

FDA initiates investigation of potential increased amputation risk with J&J's Invokana (canagliflozin) based on interim results from CANVAS CVOT - May 18, 2016

The FDA released a [Drug Safety Communication](#) this morning announcing that it is investigating the potential for increased lower limb amputations with J&J's Invokana (canagliflozin) and Invokamet (canagliflozin/metformin). The investigation is based on an interim analysis from the [CANVAS CVOT](#) showing amputation rates of 7/1,000 patient-years with 100 mg Invokana and 5/1,000 patient-years with 300 mg Invokana vs. 3/1,000 patient-years with placebo after an average of 4.5 years of follow-up. The EMA [initiated its own safety review](#) last month. There is currently no significant difference in amputations between groups in the [CANVAS-R renal outcomes trial](#) after an average of nine months of follow-up; the EMA notice indicated that the incidence of amputations in that trial is currently 7/1,000 patient-years with Invokana and 5/1,000 patient-years with placebo. In today's [announcement](#), the FDA advised patients taking Invokana to contact their HCPs if they notice new pain, tenderness, sores, ulcers, or infections in their legs or feet but did not recommend any additional actions. Notably (and reassuringly), the announcement also noted that the Independent Data Monitoring Committee for CANVAS has recommended that the trial should continue. When asked about the EMA notice during its [1Q16 update](#), J&J emphasized that the 12 previous clinical trials of Invokana have not found any signal of increased amputation risk. We are not sure whether the FDA will request information on amputations from other SGLT-2 inhibitor manufacturers as well; the amputation rates in the EMPA-REG OUTCOME trial of Lilly/BI's Jardiance (empagliflozin) [were not reported in the published paper](#), suggesting that there were no concerning signals. We will keep a close eye on these investigations going forward but do not expect this to emerge as a major concern given the lack of any previous mechanistic or clinical evidence suggesting a link between SGLT-2 inhibitors and amputation risk.

-- by Emily Regier and Kelly Close