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General Information

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Are external grants or funds being used to support this research?: No external grants or funds are being used
to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00642278 - A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally Administered SGLT2 Inhibit

NCT01106625 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemi

NCT01064414 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, 26-Week, Multicenter Study With a 26-Week Extension, to Evaluate the Efficacy, Safety and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabete

NCT01081834 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Co

NCT01106677 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequ

NCT00968812 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus

NCT01106651 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus In

NCT01106690 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemi

NCT01137812 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Con

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Bone safety of canagliflozin, aSGLT2 inhibitor, in type 2 diabetes: A retrospective analysis to evaluate fracture risk.

Narrative Summary:
Diabetes increases the risk for bone fractures. Therefore, when providers choose medications, understanding the safety profile is very important. We want to address whether a recently approved medication called InvokanaTM may further increase bone fracture risk. We will evaluate clinical trial data to identify which patients may be more susceptible to fractures after 1 year of taking this medication.

Scientific Abstract:

Background. Canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, is a new treatment for type 2 diabetes mellitus (T2DM). In the approval process, the FDA Advisory Committee reviewed data suggesting that canagliflozin increased the incidence of bone fractures. It is not known if these treatment-emergent fractures were more frequent in certain populations (e.g., post-menopausal women). Objective. To identify predictors of fractures to determine whether 1) bone-related baseline variables correlate with fracture rate and 2) changes in bone-specific variables can predict treatment-emergent fractures. Participants. Subjects from in 9 clinical trials who have sustained fractures as compared to matched controls. Study Design. Retrospective analysis of risk factors and fracture data from multiple clinical trials focusing on fractures after 1 year of therapy. Main Outcome Measures(s). The primary outcome variables are time to first fracture and time to first low trauma fracture. Statistical Analysis. We will use Cox regression to compare the fracture risk among treatment groups and to evaluate the effect of baseline and on-treatment risk factors on fracture risk. Caveats. Statistical power may be limited due to the small sample size. Ultimately, our goal is to gain information that may assist clinicians to risk-stratify patients who may be most vulnerable to developing drug-induced bone fractures. With continued studies, we may be able to suggest therapeutic approaches to minimize the fracture risk (e.g. vitamin D repletion if vitamin D deficiency is a risk factor).

Brief Project Background and Statement of Project Significance:
SGLT-2 inhibitors improve glycemia, induce modest weight loss and lower blood pressure, but may increase the risk of bone fractures. This is particularly relevant for individuals with diabetes since fracture risk is increased in those with T2DM, especially older individuals (e.g., postmenopausal women). Younger persons with T2DM may also be at higher risk due to the long duration of exposure. Furthermore, we have learned important lessons from the ADOPT trial which demonstrated that thiazolidinediones (TZDs) increase the risk of bone fractures (1). After a 1- year lag for women and 3 years for men, rosiglitazone-treated patients experienced an increase in bone fractures (2, 3). This knowledge helps prescribers monitor and risk stratify appropriate patients for TZD use. Identifying modifiable risk factors (e.g., low vitamin D) may help us propose interventions that mitigate this risk, guide optimal patient selection, and contribute to improved safety of this class of medications.

Background. At the FDA advisory committee meeting on dapagliflozin in July 2011, a disproportionate, dose-dependent fracture rate was noted after 104 weeks in diabetes patients with moderate renal impairment: 9.4% fractures (10 mg dose), 6% (5 mg dose), and no fractures on placebo (4). In patients with normal renal function, there was a 2-fold increase.

At the FDA advisory committee meeting on canagliflozin in January 2013, pooled data from 8 clinical trials (68-weeks) showed a ~30% increase in bone fractures in canagliflozin-treated patients (5). This increase was observed only after 1 year on therapy (6).

Both, fracture location and trauma classification demonstrated an imbalance in upper limb fractures (not favoring canagliflozin), which persisted in low trauma upper limb fractures and spine fractures. In a pooled analysis of all treatment arms, females on canagliflozin had a higher incidence of upper limb fractures (1.2% [31/2608]) compared to placebo (0.4% [5/1338]) (7). The location of distal extremity fractures resembled fracture sites found in other diseases, e.g., primary hyperparathyroidism (8). Subsequently, the FDA required one of five post-marketing studies on canagliflozin to include a study on bone fracture risk (9).

The following observations support potential pathophysiological mechanisms: In a pooled analysis of studies conducted for 26 weeks (n=2,313), serum phosphate increased by 5.1% at the highest dose of canagliflozin (300 mg) compared to placebo (6). In patients with renal impairment (treatment duration 26 weeks), serum phosphate also increased (+7.8%) and 1,25-hydroxyvitamin D decreased (-8.1%) from baseline (10). The most acute changes in serum phosphate occurred within a few weeks of study initiation, suggesting feedback mechanisms maintaining homeostasis (e.g. possible increases in parathyroid hormone which is known to induce phosphaturia). In fact, a small increase in mean PTH (+7.9%) had been observed with canagliflozin (6). If the data were to follow a normal distribution, then ~15% of canagliflozin-treated patients would experience a >47% increase in PTH (mean + 1 SD), a change that could be clinically significant (11).

Specific Aims of the Project:
Specific Aim #1. To evaluate baseline predictors of fracture risk.
Our goal is to investigate if baseline characteristics can predict fracture risk on canagliflozin. Certain factors are known to be related to bone health, including hormonal status (menopause, hypogonadism), age, Vitamin D deficiency, low bone mineral density, previous fractures, etc. We expect that individulas with more risk factors at baseline will have a higher fracture rate on canagliflozin than comparable individuals who were not treated with canagliflozin.
Specific Aim #2. To investigate if any treatment-emergent changes before or after 1 year can predict fracture rate.
It is plausible that treatment induced changes over time could predict an increased fracture risk. The KM curve in Figure 1 demonstrates an increase in treatment emergent fractures occurred after 1 year. It begs the question: what treatment-emergent bone-specific factors could predict fracture risk after 1 year of therapy? Even small

reductions in 1,25-dihydroxyvitamin D or increases in PTH can have detrimental long-term changes in bone metabolism (12, 13). Furthermore, persistent reductions in blood pressure or weight loss may also predict fracture rates. Therefore, we hope to analyze the patient level data before and after 1 year.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment safety

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Retrospective analysis of fracture risk in canagliflozin treated patients will be assessed by evaluating individual participant level data from the following studies: NCT01137812, NCT01106690, NCT01106651, NCT00968812, NCT01106677, NCT01081834, NCT01064414, NCT01106625, NCT00642278. In addition, we are asking (via a separate data request) for any additional information from NCT01032629, which is currently in progress. If we were able to have access to un-blinded individual participant level data that has already been made available to the FDA and presented at the FDA advisory committee, we could further identify which patients may be at the highest risk for fractures after 1-2 years of therapy, given this study is the longest study available for canagliflozin.
Inclusion criteria:
1. Men and women, any age, race, baseline BMI
2. Type 2 Diabetes diagnosis, any HbA1c
3. Fracture, any location
4. Treatment group (canagliflozin, any dose) or placebo group
Exclusion criteria:
1. Unavailable demographic information regarding sex, age
2. Unavailable information on fracture (trauma level, location)
3. Unavailable information on treatment or placebo group

Main Outcome Measure and how it will be categorized/defined for your study:
The primary outcome measures are time from randomization to first fracture and time from randomization to first low trauma fracture. Fracture is defined as an event that has been diagnosed and reported previously, including prospectively adjudicated fractures presented at the FDA advisory committee by data cutoff July 1st 2012 plus any additional data available from the participant level data. Low trauma fracture is defined as a fracture resulting from falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than falls; minimal trauma other than falls.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The predictor variables for this study will dependent on the availability of baseline data to predict fracture risk. Age, sex, race, and baseline BMI, will be included in all analyses. The following will be included if available:
1. PTH
2. 1, 25 dihydroxyvitamin D and 25-OH vitamin D
3. Bone biomarkers (e.g. C-telopeptide, P1NP, osteocalcin, N-Telopeptide)
4. Alkaline phosphatase (bone specific, if available)
5. Serum calcium, iCa
6. Phosphate
7. Urinary calcium, phosphate, creatinine

Because of the relatively small number of events we will use continuous predictor variables when possible. Categorical variables may be created depending on the distribution of the baseline variables. This decision will be made prior to analyzing the fracture data.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Other variables of interest include: LH, FSH, estradiol, testosterone levels. If available, these variables are also important in the evaluation of bone health and fracture rate.

Statistical Analysis Plan:

We will first perform life-table analyses of time to first fracture and time to first low trauma fracture in order to determine the unadjusted event rates for each treatment group. We will then evaluate the baseline data to determine the amount of missing data. We will examine the correlations among the other variables and will select predictors with the least amounts of missing data. Data will be transformed or grouped into categories if appropriate. We will also evaluate the rates within individual studies.

We will use Cox regression to evaluate the effect of baseline predictors. Treatment group, age, sex, and BMI will be included in all analyses. We will add each of the other variables individually to select the ones that are predictive. If there are sufficient events we will then perform a stepwise Cox regression analysis.

For the second primary aim we will use time dependent Cox regression to evaluate the effect of changes in BMI and bone-specific parameters on fracture risk. Analyses will be performed using SAS® 9.3.

The power of these analyses will depend on the number of events. We have not performed power analyses at this time because we need more information about the number of events in the available data.

Project Timeline:
Yoda application submission: February 2015
Project start date: March 2015
Analysis completion date: June 2015
Date manuscript drafted and ready for submission: Fall2015
Date results reported back to YODA project: Fall 2015

Dissemination Plan:
We anticipate the target audience of this publication to be general medical journals and sub-specialty journals, which will be determined after data analysis.

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Supplementary Material: 🔲 figure_1._kaplan-meier.pdf

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