

## SYNOPSIS

**Sponsor:** Theracos Sub, LLC

**Individual Study Table**  
**(For National Authority Use only)**  
**Referring to Part of the Dossier**

**Name of Finished Product:**  
**Bexagliflozin Tablets**

**Volume:**

**Name of Active Ingredient:**  
**Bexagliflozin**

**Page:**

**Study Title:**

A Phase 3, randomized, double-blind active-controlled study to evaluate the effects of bexagliflozin versus sitagliptin in subjects with type 2 diabetes mellitus who have inadequate glycemic control by metformin

**Investigators and Study Centers:** Multicenter (see [Appendix 16.1.4](#))

**Publication (reference):** see [Appendix 16.1.11](#)

**Studied Period:**

12 October 2017 (first patient enrolled) to  
31 October 2018 (last patient completed)

**Study Phase:** 3

**Objectives:**

The primary objective was to demonstrate that bexagliflozin was non-inferior to sitagliptin by evaluating the treatment effect on HbA<sub>1c</sub> reduction at week 24.

The key secondary objectives were to evaluate the treatment effect of bexagliflozin vs. sitagliptin on the changes in fasting plasma glucose, body weight in subjects with baseline body mass index  $\geq 25 \text{ kg m}^{-2}$  and systolic blood pressure at week 24.

The exploratory objectives were to assess the treatment effect of bexagliflozin vs. sitagliptin over time on the change in the proportion of subjects achieving HbA<sub>1c</sub> < 7.0%, on the change in hemoglobin A<sub>1c</sub>, in fasting plasma glucose, in body weight and in systolic blood pressure.

The safety objectives were to compare the effects of bexagliflozin vs. sitagliptin on the incidence of adverse events, adverse events of interest and general safety assessments on clinical laboratory parameters, 12-lead electrocardiograms parameters, physical examinations, vital signs including orthostatic blood pressure and use of concomitant medications.

**Methodology:**

In this multi-center, randomized, double-blind, parallel-group study, all subjects were to have taken metformin at a stable dose of  $\geq 1500 \text{ mg per day}$  for  $\geq 8$  weeks and have received diet and exercise counseling. Subjects who successfully completed a 1-week run-in and who met all eligibility criteria were to be randomized in a 1:1 ratio to receive once daily double-blind treatment of either bexagliflozin or sitagliptin tablets. Study subjects were to continue receiving open-labeled metformin during the entire study at a stable dose

and frequency. Subjects were to complete clinical visits at week 0 (day of randomization), weeks 6, 12, 18, 24 (last day of dosing) and 26 (post-dose follow up) in an outpatient setting.

**Number of Subjects (Planned and Analyzed):**

Three hundred and seventy four (374) subjects were planned; 384 were analyzed.

**Diagnosis and Main Criteria for Inclusion:**

Male and non-pregnant female  $\geq 18$  years of age who were diagnosed with type 2 diabetes mellitus, had HbA<sub>1c</sub> levels between 7.0% and 11%, had a BMI  $\leq 45$  kg per m<sup>2</sup>, were treated with a stable dose of  $\geq 1500$  mg per day metformin for  $\geq 8$  weeks, had a BMI  $\leq 45$  kg m<sup>-2</sup> and adhered to the investigational product administration requirements as evidenced by missing no more than 1 day of run-in medications were enrolled.

**Test Product, Dose and Mode of Administration, Lot Number:**

Description	Name	Dose (mg)	Mode of Administration	Lot Number (Manufacture/Packaging)
Test product	Bexagliflozin tablet	20	oral; once per day	B13446/B13452
Active comparator	Sitagliptin tablet	100	oral; once per day	364572/B15437

**Duration of Treatment:** 24 weeks

**Criteria for Evaluation:**

**Efficacy:**

- Hemoglobin A<sub>1c</sub> and fasting plasma glucose determined by a central laboratory
- Systolic blood pressure and body weight determined during scheduled clinical visits

**Safety:**

Adverse event record, physical exam results, vital signs, ECG results and clinical lab measurements of serum chemistry, hematology, serum lipids, glycemic control parameters and urine specimens

**Statistical Methods:**

The sample size was calculated based on a two-group t test with a one sided significance test at the 2.5% level. The non-inferiority margin for the change from baseline to week 24 in HbA<sub>1c</sub> comparing bexagliflozin to sitagliptin arms was 0.35% and the standard deviation was assumed to be 1%. A total of 172 per arm was required to power the study at 90% level and 187 per arm was planned to account for an estimated 8% early withdrawal.

Safety analysis set included all subjects randomized and had taken any double-blind study medications. Intention-to-treat (ITT) analysis set included all subjects randomized regardless of treatment adherence or availability of follow up data. Per protocol (PP) analysis set included all eligible subjects in the ITT who had no major protocol deviations that would have affected the validity of the effectiveness measurements.

**Efficacy:**

The primary efficacy analysis to estimate the difference in HbA<sub>1c</sub> change from baseline for the two study arms at week 24 was based on the ITT analysis set. HbA<sub>1c</sub> values collected after the start of rescue medication were included. Data collected from subjects who

discontinued treatment but had effectiveness measurements at week 24 were to be used for imputation. Missing data were imputed via multiple imputations. If no sufficient week 24 values from treatment discontinued subjects were available for imputation, the mixed model repeat measurement analysis was to be performed using all available data.

In the non-inferiority analysis, a confidence interval (CI) was to be calculated to estimate the range of values in which the treatment difference was observed. If the 95% CI was below the non-inferiority margin 0.35%, the results would have led to a conclusion of non-inferiority of bexagliflozin treatment compared to sitagliptin treatment. Superiority of bexagliflozin group over sitagliptin group was to be declared if the upper bound of 95% CI was less than 0. The following sensitivity analyses were to be conducted:

1. HbA<sub>1c</sub> values collected after the start of rescue medication were to be considered missing and the MMRM analyses were to be performed.
2. A tipping point analysis was to be conducted considering data after rescue medication as missing.

### **Safety:**

Observed data were summarized by treatment group as counts and percentages for discrete variables and means, standard deviations, medians, inter quartile range, minimum and maximum for continuous variables.

A total of 384 subjects were randomized and 368 (95.3%) subjects completed the 24-week dosing period with comparable treatment compliance between the two arms. Relatively few subjects withdrew from the bexagliflozin arm (5.7%) and the sitagliptin arm (2.1%). The study subjects were predominantly Caucasian and non-Hispanic. There were more male subjects than female subjects in the study. The mean age of subjects was 59.4 years. The treatment groups were comparable with respect to age, sex, race, ethnicity, height, body weight and BMI. The population had an average baseline HbA<sub>1c</sub> of 7.99%. The majority of subjects were overweight or obese (mean baseline BMI of 31.72 kg m<sup>-2</sup>), hypertensive (mean baseline SBP of 135.3 mm Hg), hyperglycemic (mean baseline FPG of 9.9 mmol L<sup>-1</sup>) and had normal renal function (mean baseline eGFR of 87.92 mL min<sup>-1</sup> per 1.73 m<sup>2</sup>). The average duration since T2DM diagnosis was 9 years and all subjects were taking at least 1500 mg per day of metformin as their sole hypoglycemic medication at baseline. Baseline characteristics of study subjects were comparable in the two treatment arms.

The model-adjusted mean change from baseline to week 24 in HbA<sub>1c</sub> was -0.74% (95% CI - 0.86%, -0.62%) in the bexagliflozin arm and - 0.82% (95% CI -0.93%, -0.71%) in the sitagliptin arm, respectively. The improvement of glycemic control in both treatment arms was clinically meaningful. The intergroup difference for the change in HbA<sub>1c</sub> was 0.08% with a 95% CI between -0.07% and 0.22%. The upper boundary of the 95% CI was within the pre-specified margin of 0.35% and the non-inferiority of bexagliflozin treatment to sitagliptin treatment was established. The primary effectiveness objective was met. Using the per protocol analysis set, the difference of LS means in HbA<sub>1c</sub> reduction from sitagliptin arm was 0.08% with the 95% CI between -0.06% and 0.23%, comparable to the difference based on the ITT analysis set.

In addition to the 14 subjects who did not provide HbA<sub>1c</sub> values at week 24 due to early withdrawal, 2 (1.0%) subjects in the bexagliflozin arm and 12 (6.2%) subjects in the sitagliptin arm received rescue medications. A sensitivity analysis found that exclusion of the post-rescue values led to an intergroup treatment effect difference of 0.06% and the upper boundary of the 95% CI was 0.21%. Following a tipping point sensitivity analysis, adding and subtracting up to 0.5% to the imputed HbA<sub>1c</sub> values to subjects in the bexagliflozin arm or the sitagliptin arm gave confidence intervals for which upper limit was less than 0.35% in each of the 25 scenarios. Collectively, the sensitivity analyses established that the conclusion of the main analysis was robust to alternative hypotheses regarding missing data.

The treatment effect was analyzed for sub-populations characterized by age, gender, race, geographical region or baseline HbA<sub>1c</sub>. Slightly larger bexagliflozin treatment effects were observed among subjects who were < 65 years of age or who had a baseline HbA<sub>1c</sub> ≥ 8.5%. Although some subgroups had small sample sizes and correspondingly wide confidence intervals, there were no substantial differences in treatment effect between the bexagliflozin and sitagliptin arms when analyzed by subgroup. A slightly better treatment effect was observed for Caucasian subjects exposed to sitagliptin.

The key secondary endpoints were analyzed at a one-sided 0.025 significance level in a pre-specified hierarchy sequence using the ITT analysis set. A sensitivity analysis was conducted using the PP analysis set.

1. Bexagliflozin was superior to sitagliptin for reduction of FPG from baseline to week 24. The difference of -0.37 (95% CI -0.70, -0.05) at week 24 was statistically significant ( $p = 0.0123$ ).
2. Bexagliflozin was superior to sitagliptin for reduction of body weight from baseline to week 24 among subjects with a baseline BMI ≥ 25 kg m<sup>-2</sup>. The intergroup difference was - 2.54 kg; (95% CI -3.15 kg, -1.92 kg) with a  $p$ -value < 0.0001.
3. A reduction of SBP by 4.23 mm Hg from baseline to week 24 was observed among participants in the bexagliflozin arm. The intergroup difference was -2.33 mm Hg (95% CI -4.70 mm Hg, 0.05 mm Hg) and was not statistically significant ( $p = 0.0276$ ).

An exploratory endpoint analysis demonstrated that treatment with bexagliflozin or sitagliptin increased the proportion of subjects who achieved HbA<sub>1c</sub> < 7%. The improvement in glycemic control was apparent as early as 6 weeks after the treatment started and the trend continued for the entire course of 24 weeks with comparable effects of 45.3% or 41.7% of subjects in the sitagliptin or bexagliflozin arms, respectively.

The following conclusions are based on the results of safety analyses:

- Daily dosing of bexagliflozin tablets, 20 mg, or sitagliptin tablets, 100 mg, for 24 weeks was well-tolerated by the study subjects. Investigational product administration was discontinued due to adverse events by 6 subjects (3.1%) in the bexagliflozin arm and 1 subject (0.5%) in the sitagliptin arm. One death was reported among participants in the bexagliflozin arm as a result of sigmoid adenocarcinoma which was assessed as unrelated to the IP administration.

- The number of subjects who experienced any treatment-emergent adverse event was slightly higher in the sitagliptin arm (56.0%) than in the bexagliflozin arm (47.1%).
- The highest frequency of adverse events occurred in the category of infections with 45 subjects (23.6%) reporting such events in the bexagliflozin arm and 59 subjects (30.6%) in the sitagliptin arm. Higher percentages of subjects in the bexagliflozin arm reported adverse events in the system organ classes of gastrointestinal disorders and renal and urinary disorders compared to the sitagliptin arm.
- The most common adverse events were nasopharyngitis, influenza, urinary tract infection and hypoglycemia which occurred in 7.9%, 1.6%, 3.7% and 3.1%, respectively, of subjects in the bexagliflozin arm and 13.0%, 5.2%, 2.1% and 5.2%, respectively, of subjects in the sitagliptin arm. UTI affected a higher percentage of subjects in the bexagliflozin arm by 1.6%. The other common adverse events occurred more frequently among subjects in the sitagliptin arm.
- There were 14 SAEs; eight events occurred in 7 subjects (3.7%) in the bexagliflozin arm and 6 events occurred in 4 subjects (2.1%) in the sitagliptin arm. SAEs were dispersed and no substantial imbalance of subjects with SAE was observed.
- No events were reported for the categories of acidosis, hepatotoxicity, hypersensitivity reactions, hypotensive episodes, renal failure and pyelonephritis/urosepsis during the study period. Diuretic effects, UTI and GMI were represented more frequently among subjects assigned to the bexagliflozin arm.
- One of four suspected MACE cases was confirmed by the cardiovascular endpoint adjudication committee. A subject assigned to the sitagliptin arm had a heart failure event on day 169. The event was moderate in intensity and resolved on day 182.
- Among the hematology parameters, there were no treatment-dependent or clinically meaningful changes in the white blood cell (WBC), differential count of leukocytes or platelets. Slight increases in erythrocytes, hematocrit and hemoglobin in the bexagliflozin group were observed. The changes were modest in magnitude and had substantially reverted 2 weeks after the last dose likely reflecting the mild volume contraction due to diuresis.
- Bexagliflozin treatment resulted in a substantial decrease in serum glucose and urate, consistent with the expected pharmacodynamic effects of SGLT2 inhibition. A slight increase in magnesium and phosphate concentration was observed in the bexagliflozin arm. Increases were observed in total cholesterol, LDL-cholesterol and HDL cholesterol in the bexagliflozin arm.
- A slight increase in serum creatinine concentration and decrease in estimated GFR were observed transiently in the bexagliflozin arm from week 6 to week 18. The changes were reversed and showed a slight decrease in creatinine concentration and an increase in estimated GFR at week 26, 2 weeks after the last dose of the bexagliflozin. These changes were likely related to the mechanism of action of bexagliflozin.

## CONCLUSIONS

Bexagliflozin produces a clinically meaningful reduction in the percent HbA<sub>1c</sub> of adults with type 2 diabetes whose disease is inadequately controlled by metformin. The reduction is non-inferior to that elicited by sitagliptin. Bexagliflozin is superior to sitagliptin for the reduction of fasting plasma glucose and body mass over 24 weeks. Both populations experienced an improvement in systolic blood pressure and the fraction of participants achieving an HbA<sub>1c</sub> < 7.0%.

Adverse increased rates of genital mycotic infection and diuretic effects disproportionately affected participants in the bexagliflozin arm and in some cases led to withdrawal from the study. A greater fraction of participants in the sitagliptin arm received rescue medication. The results of this study support the continued exploration of the potential utility of bexagliflozin for the treatment of type 2 diabetes in adults.

**Final Date:** 26 March 2019

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