launch Entresto – this is added pressure on top of the drug's slow uptake and missed sales targets,” Roger Longman, CEO of reimbursement strategy company RealEndpoints, told *Scrip*. Additionally, many CHF patients are also type 2 diabetics, so use of SGLT-2 therapies in CHF could be very attractive to payers and physicians (see *chart next page*).

Heart Failure Pipeline By Development Phase Or Market Status



Source: Informa Pharma Intelligence's Biomedtracker

Other diabetes therapies are also being assessed for their benefits in cardiovascular conditions including DPP-4 inhibitors and GLP-1 agonists, such as Novo Nordisk's market leading diabetes therapy *Victoza* (liraglutide), though the SGLT-2 class is leading the way when it comes to clinical testing in CHF patients with new regulatory labels in mind. AstraZeneca's *Farxiga* and BI/Lilly's *Jardiance* are both already in Phase III studies for use in CHF.

Meanwhile, earlier in the CHF pipeline, **Theravance Bio-pharma Inc.** has two Phase I drugs in development that Longman highlighted as "ones to watch." TD-0714 and TD-1439 – both inhibitors of neprilysin (NEP) the enzyme responsible for degradation of natriuretic peptides ANP, BNP and CNP, like sacubitril – are structurally distinct but are both being investigated as novel treatments for CHF.

Cardiologist Vs. Diabetes Docs

One challenge already concerning doctors around the potential use of SGLT2 therapies in diabetics with heart failure is the lack of infrastructure in place for cardiologists to educate and follow up on diabetic patients. Also, there is worry that an overlap in therapy for diabetes and CHF will see CV doctors infringing on the role of the primary diabetes provider.

These worries were raised during sessions at the ACC's annual meeting, held in Washington, DC in March.

There were several sessions about how cardiologists should view the CV benefits recently discovered in the CV outcomes trials of certain diabetes drugs during the conference. According to Biomedtracker's post-ACC report, in one session, Harvard cardiologist Jorge Plutzky said there is interest from organizations like the ACC to have cardiologists more actively involved in diabetes treatment.

Marketed SGLT-2 Therapies

Drug Name	Company	First Approved	Ongoing CV Studies
<i>Farxiga</i> (dapagliflozin)	AstraZeneca	US approval in 2014 for use in patients with type 2 diabetes	AstraZeneca announced a Phase III to evaluate the effect of dapagliflozin on the incidence of worsening heart failure or cardiovascular death in patients with chronic heart failure with reduced ejection fraction in February 2017.
<i>Invokana</i> (canagliflozin)	Johnson & Johnson	US approval in 2013 for use in patients with type 2 diabetes	While Invokana was included in AstraZeneca's CVD-REAL trial, J&J does not have a clinical program ongoing for the drug as a treatment for CHF. Invokana is in Phase II for obesity.
<i>Jardiance</i> (empagliflozin)	Boehringer & Eli Lilly	US approval in 2014 for use in patients with type 2 diabetes	The companies announced the start of the EMPEROR HF clinical trial program in March 2017, which consists of two event-driven Phase III clinical trials that will investigate empagliflozin for the treatment of adults with chronic heart failure with either preserved ejection fraction or reduced ejection fraction.

Plutzky had concerns that neither the primary diabetes provider nor the cardiologists might take action on the results from the CV outcomes studies for diabetes drugs, as both would think it is the responsibility of the other. He said his institution was interested in learning how to share resources, such as diabetes educators, across two divisions, to facilitate involvement of cardiologists.

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Plutzky also pointed to the need for ACC or American Heart Association guidelines on the role of these diabetic medications, Biomedtracker analysts said. Meanwhile, European Society of Cardiology heart failure guidelines already recommend that Jardiance be considered to delay or prevent the onset of heart failure and prolong life.

[Editor’s note: For more information, see Biomedtracker’s 2017 Post-ACC report.]

Reducing HF Patient Numbers

While the introduction of diabetes drugs to the CHF market is looming – pending the results of more CV outcomes studies in non-diabetics – Entresto and the wider heart failure market are also facing erosion from these drugs from another angle.

New diabetes therapies, such as the SGLT2 class, have demonstrated their significant benefits on diabetic patients when it comes to preventing the onset of cardiovascular issues. In the CVD-REAL study SGLT2 inhibitors had a 39% lower rate of hospitalization for heart failure and 51% lower rate of all-cause death than those newly started on other glucose lowering drugs. These benefits could eventually have an impact on the number of diabetic patients requiring any therapy for heart failure or the length of treatment needed for a cardiovascular condition.

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