2 SYNOPSIS

Sponsor:
Theracos Sub, LLC

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Name of Finished Product:
Bexagliflozin Tablets

Name of Active Ingredient:
Bexagliflozin

Study Title:
A double blind placebo controlled study to evaluate the effect of bexagliflozin tablets on hemoglobin A_{1c} in patients with type 2 diabetes mellitus and moderate renal impairment

Investigators and Study Centers: Multicenter (see Appendix 16.1.4)

Publication (reference): None

Studied Period:
23 September 2016 (First patient enrolled) to 11 January 2018 (last patient completed)

Study Phase: 3

Primary Objective:
To determine the effectiveness of bexagliflozin for the reduction of HbA_{1c} in patients with T2DM and moderate renal impairment after 24 weeks of treatment.

Key Secondary Objectives:

- To assess the effect of bexagliflozin on the change in body weight at week 24 in subjects with baseline body mass index (BMI) $\geq$ 25 kg m^{-2}
- To assess the effect of bexagliflozin on the change in systolic blood pressure (SBP) at week 24 in subjects with baseline SBP $\geq$ 130 mm Hg
- To evaluate the change in HbA_{1c} in subjects with eGFR 45 to 59 mL min^{-1} per 1.73 m^2 at week 24
- To evaluate the change in HbA_{1c} in subjects with eGFR 30 to 44 mL min^{-1} per 1.73 m^2 at week 24

Exploratory Secondary Objectives:

- To assess the change in HbA_{1c} over time
- To assess the proportion of subjects achieving $HbA_{1c} \leq 7.0\%$ over time
- To assess changes in fasting plasma glucose (FPG) over time
- To measure the proportion of subjects experiencing a $\geq$ 5% reduction of body weight among subjects with baseline BMI $\geq$25 kgm^{-2} at week 24
- The change in body weight in all subjects over time
- Changes in SBP and diastolic BP over time in all subjects
- The change in urine albumin creatinine ratio (UACR) from baseline to week 24 in all subjects and in subjects with baseline macroalbuminuria (UACR $\geq$ 300)

Safety Objective

- To assess the safety of exposure to bexagliflozin for 24 weeks
- To assess the contribution of MACE to an eventual meta-analysis that is intended to exclude excessive cardiovascular risks for subjects exposed to bexagliflozin compared to subjects exposed to placebo during the investigational phase of bexagliflozin development.

Methodology:
THR-1442-C-448 was a phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral administration of bexagliflozin at 20 mg versus placebo in subjects with T2DM, moderate renal impairment and inadequate glycemic control.

The study enrolled male and female participants who had T2DM with an HbA_{1c} between 7.0 and 10.5% (inclusive) and stage 3 chronic kidney disease (CKD) as defined by an eGFR of ≥ 30 and< 60 mL min^{-1} per 1.73 m^2 at the screening visit and one additional time of measurement between 1 and 12 months prior to screening which was obtained from available medical records at the time of screening. Subjects were either treatment naïve or were treated with a stable regimen of anti-diabetic medications. At the time of screening, the doses and frequency of all anti-diabetic medications had to be stable for 8 weeks.

All eligible subjects entered a one-week single-blind, placebo run-in period to allow for diabetes education and optimization of compliance with diet and exercise recommendations. Subjects who were compliant in taking run-in medication, had screening eGFR ≥ 30 and< 60 mL min^{-1} per 1.73 m^2, and had stable GFR (no more than 20% change in eGFR between a historical value and the value determined at the screening visit) were eligible for randomization to receive active agent or placebo in a 1:1 ratio.

Out of 490 prospective participants, 312 were randomized to either the bexagliflozin arm (=157) or the placebo arm (n=155). All randomized subjects were included in the ITT and the safety populations. Randomization was stratified by HbA_{1c} level (7.0 to 8.5% or 8.6 to 10.5%), anti-diabetic treatment regimen (with insulin or without) and eGFR (30 – 44 mL min^{-1} per 1.73 m^2 or 45 – 59 mL min^{-1} per 1.73 m^2) at the screening visit. At least 135 subjects in each of the eGFR groups were planned. Stage 3a CKD referred to subjects with a baseline eGFR 45 – 59 mL min^{-1} per 1.73 m^2 whereas stage 3b CKD referred to subjects with a baseline eGFR 30 – 44 mL min^{-1} per 1.73 m^2.

Study subjects scheduled clinic visits at weeks 2, 6, 12, 18, and 24 for safety and efficacy evaluation. At weeks 2 and 18, the visits were conducted via phone interviews unless an in-person visit was considered clinically advisable. A final follow-up visit was conducted at week 26 or two weeks after the last dose of investigational product if the subject withdrew prior to Week 24.

Number of Patients (Planned and Analyzed):
There were 490 prospective participants, 312 were randomized to either the bexagliflozin

arm (n=157) or the placebo arm (n=155). All randomized subjects were include in the ITT and the safety populations.

Three hundred and twelve (312) subjects were analyzed for safety; Three hundred and twelve (312) subjects were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion:
The study enrolled:

1. Male or non-pregnant female ≥ 20 years of age. Women of childbearing potential were required to agree to use contraception throughout the study to avoid any possible pregnancy. Females who were surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses for greater than 12 months and age > 45 years) were eligible if they tested negative on the urine pregnancy test.
2. Subjects with T2DM with an HbA_{1c} between 7.0 and 10.5% (inclusive) at the time of screening.
3. Subjects who were treatment naïve or to have been treated with a stable regimen of anti-diabetic medications. At the time of screening, the doses and frequency of all anti-diabetic medications were to have been stable for 8 weeks.
4. Subject with eGFR ≥ 30 and <60 mL min^{-1} per 1.73 m^2 at 2 time points: screening (V1)
5. Subject with BMI ≤ 45 kg per m^2 (inclusive).
6. Subjects taking stable doses of medications for hypertension or hyperlipidemia (if applicable) for at least 30 days prior to randomization
7. Subjects who have stable eGFR between the historic value and day of screening (no more than 20% change in eGFR between the most recent historical value and the value determined at the screening visit V1).

Test Product, Dose and Mode of Administration, Lot Number:
Bexagliflozin tablets, 20 mg or placebo, once daily orally

Lot number (Run-in Period): placebo B09709

Lot number (Treatment Period): Bexagliflozin and placebo B10904 and B11171

Duration of Treatment: 25 weeks: 1 week run-in, 24 weeks of treatment

Criteria for Evaluation:
Efficacy:
Primary efficacy assessment was:

- To assess change of HbA_{1c} from baseline to week 24

Secondary efficacy assessments were:

- To assess change in body weight in subjects with baseline BMI ≥ 25 kg/m
- To assess changes in SBP over time in subjects with baseline SBP ≥130 mmHg
- To evaluate change in HbA_{1c} over time in subjects with eGFR 45 to 59 mL min^{-1} per 1.73 m^2
- To evaluate change in HbA_{1c} over time in subjects with eGFR 30 to 44 mL min^{-1} per 1.73 m^2

Samples for population PK analysis was collected and the required plasma concentrations determined. The PK parameters were assessed separately as part of the population PK analysis.

Safety:
Safety was assessed based on an analysis of the adverse events record; of laboratory data, including hematology, serum chemistry, urinalysis, urinary electrolytes and creatinine; of electrocardiograms (ECGs), vital signs and physical examinations; and of concomitant medication use.

Statistical Methods:
Data summaries reported descriptive statistics (number of subjects [n], mean, standard deviation [SD], Q1, median, Q3, minimum and maximum) for continuous variables, and frequency and percentage of subjects for categorical and ordinal variables, unless otherwise specified. All data collected were included in by-subject data listings.

Unless otherwise specified, all statistical tests were two-tailed using a 0.05 level of significance. All confidence intervals (CIs) were two-sided 95% CIs.

For safety endpoints, the baseline value was defined as the last value before the first dose of double-blind study medication. For baseline demographics and efficacy endpoints, the baseline value was defined as the last value before the randomization date. No data imputation was applied for missing values, unless otherwise specified

Efficacy:
The primary efficacy hypothesis was that the placebo-corrected change in HbA_{1c} from baseline to week 24 would be significant. The analysis of the change in HbA_{1c} from baseline to week 24 was based on the ITT Analysis Set. All efficacy analyses were performed based on the ITT analysis set. The primary endpoint analysis was conducted using the PP Analysis Set (if deemed different from ITT analysis set). The hypothesis was tested in the ITT analysis set using all observed data and an MMRM analysis with baseline HbA_{1c} as a covariate fitted to the available data, incorporating all visits at which HbA_{1c} was measured for each subject, including the scheduled and unscheduled visits for measurement of HbA_{1c}. Treatment, visit, treatment-by-visit, screening anti-diabetic treatment regimen [insulin treated, other], baseline eGFR [30-44 or 45-59 mL min^{-1} per 1.73 m^2], region, and baseline HbA_{1c} were applied as fixed effects. From the model, a point estimate of the mean treatment difference at week 24 was generated and an assessment of whether this estimate was significantly different from 0 when compared at a two-sided 0.05 level of significance. An unstructured within-patient covariance structure was assumed. If the model with the unstructured covariance structure did not converge, an autoregressive(1) covariance structure was to be used. HbA_{1c} values obtained after the start of rescue medication were excluded from the primary analysis. For the primary analysis, it was assumed that a majority of the missing values would be missing at random (MAR) or missing completely at random (MCAR).

Sample size determination:
Assuming SD for the change in HbA_{1c} to be 1%, an estimated sample size of 133 evaluable subjects per treatment was predicted to have 90% power to detect a difference between

groups of 0.5% in mean HbA_{1c} change at a two-sided 0.05 significance level. To account for an estimated drop-out rate of approximately 12%, the study design anticipated randomizing 150 subjects to each of the study arms.

Safety:
Safety data included AEs, physical exam results, vital signs, ECG results, and clinical lab measurements of serum chemistry, hematology, serum lipids, glycemic control parameters and urine specimens. Observed data was summarized using descriptive statistics by treatment group based on the Safety Analysis Set. All safety data were presented in by-subject listings.

Summary of Results

Efficacy:
Demographics and baseline characteristics were balanced between the treatment arms. The study subjects were predominantly Caucasian and Asian. There were more male (62.8%) than female subjects (37.2%). The mean age of subjects was 69.6 years. Approximately 80% of the subjects were overweight and 70% had baseline SBP ≥ 130 mm Hg. The subjects had diabetes for nearly 16 years on average and 56% administered insulin as part of the regimen for glycemic control. Baseline HbA_{1c} was 7.98 ± 0.798% and 80% had $HbA_{1c} \leq 8.5\%$.

The primary objective to establish the effectiveness of bexagliflozin for reduction of HbA_{1c} in subjects with T2DM and moderate renal impairment was met. The reduction in HbA_{1c} of 0.59 % in subjects assigned to the bexagliflozin arm was considered a clinically meaningful improvement. The placebo-corrected change from baseline in HbA_{1c} was - 0.28% (95% CI, -0.46 to -0.10). Using all observed data in the ITT analysis set the treatment effect was statistically significant ($p = 0.0026$). A placebo-corrected HbA_{1c} reduction of 0.29 % (95% CI -0.48, -0.11, $p = 0.0019$) was observed using the per protocol analysis set, in which 8 subjects were excluded for major protocol deviations.

Sensitivity analyses were conducted using 4 methods to handle the missing data. Bexagliflozin produced a statistically significant HbA_{1c} reduction in all 4 sensitivity analyses, supporting the results of the primary analysis that bexagliflozin improved glycemic control in subjects with T2DM and moderate renal impairment.

Subjects who were assigned to the bexagliflozin arm experienced an average reduction from baseline of HbA_{1c} of 0.5% to 0.7%. Subjects assigned to the placebo arm also benefited from participation in the trial. Bexagliflozin treatment resulted in similar changes from baseline HbA_{1c} of - 0.63% and - 0.57% in sub-groups of stage 3a and stage 3b CKD subjects, respectively. The placebo adjusted treatment effect appeared to be larger in the stage 3b CKD group at -0.37%, compared to the stage 3a CKD group at -0.2%. The placebo effect, however, was substantially larger in the stage 3a CKD group. A post-hoc analysis using the LOCF method to exclude post-rescue medication values showed placebo-corrected bexagliflozin treatment effects on HbA_{1c} (95% CI) to be -0.31 (- 0.53,

-0.09), $p = 0.0068$ or -0.43 (-0.69, - 0.16), $p = 0.0017$ in subjects with CKD 3a or CKD 3b, respectively.

For the key secondary endpoint of detecting a significant change in body weight from baseline to week 24 in subjects with a BMI ≥ 25 kg m^{-2} was met. The placebo-corrected change after 24 weeks of treatment was -1.76 kg (95% CI, -2.50 to -1.03) and was statistically significant. There were 219 (68%) subjects with baseline SBP ≥ 130 mm Hg and at least one value post-baseline included in the bexagliflozin effect on SBP analysis. The mean baseline SBP (SD) was 142.92 (10.091) mm Hg and decreased at week 24 by 10.14 and 7.51 mm Hg in bexagliflozin and placebo arms, respectively. The placebo corrected SBP change of -2.63 mm Hg (95% CI, -6.70 to 1.44, $p = 0.2035$) was not statistically significant.

The hypothesis testing of bexagliflozin effects on HbA_{1c} reduction at week 24 in subjects with stage 3a CKD and stage 3b CKD was not performed because the SBP reduction did not reach statistical significance. Descriptive statistics of change from baseline in HbA_{1c} (%) in subjects with baseline stage 3a CKD showed that the HbA_{1c} LS mean change from baseline at week 24 was -0.63% (95% CI, -0.80 to -0.47,). The difference from the placebo arm was -0.2% (95% CI, -0.44 to 0.05). For subjects with stage 3b CKD, the HbA_{1c} LS mean change from baseline at week 24 was -0.57% (95% CI, -0.77 to -0.37,). The difference from placebo arm was -0.37% (95% CI, -0.65 to -0.10,). Mean HbA_{1c} decreased over time in the bexagliflozin group. Mean HbA_{1c} in placebo group also decreased over time, but with lesser magnitude. Bexagliflozin group achieved reduced fasting plasma glucose compared to placebo group. Higher proportion of subjects in the bexagliflozin arm than in the placebo arm achieved ≥ 5% weight reduction and target HbA_{1c} of < 7% after 24 weeks of treatment. Bexagliflozin treatment lowered the mean SBP and DBP of all subjects. The mean SBP was reduced by -3.84 mm Hg (95% CI -7.09, -0.60). The effect of treatment on DBP was -3.0 mm Hg compared to the effect of placebo of -2.1 mmHg. Bexagliflozin treatment significantly lowered albuminuria from baseline to week 24.

Safety:
Subjects who participated in THR-1442-C-448 protocol have tolerated the 24-week dosing well. Bexagliflozin tablets were well-tolerated by the study subjects. Overall, 3.5% of the subjects discontinued dosing due to TEAE and 1.6% of the study subjects withdrew from the study due to TEAE. Four of the subjects, 3 in the bexagliflozin arm and 1 in the placebo arm, discontinued IP administration due to asymptomatic stage 1 AKI.

The number of subjects who experienced any treatment-emergent AEs was balanced between the two treatment arms with 69.4% and 67.7% of the subjects reporting any TEAE in the bexagliflozin and placebo arm, respectively. The highest frequency of AEs occurred in the system organ class of metabolism and nutrition disorders, primarily due to hypoglycemia, affecting 47 subjects (29.9%) assigned to the bexagliflozin group and 45 subjects (29.0%) assigned to the placebo group. A higher percentage of subjects in the bexagliflozin arm reported TEAEs by ≥ 5% in the SOC of infection and infestations and renal and urinary disorders compared to the placebo arm.

The most commonly reported TEAEs were hypoglycemia, nasopharyngitis, nausea, and polyuria, all but the last of which occurred with comparable frequencies among subjects assigned to each treatment arm. Polyuria occurred more frequently in the bexagliflozin arm. Polydipsia, UTI, bronchitis, sinusitis, polyuria, and hypertension occurred in a higher percentage of subjects assigned to the bexagliflozin arm than to the placebo arm by ≥ 2%.

No death was reported during the study. SAEs occurred in 11 subjects (7%) in the bexagliflozin arm and 9 subjects (5.8%) in the placebo arm. SAEs were dispersed among SOCs and no statistically significant imbalance of subjects with SAE was observed. No DKA was reported during the study period. A single episode of hepatotoxicity was ascribed to initiation of a concomitant medication and resolved upon discontinuation of administration of the suspect medication. Exposure to bexagliflozin had little or no effect on the incidence of hypoglycemia, renal failure events, falls and fractures, hypersensitivities, malignancies, rashes, acid/based disorders or syncope. Of five candidate MACE events, two were adjudicated to represent MACE, and both affected individuals assigned to the bexagliflozin arm. The number of MACE events was too small to impute a safety signal to the observations. Diuretic effects, UTI, and GMI were represented more frequently by > 2% among subjects assigned to the bexagliflozin arm.

Approximately 55% of the study subjects were prescribed insulin at baseline. The incidence of hypoglycemia, including all severity categories, was comparable between participants assigned to the bexagliflozin (n = 39, 24.8%) and placebo (n = 39, 25.2%) arms. However, more subjects assigned to the bexagliflozin arm reported severe or symptomatic hypoglycemia than subjects assigned to the placebo arm. All but two of the 43 subjects with severe or symptomatic hypoglycemia were prescribed insulin for glycemic control. All AKI events were stage 1 and asymptomatic. Among the 22 subjects with at least one event that met the definition of AKI, 14 were assigned to the bexagliflozin arm and 8 were assigned to the placebo arm. Most of the events occurred in male subjects and 9 of the 14 subjects had stage 3b CKD at baseline. No SAE of AKI was reported. IP administration was discontinued for 6 subjects in the bexagliflozin arm and 1 subject in the placebo arm. Two subjects, one in the bexagliflozin arm and one in the placebo arm, withdrew from the study due to AKI. Two MACE were confirmed by the cardiovascular endpoint committee. A non-fatal stroke occurred on day 121 and a hospitalization for unstable angina occurred on day 62. Both events affected subjects assigned to the bexagliflozin arm.

Among the hematology parameters, there were no treatment-dependent or clinically meaningful changes in the WBC, differential count of leukocytes or platelets. The mean MCHC decreased by 2% among participants assigned to the bexagliflozin arm. The change was not considered clinically significant. Slight increases in erythrocytes, hematocrit and hemoglobin in the bexagliflozin group were observed. The changes had substantially reverted 2 weeks after the last dose. The magnitudes of change were modest and not considered of clinical significance.

There were no clinically significant mean changes from baseline values between participants in the bexagliflozin arm and the placebo arm for electrolytes, albumin, direct

and total bilirubin, total protein, BUN, total cholesterol, triglycerides, or LDL-cholesterol. An approximately 2% increase in HDL-cholesterol was observed throughout the treatment period.

An increase in creatinine concentration of 6.7 μmol L^{-1} (0.06 mg dL^{-1}), equivalent to a decrease in eGFR of 2.41 mL min^{-1} per 1.73 m^2 at week 24 among subjects assigned to the bexagliflozin arm was observed and thought to reflect decreased glomerular filtration due to tubuloglomerular feedback associated with bexagliflozin-induced natriuresis. There was a numerically larger decrease in eGFR among subjects with stage 3a CKD although the change was not considered clinically significant for either CKD subgroup.

A significant mean decrease in urine creatinine concentration of 1.741 (SD = 4.461) mmol L^{-1} at week 24 was observed among subjects assigned to the bexagliflozin arm. The decreased creatinine concentration was attributed to an increased urine volume due to diuresis. No other findings from review of the urine parameters were considered clinically significant.

No clinically meaningful finding was considered a significant risk for study subjects in other safety measurements including vital signs, electrocardiography, and physical examinations.

CONCLUSIONS

Efficacy Conclusions:
The primary objective to establish the effectiveness of bexagliflozin for reduction of HbA_{1c} in subjects with T2DM and moderate renal impairment was met.

In a study population consisting of predominantly elderly individuals with poorly controlled diabetes and moderate renal impairment, exposure to bexagliflozin was found to produce a statistically significant and clinically meaningful decrease in the percent HbA_{1c}. The antidiabetic treatment effect was more marked in the sub-population exhibiting greater impairment, a circumstance believed attributable to a larger placebo contribution in the sub-population exhibiting lesser impairment.

Safety Conclusions:
Bexagliflozin tablets were well-tolerated by the study subjects who participated in THR-1442-C-448 study. Overall, 3.5% of the subjects discontinued dosing due to TEAE and 1.6% of the study subjects withdrew from the study due to TEAE. Four of the subjects, 3 in the bexagliflozin arm and 1 in the placebo arm, discontinued IP administration due to asymptomatic stage 1 AKI. The most commonly reported TEAEs were hypoglycemia, nasopharyngitis, nausea, and polyuria, all but the last of which occurred with comparable frequencies among subjects assigned to each treatment arm. Polyuria occurred more frequently in the bexagliflozin arm.

Polydipsia, UTI, bronchitis, sinusitis, polyuria, and hypertension occurred in a higher percentage of subjects assigned to the bexagliflozin arm than to the placebo arm by ≥ 2%.

No death was reported during the study. SAEs occurred in 11 subjects (7.0%) in the bexagliflozin arm and 9 subjects (5.8%) in the placebo arm.

Exposure to bexagliflozin had little or no effect on the incidence of hypoglycemia, renal failure events, falls and fractures, hypersensitivities, malignancies, rashes, acid/based disorders or syncope. Of five candidate MACE events, two were adjudicated to represent MACE, and both affected individuals assigned to the bexagliflozin arm. The number of MACE events was too small to impute a safety signal to the observations. Among the hematology parameters, there were no treatment-dependent or clinically meaningful changes in the WBC, differential count of leukocytes or platelets.

The mean MCHC decreased by 2% among participants assigned to the bexagliflozin arm. The change was not considered clinically significant. Slight increases in erythrocytes, hematocrit and hemoglobin in the bexagliflozin group were observed. The changes had substantially reverted 2 weeks after the last dose. The magnitudes of change were modest and not considered of clinical significance.

Results from THR-1442-C-448 study demonstrated that bexagliflozin tablets, 20 mg, were safe and effective in improving glycemic control in subjects with T2DM and moderate renal impairment.

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