YODA Project 2015-0416, Bone safety of canagliflozin, a SGLT2 inhibitor, in type 2 diabetes: A retrospective analysis to evaluate fracture risk.

Objective: The objective of this project was to evaluate the effect of canagliflozin on fracture risk by evaluating predictors of fracture events and changes in bone mineral density and bone biomarkers.

Methods Used: We requested and received data from 9 protocols in April 2015. We reviewed each of the protocols and the available data. We then prepared analysis data sets for baseline data, fracture events, bone mineral density, and bone biomarkers. We used Cox regression to evaluate the effect of baseline predictors and treatment group on fracture risk. We used analysis of covariance to evaluate changes in bone mineral density and bone biomarkers using a model with treatment and stratification factors (baseline T-score category (<-1.5, ≤-1.5), and PPARγ at baseline) as fixed effects, and the corresponding baseline value as a covariate. This was the model specified in the trial statistical analysis plan.

Results: After careful review of each of the protocols and available data we determined that only one of the protocols, NCT01106651, 28431754-DIA3010, had sufficient data on fractures, bone mineral density, and bone markers. We replicated the baseline data and the number of fractures per group as reported in Bode 2015. We were not able to evaluate multiple risk factors in a Cox regression because there were only 22 fracture events. We analyzed changes in bone mineral density and bone biomarkers at 52 and 104 weeks and, although there were minor differences, our results were similar to those in the clinical study report and the November 2015 publication (Bilezikian).
Although the Due Diligence Assessment indicated that two fracture risks and bone parameter manuscripts were underway, we hoped that we would be able to complete our analyses either before these were published or provide additional analyses. We had completed many of our analyses when these papers were published electronically in November 2015. We confirmed their analyses and considered additional analyses, but thought it would be difficult to get the results published.

Conclusions: We were able to replicate published results, but determined that there was not enough new information to justify an additional publication. The CANVAS trial, NCT01032629, was completed in February 2017 and results have been published (Neal 2017). They reported an increased risk for low-trauma fracture in the canagliflozin group (HR 1.56, 95% CU 1.18-2.06), but bone mineral density and bone parameters were not included in this protocol. When these data are available we will consider requesting this data set for a more detailed Cox regression analysis.

References

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