Evaluate Vantage

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ISN 2019 – Kidney benefit could help Invokana compete again

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Johnson & Johnson's Invokana has fallen behind SGLT2 rivals over amputation fears, but success in the Credence renal trial, profiled at the International Society of Nephrology meeting, could help it regain ground.

Johnson & Johnson's type 2 diabetes therapy Invokana has already shown a cardiovascular benefit. But an increased risk of amputations has put the drug behind its SGLT2 inhibitor rivals, Lilly and Boehringer's Jardiance and Astrazeneca's Farxiga.

Now a win in the Credence renal outcomes study, which tested Invokana in type 2 diabetics with chronic kidney disease, could give J&J's product an edge over the other SGLT2s, at least for now. And, importantly, the trial's finding of similar amputation rates with Invokana and placebo might help assuage concerns, although these are unlikely to disappear entirely.

Invokana is the first SGLT inhibitor to report results from a kidney disease outcomes trial, though studies of Jardiance and Farxiga are already under way. Interestingly, the Dapa-CKD trial of Farxiga and the Empa-Kidney study of Jardiance are evaluating kidney disease patients both with and without type 2 diabetes.

Meanwhile, Sanofi and Lexicon are also testing their SGLT1/2 inhibitor Zynquista in kidney disease; that project's lead indication is type 1 diabetes, with phase III results in type 2 disease expected later this year.

Selected renal outcomes studies with the SGLT2s					
Product	**Company**	**Study**	**Setting**	**Trial ID**	**Primary completion**
Invokana	Johnson & Johnson	Credence	T2DM and CKD	NCT02065791	Reported
Farxiga	Astrazeneca	Dapa-CKD	Chronic kidney disease	NCT03036150	Nov 2020
Zynquista	Sanofi/Lexicon	Scored	T2DM and CKD	NCT03315143	Mar 2022
Jardiance	Lilly/Boehringer Ingelheim	Empa-Kidney	Chronic kidney disease	NCT03594110	Jun 2022
Source: EvaluatePharma, Clinicaltrials.gov.					

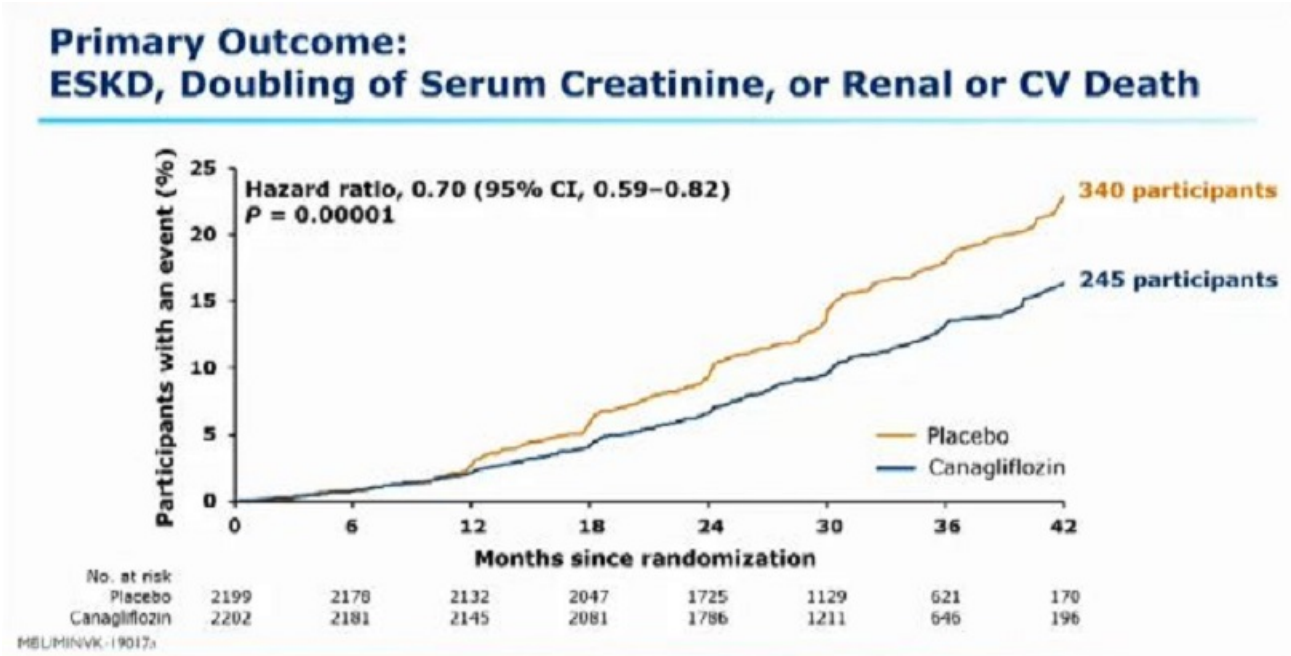
Renal outcomes data with Invokana's rivals are not due for at least another year, so J&J will be keen to make the most of its advantage. The company has already filed a supplemental US NDA, asking for the renal benefit to be included in Invokana's label.

J&J hopes for approval by January 2020, a spokesperson told *Vantage*, although this could come earlier if the application gets priority review.

Credible

Credence enrolled type 2 diabetics with an estimated glomerular filtration rate of 30-90ml/min/1.73m^2, equivalent to stage 2 or 3 chronic kidney disease.

Its primary endpoint was a composite of end-stage kidney disease, doubling of serum creatinine, and renal or cardiovascular death. Invokana reduced the risk of these outcomes by 30%, with a p value of 0.00001. Credence also met various secondary endpoints, but fell short of showing a reduction in cardiovascular deaths.



Summary

Primary	Hazard ratio (95% CI)	*P* value	
1. ESKD, doubling of serum creatinine, or renal or CV death	0.70 (0.59–0.82)	0.00001	✔
Secondary			
2. CV death or hospitalization for heart failure	0.69 (0.57–0.83)	<0.001	✔
3. CV death, MI, or stroke	0.80 (0.67–0.95)	0.01	✔
4. Hospitalization for heart failure	0.61 (0.47–0.80)	<0.001	✔
5. ESKD, doubling of serum creatinine, or renal death	0.66 (0.53–0.81)	<0.001	✔
6. CV death	0.78 (0.61–1.00)	0.0502	Not significant
7. All-cause mortality	0.83 (0.68–1.02)	–	Not formally tested
8. CV death, MI, stroke, hospitalization for heart failure, or hospitalization for unstable angina	0.74 (0.63–0.86)	–	Not formally tested

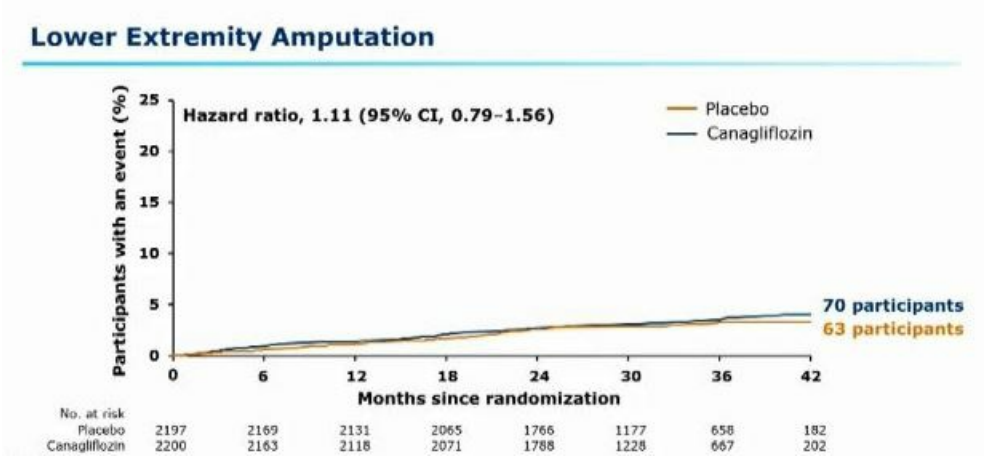
Source: ISN presentation

Another important finding from Credence was that the risk of amputation was not higher with Invokana than with placebo. An imbalance in amputations in the Canvas cardiovascular outcomes programme led to a warning on Invokana's label, and contributed to its declining market share.

On a conference call today the lead investigator of Credence, Professor Vlado Perkovic of The George Institute, Australia, was asked to explain the the discrepancy in amputation rates between the studies, and noted that Credence had several measures designed to prevent amputations.

These included checking patients' feet for diabetic ulcers every time they came to the clinic, something he said doctors should be doing anyway. In addition, if patients developed a lesion they discontinued treatment temporarily until this cleared up.

Professor Perkovic said it was unclear whether these measures were behind the improved amputation numbers, adding that this strategy started fairly late in the course of Credence, and that there had been no separation in amputation rates early on in the trial.



Source: ISN presentation

He concluded that doctors should now be reassured that Invokana is unlikely to increase the risk of amputations if they use a “sensible risk-management” strategy.

J&J said it was working with the FDA to incorporate the findings into Invokana’s label. Still, doubts about amputation risk could linger, particularly as Jardiance and Farxiga have not been linked with this problem.

These rival drugs have not – yet – shown that they improve outcomes in chronic kidney disease patients, but this might only be a matter of time. After all, the SGLT2s’ cardiovascular benefit is increasingly looking like a class effect.

Professor Perkovic acknowledged that the drugs might have a similar affect on renal outcomes, but said more data would be needed to prove this, and noted that Invokana was so far the only SGLT2 shown to prevent kidney failure.

J&J will hope that this is enough to regain ground with Invokana before its rivals catch up.