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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.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

<https://yoda.yale.edu/system/files/disclosure-echrist.pdf>
<https://yoda.yale.edu/system/files/disclosure-febrahimi.pdf>
<https://yoda.yale.edu/system/files/disclosure-mheim.pdf>
<https://yoda.yale.edu/system/files/disclosure-aborisov2.pdf>
<https://yoda.yale.edu/system/files/disclosure-mcc.pdf>

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

1. [NCT01032629 - 28431754DIA3008 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of JNJ-28431754 on Cardiovascular Outcomes in Adult Subjects With Type 2 Diabetes Mellitus](#)
2. [NCT01989754 - 28431754DIA4003 - A Randomized, Multicenter, Double-Blind, Parallel, Placebo-Controlled Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects With Type 2 Diabetes Mellitus](#)

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

Research Proposal

Project Title

Canagliflozin and Non-Alcoholic Fatty Liver Disease in Type 2 Diabetes (CaNAFLD) – A Post-Hoc Analysis of RCTs

Narrative Summary:

Patients with type 2 diabetes mellitus (T2DM) have a high prevalence of nonalcoholic fatty liver disease (NAFLD), which can progress to liver cirrhosis and hepatocellular cancer and is projected to become the leading cause for end-stage liver disease at global scale. However, to date there are no approved therapies for NAFLD.

Sodium glucose co-transporter 2 (SGLT2) inhibitors represent novel treatments approved for T2DM. Recent data suggest that SGLT2 inhibitors may reduce liver fat content and inflammation.

CaNAFLD is a post hoc analysis of two large placebo-controlled RCTs investigating the effects of the SGLT2 inhibitor canagliflozin on liver related outcomes in patients with T2DM.

Scientific Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) is highly prevalent among patients with type 2 diabetes (T2DM). To date, there is no approved treatment for NAFLD. SGLT2 inhibitors are potential candidates since they have proven to reduce liver fat and inflammation.

Objective: To assess the effect of canagliflozin compared to placebo on liver-related outcomes in patients with T2DM and to identify subgroups that benefit most from such treatment.

Design: Post-hoc individual participant level pooled analysis of two RCTs that assessed canagliflozin versus placebo in participants with T2DM who were at high risk of cardiovascular events.

Participants: Patients enrolled in phase III RCTs of Canagliflozin in T2DM.

Main Outcome Measures: Change in clinical and laboratory indices from baseline to end of study in patients with T2DM and elevated alanine aminotransferase (ALT) levels. These include changes in ALT; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; C reactive protein, HbA1c, BMI, body weight and waist circumference (where available) as well as prognostic NAFLD scoring systems.

Statistical Analysis: A linear mixed model will be used to account for the correlation between repeated measures on

individual patients that are clustered within studies and the time intervals of outcome assessment. Fixed effects include drug treatment (canagliflozin, placebo), time, treatment-time interaction, study, and additional patient-level covariates (age, gender, comorbidities). The analysis will include random effects for patient and patient-time interaction.

Brief Project Background and Statement of Project Significance:

Non-alcoholic fatty liver disease (NAFLD) has evolved to the leading cause of liver disease at global scale.¹ In fact, the global prevalence of NAFLD is estimated to be approximately 25%,² and it can be as high as 60% to 70% in patients with T2DM.³ Non-alcoholic steatohepatitis (NASH), the aggressive form of NAFLD, can progress to cirrhosis and hepatocellular cancer (HCC) and is rapidly becoming the leading cause for end-stage liver disease or liver transplantation.^{1,4} Despite the increasing burden of the disease, there are still no approved pharmacotherapies for NASH/ NAFLD.⁵ The current cornerstone of therapy is exercise and caloric restriction (most importantly carbohydrates), unfortunately adequate lifestyle change is not achieved or maintained by many patients underscoring the dire need for effective pharmacotherapies.⁶

SGLT2 inhibitors have shown significant reductions in body weight and HbA1c in patients with T2DM and NAFLD.⁷ Other small proof-of-concept studies also reported improvement in hepatic steatosis and liver fibrosis as well as histology upon treatment with SGLT2 inhibitors^{8–11}. In addition, pleiotropic effects such as lowered uric acid levels, a potential anti-inflammatory activity and reduction of oxidative stress have been discussed to improve liver function.¹² Against this background, there is a need to further investigate SGLT2 inhibitors as promising novel treatments in order to address the ever-growing burden of chronic liver disease due to NAFLD. However, high quality data from large RCTs are still missing, despite the known benefits of cardiovascular risk reduction and general safety of these medications.^{13,14}

Although liver biopsy has been heavily relied on in diagnosis and staging of NAFLD, it is difficult to obtain and large studies have not been conducted due to its invasive nature. Instead, in this study we will analyse the best available surrogate markers such as common liver tests, Fatty liver index, NAFLD ridge score, NAFLD fibrosis score, Fibrosis improvement lifestyle intervention score^{15–17}. The CaNAFLD study is a secondary analysis of two randomized controlled trials of patients with T2DM and will provide relevant novel information on possible benefits of SGLT2-inhibitors in NAFLD / NASH.

Specific Aims of the Project:

Specific aim #1: To evaluate effects of canagliflozin on liver-related outcomes in patients with T2DM.

Hypothesis: There is a significant reduction of liver enzyme values in patients receiving canagliflozin as an established surrogate of reduced of liver fat amount and inflammation.

Specific aim #2: To examine the association of clinically available baseline factors with liver enzyme normalization in order to develop a prediction score which patients would benefit most from such a treatment.

Hypothesis: We hypothesize a heterogeneity in the effects of canagliflozin on liver-related outcomes with highest effects among those patients with highest insulin resistance, body weight, ALT levels and HbA1c.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Trials of Canagliflozin in T2DM (NCT01989754 and NCT01032629).

Inclusion criteria:

1. Men and women, any age, race, baseline BMI
2. Type 2 Diabetes diagnosis, any HbA1c
3. Treatment group (canagliflozin, any dose) or placebo group

Exclusion criteria:

1. Unavailable demographic information regarding sex, age, weight (BMI)

2. Unavailable information regarding ALT levels

Subgroup analysis of patients with ALT levels >30IU/L vs. ?30IU/L.

Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome measure is the change in ALT levels from baseline in the canagliflozin group compared to placebo .

Secondary outcomes include:

- Change from baseline in AST and Gamma-GT with canagliflozin compared to placebo.
- Rate of liver enzyme normalization (ALT, AST, Gamma-GT) with canagliflozin compared to placebo .
- Association of clinically available baseline factors with liver enzyme normalization .
- Change from baseline in ALT:AST ratio; inflammation markers (CRP, TNF).
- Change from baseline in Fatty Liver Index score (BMI, WC, triglycerides and GGT).
- Change from baseline in NAFLD ridge score (ALT, HDL- C, triglycerides, HbA1c, WBC and hypertension).
- Change from baseline in NAFLD fibrosis score (Age, BMI, impaired fasting glucose and/or diabetes, AST, ALT, platelet count and albumin).
- Change from baseline in Fibrosis improvement LI score (ALT, HbA1c, platelets).

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 risk for NASH and liver fibrosis.

The following will be included if available:

1. Liver function tests (ALT, AST, ALP, GGT, albumin, bilirubin)
2. MELD score (calculated from creatinine, bilirubin and albumin)
3. Lipid panel (total cholesterol, triglycerides, HDL, LDL, non HDL cholesterol)
4. Fasting glucose, HbA1c
5. BMI, body weight
6. Platelets, WBC
7. Inflammatory markers (CRP, TNF, if available)
8. Hypertension

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: insulin, LH, FSH, estradiol, testosterone and SHBG levels, if available.

Statistical Analysis Plan:

A linear mixed model will be used to account for the correlation between repeated measures on individual patients that are clustered within studies and the time intervals of outcome assessment (defined as time elapsed since baseline assessment). The study will include fixed effects of drug treatment (canagliflozin, placebo), time, treatment-time interaction, study, and additional patient-level covariates. The analysis will include random effects for patient and patient-time interaction.

Frequency comparison will be done by chi-square test. Two-group comparison of normally distributed data will be performed by Student's t-test. For multigroup comparisons, one-way analysis of variance (ANOVA) with least square difference for posthoc comparison will be applied. For data not normally distributed, the Mann-Whitney-U test will be used if only two groups are compared and the Kruskal-Wallis one-way analysis of variance will be used if more than two groups are being compared. Correlation analysis will be performed using Spearman rank correlation. Standard definitions of sensitivity, specificity, and likelihood ratio (LR) will be used. We will construct receiver operating characteristic (ROC) curves and use areas under the ROC curve (AUC) to compare the diagnostic potential of different parameters. All statistical tests will be 2-tailed. P < 0.05 will be considered significant.

Software Used:

STATA

Project Timeline:

Yoda application submission: August 2020

Project start date: September 2020

Analysis completion date: October 2020

Date manuscript drafted and ready for submission: Spring 2021

Date results reported back to YODA project: Spring 2021

Dissemination Plan:

We anticipate producing one manuscript which will address whether SGLT2 inhibitors are suitable therapeutic agents in NAFLD.

Our target audiences are gastroenterologists, endocrinologists, internal medicine physicians, general practitioners, and pharmacologists.

We will do our best to share our findings in conferences and open access publications in peer reviewed journals but also beyond academia through brief articles, with the aim to ameliorate the future approach to NAFLD and strengthen prevention of end stage liver disease.

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/revision_20200928.pdf