CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214373Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214373
PDUFA Goal Date	January 22, 2023
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Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Associate Director for REMS	Laura Zendel, Pharm.D.
Design and Evaluation	
Review Completion Date	January 10, 2023
Subject	Evaluation of the need for a REMS
Established Name	bexagliflozin
Trade Name	Brenzavvy
Name of Applicant	Theracos Sub LLC
Therapeutic Class	sodium-glucose co-transporter 2 (SGLT2) inhibitor
Formulation(s)	20 mg tablet
Dosing Regimen	20 mg once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Brenzavvy (bexagliflozin) is necessary to ensure the benefits outweigh its risks. Theracos Sub LLC submitted a New Drug Application (NDA) 214373 for bexagliflozin with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The serious risks associated with the use of bexagliflozin are ketoacidosis, lower limb amputations, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's Gangrene), and genital mycotic infections. The Applicant did not submit a REMS with this application; but proposed a non-REMS risk management plan consisting of labeling and routine pharmacovigilance.

The Division of Risk Management (DRM) and the Division of Diabetes, Lipid Disorders, and Obesity (DDLO) have determined that a REMS is not necessary to ensure the benefits of bexagliflozin outweigh its risks. Bexagliflozin appeared efficacious in its primary outcome of significant reductions in the hemoglobin A1c (HbA1c) at week 24, and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer stated that bexagliflozin shows clinically meaningful benefit and recommends approval of bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM with the following Limitation of Use statement: Not recommended in patients with type 1 diabetes mellitus; it may increase the risk of diabetic ketoacidosis in these patients. The safety profile is similar to other SGLT2 inhibitors approved for similar indications which do not require a REMS. If approved, labeling will be similar to the currently approved other SGLT2 inhibitors, such as ertugliflozin (Steglatro). Management of the adverse events of bexagliflozin will be communicated in Warnings and Precautions, Patient Counseling Information, and the Medication Guide. The review team concluded that there are no new safety findings were observed in the bexagliflozin clinical development program that significantly impact the overall risk profile.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Brenzavvy (bexagliflozin) is necessary to ensure the benefits outweigh its risks. Theracos Sub LLC submitted a New Drug Application (NDA) 214373 for bexagliflozin with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).[1] This application is under review in the Division of Diabetes, Lipid Disorders, and Obesity (DDLO). The Applicant did not submit a REMS with this application; but proposed a non-REMS risk management plan consisting of, labeling and routine pharmacovigilance.

2 Background

2.1 PRODUCT INFORMATION

Bexagliflozin is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[a] This product is an inhibitor of sodium-glucose co-transporter 2 (sodium-glucose linked transporter 2, SGLT2), the low-

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

affinity, high-capacity concentrative transporter responsible for reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule.[1] Bexagliflozin is proposed to be supplied as 20 mg tablets. The recommended dosage of bexagliflozin is 20 mg administered once daily taken (b) (4) (b) (4) with or without food. (b) (4) 30 mL/min/1.73 m^2 [b,1] Bexagliflozin is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for bexagliflozin (BLA 214373) relevant to this review:

- 01/07/2009 Investigation New Drug (IND) 103822 submission for bexagliflozin received.
- 10/22/2021: BLA 214373 submission for bexagliflozin with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, received.
- 12/13/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that the Medication Guide for bexagliflozin would be similar to those for FDA approved SGLT2 inhibitors, and based on the currently available data, there were no safety issues that require a REMS for bexagliflozin.
- 06/28/2022: On June 6, 2022, FDA received a submission from the Applicant including re-analysis of phase 3 data that triggered a major amendment. The user fee goal date is extended to January 22, 2023.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

The American Diabetes Association (ADA) classifies T2DM as a disorder related "to a progressive loss of beta-cell insulin secretion, frequently on the background of insulin resistance (IR)," in the setting of metabolic stressors, inflammation, and genetic risk.[2] Common clinical manifestations of type 2 diabetes include polyuria, polydipsia, polyphagia, weight loss, blurred vision, lower extremity paresthesias and infections of the skin. Diabetes can affect many different organ systems in the body and, over time, can lead to serious complications. Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy). Macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease. Peripheral vascular disease may lead to bruises or injuries that do not heal, gangrene, and, ultimately, amputation.[3]

As of 2019, 37.3 million Americans or 11.3% of the population, had diabetes. Of the 37.3 million adults with diabetes, 28.7 million were diagnosed, and 8.5 million were undiagnosed. Approximately 1.4

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

million Americans are diagnosed with diabetes each year with 29.2% aged 65 and older.[c] About 283,000 Americans under age 20 are estimated to be diagnosed with diabetes, approximately 0.35% of that population. In 2014–2015, the annual incidence of diagnosed diabetes in youth was estimated at 18,200 with type 1 diabetes, 5,800 with type 2 diabetes. Diabetes remains the 7th leading cause of death in the United States. In 2019, diabetes was mentioned as a cause of death in a total of 282,801 certificates.[4,d] Cardiovascular disease (CVD) is the primary cause of mortality in patients with T2DM, accounting for up to two-thirds of all deaths, and increased HbA1c levels are strongly correlated to an increased risk of heart disease and overall mortality.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

At present, there are different treatments, both oral and injectable, available for T2DM. Initial intervention focuses on lifestyle changes. To achieve and maintain good metabolic control in diabetes, a combination of changes in lifestyle and pharmacological treatment is necessary.[5] While lifestyle modifications and metformin are the cornerstone of the initial management of T2DM, there are different families of oral and injectable drugs, available for the treatment of T2DM, which include sulfonylureas, meglitinides, insulin, thiazolidinediones and alpha-glucosidase inhibitors, glucagon-like peptide-1 (GLP1) receptor agonists, dipeptidylpeptidase 4 inhibitors (DPP4) and SGLT2 inhibitors.[5] A meta-analysis published in 2020 demonstrated that several glucose-lowering strategies, particularly those that reduced body weight, decrease the risk of major adverse cardiovascular events, which demonstrates the usefulness of diabetic therapies in providing beneficial cardiovascular effects.[6] Metformin remains the first choice of treatment for most patients. Other alternative or second-line treatment options should be individualized taking into consideration patient characteristics such as degree of hyperglycemia, presence of co-morbidities, and patient preference and ability to access treatments as well as properties of the treatment including effectiveness and durability of lowering blood glucose, risk of hypoglycemia, effectiveness in reducing diabetes complications, effect on body weight, side effects and contraindications.[5]

Bexagliflozin belongs to the class of SGLT2 inhibitors. There are currently four SGLT2 inhibitor drugs approved in the United States (US): canagliflozin[7] (approved 2013, NDA 204042), empagliflozin[8] (approved 2014, NDA 204629), dapagliflozin[9] (approved 2014, NDA 202293), and ertugliflozin[10] (approved 2017, NDA 209803). With the exception of canagliflozin (Invokana), the SGLT2 inhibitor class does not include a Boxed Warning. Canagliflozin was initially approved in March 2013 with a boxed warning for lower limb amputation, which was removed in August 2020. None of the SGLT2 inhibitor products required REMS for approval.

Achieving near normal glycated hemoglobin significantly decreases risk of macrovascular and microvascular complications. Treatment algorithms are designed to reduce the development or progression of the complications of diabetes which emphasizes the need for effective glycemic control.[5] Despite major advances in primary and secondary prevention of the past 50 years, patients with

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

diabetes still are at increased risks of CVD relative to those without diabetes.[11] Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease.

4 Benefit Assessment

The efficacy of bexagliflozin was evaluated as monotherapy and in combination therapy. Bexagliflozin has also been studied in patients with type 2 diabetes mellitus with moderate renal impairment and in patients with either established cardiovascular disease or who were at risk for cardiovascular disease.[1] At the time of this review, labeling negotiations were ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for bexagliflozin.

4.1 MONOTHERAPY

A total of 207 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on diet and exercise participated in a randomized, double-blind, multi-center, 24-week, placebo-controlled study, C-450 (NCT02715258) to evaluate the efficacy and safety of bexagliflozin monotherapy. These patients, who were either treatment naïve or had discontinued a single oral antihyperglycemic treatment ≥ 6 weeks prior to entering a 2-week, single-blind, placebo run-in period. Upon completion of the run-in period, they were randomized (1:2) to placebo or bexagliflozin 20 mg administered once daily. At week 24, treatment with bexagliflozin 20 mg provided statistically significant reductions in the primary efficacy endpoint, HbA1c, compared to placebo. Bexagliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared with placebo. The efficacy results are summarized in Table 1.[1,e]

Table 1: Results at week 24 from a placebo-controlled monotherapy study of bexagliflozin in patients with type 2 diabetes mellitus[1,e]

	Bexagliflozin N = 138	**Placebo N = 69**
HbA1c (%)		
Baseline mean	8.1	7.9
Change from baseline [adjusted mean (SE)] [a]	-0.5 (0.07)	-0.1 (0.1)
Difference from placebo [adjusted mean] (95% CI)	-0.4 (-0.6, -0.1)*	
Proportions of patients (%) achieving HbA1c <7% [b]	31%	20%
FPG (mg/dL)		
Baseline mean	169	170
Change from baseline [adjusted mean (SE)][c]	-16 (3)	-3 (4)
Difference from placebo [adjusted mean] (95% CI)	-14 (-24, -3)	

SE: Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose
*Statistically significant (multiplicity adjusted one-sided p-value <0.025)
[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 24 (9% and 7% for bexagliflozin

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

Table 1: Results at week 24 from a placebo-controlled monotherapy study of bexagliflozin in patients with type 2 diabetes mellitus[1,e]

	Bexagliflozin N = 138	Placebo N = 69
and placebo, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, country, background anti-diabetes treatment status (treatment naïve or not) and the baseline HbA1c value as a covariate.		
[b] Crude proportion using imputed HbA1c values for missing data at week 24 and averaged across multiply imputed dataset		
[c] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.		

4.2 ADD-ON COMBINATION THERAPY WITH METFORMIN

A total of 317 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7.5% and 10.5%) on metformin monotherapy (≥1,000 mg/day for ≥8 weeks) participated in a randomized, double-blind, multi-center, 24-week, placebo-controlled study, C-419 (NCT03259789) to evaluate the efficacy and safety of bexagliflozin in combination with metformin. Patients entered a 1-week, single-blind, placebo run-in, and were randomized (1:1) to placebo or bexagliflozin 20 mg administered once daily in addition to the background metformin therapy. At week 24, treatment with bexagliflozin provided statistically significant reductions in HbA1c compared to placebo. Bexagliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo. The efficacy results are summarized in Table 2.[1,e]

Table 2: Results at week 24 from a placebo-controlled study for bexagliflozin used in combination with metformin in patients with type 2 diabetes mellitus[1,e]

	Bexagliflozin N = 158	Placebo N = 159
HbA1c (%)		
Baseline mean	8.6	8.5
Change from baseline [adjusted mean (SE)] [a]	-1.0((b) (4))	-0.5 ((b) (4))
Difference from placebo [adjusted mean] (95% CI)	-0.5 (-0.7, -0.3)*	
Proportions of patients (%) achieving HbA1c < 7% [b]	26%	10%
FPG (mg/dL)		
Baseline mean	186	190
Change from baseline [adjusted mean (SE)][c]	-42 (3)	-20 (3)
Difference from placebo [adjusted mean] (95% CI)	-22 (-31, -12)	
SE: Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose		
*Statistically significant (multiplicity adjusted one-sided p-value <0.025)		
[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 24 (10% and 9% for bexagliflozin and placebo, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, baseline HbA1c value and country (US or Japan).		
[b] Crude proportion using imputed HbA1c values for missing data at week 24 and averaged across multiply imputed datasets		
[c] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.		

4.3 ACTIVE-CONTROLLED STUDY VERSUS GLIMEPIRIDE AS ADD-ON THERAPY WITH METFORMIN

A total of 426 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 10.5%) on metformin monotherapy participated in a randomized, double-blind, multi-center, 60-week, active comparator-controlled study, C-480 (NCT02769481) to evaluate the efficacy and safety of bexagliflozin in combination with metformin. Patients receiving metformin (≥1,500 mg/day) as a monotherapy or who had discontinued the use of a single additional oral hypoglycemic agent in addition to metformin for ≥6 weeks entered a 2-week, single-blind, placebo run-in period. Upon completion of the run-in period they were randomized (1:1) to glimepiride or bexagliflozin 20 mg administered once daily in addition to continuation of background metformin therapy. Glimepiride therapy was initiated at 2 mg/day and titrated up to 6 mg/day or the maximum tolerated dose. The mean daily dose of glimepiride was 5.4 mg. Bexagliflozin 20 mg was non-inferior to glimepiride after 60 weeks of treatment. The efficacy results are summarized in Table 3.[1,e]

Table 3: Results at week 60 from an active-controlled study comparing bexagliflozin to glimepiride as an add-on therapy for patients inadequately controlled by metformin[1,e]

	Bexagliflozin N = 213	**Glimepiride N = 213**
HbA1c (%)		
Baseline mean	8.0	8.0
Change from baseline [adjusted mean (SE)] [a]	-0.7 ((b) (4))	-0.6 ((b) (4))
Difference from glimepiride [adjusted mean] (95% CI)	(b) (4) (-0.2, 0.1)* [b]	
Proportions of patients (%) achieving HbA1c < 7% [c]	35%	33%
FPG (mg/dL)		
Baseline mean	172	174
Change from baseline [adjusted mean (SE)] [d]	-22 (2)	-14(3)
Difference from glimepiride [adjusted mean] (95% CI)	-8 (-15, -1)	

SE:Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose (b) (4)

[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 60 (9% and 10% for bexagliflozin and glimepiride, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, region, background treatment status (metformin-only or metformin + OHA), eGFR at baseline (≥90 vs. < 90 mL min^{-1} per 1.73m^2), and baseline HbA1c value. Non-inferiority is declared if the 95% confidence interval for the difference from glimepiride lies below 0.35.

[b] Non-inferior

[c] Crude proportion using imputed HbA1c values for missing data at week 60 and averaged across multiply imputed datasets

[d] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.

4.4 ACTIVE-CONTROLLED VERSUS SITAGLIPTIN AS ADD-ON THERAPY WITH METFORMIN

A total of 384 patients with type 2 diabetes mellitus inadequately controlled (HbA1c between 7% and 11%) on metformin monotherapy participated in a randomized, double-blind, multi-center, 24-week, active comparator-controlled study, C-423 (NCT03115112) to evaluate the efficacy and safety of bexagliflozin in combination with metformin. These patients, who were receiving metformin monotherapy (≥1,500 mg/day for ≥8 weeks), entered a 1-week, single-blind, placebo run-in period and were randomized to sitagliptin 100 mg or bexagliflozin 20 mg administered once daily in addition to the

background metformin therapy. Bexagliflozin (b) (4) was non-inferior to glimepiride after 24 weeks of treatment. The efficacy results are summarized in Table 4.[1,e]

Table 4: Results at week 24 from an active-controlled study comparing bexagliflozin to sitagliptin as an add-on therapy for patients inadequately controlled by metformin[1,e]

	Bexagliflozin N = 191	Sitagliptin N = 193
HbA1c (%) [a]		
Baseline mean	7.9	8.0
Change from baseline [adjusted mean (SE)] [a]	-0.8 ((b) (4))	-0.9 ((b) (4))
Difference from sitagliptin [adjusted mean] (95% CI)	0.1 (-0.1, 0.2) [b]	
Proportions of patients (%) achieving HbA1c < 7% [c]	40%	45%
FPG (mg/dL) [c]		
Baseline mean	176	180
Change from baseline [adjusted mean (SE)] [d]	-31 (2)	-26 (2)
Difference from sitagliptin [adjusted mean] (95% CI)	-5 (-11, 1)	

SE:Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose

(b) (4)

[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 24 (6% and 2% for bexagliflozin and sitagliptin, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, baseline HbA1c value and region. Non-inferiority is declared if the 95% confidence interval for the difference from sitagliptin lies below 0.35.

[b] Non-inferior

[c] Crude proportion using imputed HbA1c values for missing data at week 24 and averaged across multiply imputed datasets

[d] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.

4.5 Add-on Combination Therapy in Patients with Increased Risk for Major Adverse Cardiovascular Events

The efficacy of bexagliflozin was assessed in a multicenter, randomized, double-blind, placebo-controlled study, C-476 (NCT02558296) of patients with inadequately controlled type 2 diabetes mellitus (HbA1c between 7% and 11%) who had either established cardiovascular disease, including a history of atherosclerotic vascular disease or a history of heart failure, or multiple risk factors for cardiovascular disease. There were no restrictions on background antihyperglycemic medication use, aside from treatment with an SGLT2 inhibitor. After a single-blind, 2-week, placebo run-in period, 1701 patients were randomized to receive placebo (N=567) or bexagliflozin 20 mg (N=1134) once daily. At baseline, nearly all patients (99.4%) were treated with one or more antidiabetic medications including biguanides (metformin) (77%), insulin (53%), sulfonylureas (40%) DPP-4 inhibitors (13%) and thiazolidinediones (3%). The mean duration of type 2 diabetes mellitus was 15 years, the mean HbA1c at baseline was 8.3% and the mean eGFR was 77 mL/min/1.73 m^2. At week 24, treatment with bexagliflozin provided statistically significant reductions in HbA1c compared to placebo. Bexagliflozin also resulted in a greater proportion of patients achieving an HbA1c <7% compared to placebo. The efficacy results are summarized in Table 5.[1,e] In addition, bexagliflozin provided a statistically significant reduction in HbA1c compared to placebo in a subset of patients using background insulin (N=902, difference from placebo -

0.5% [95% CI: -0.6, -0.4]) and in a subset of patients using background sulfonylureas (N=313, difference from placebo -0.4% [95% CI:-0.6, -0.2]).

Table 5: Results at week 24 from a placebo-controlled study evaluating bexagliflozin as an add-on therapy for patients inadequately controlled by standard of care (SOC) therapy[1,e]

	Bexagliflozin N = 1133	**Placebo N = 567**
HbA1c (%)		
Baseline mean	8.3	8.3
Change from baseline [adjusted mean (SE)] [a]	-0.8 (0.03)	-0.4 (0.04)
Difference from placebo [adjusted mean] (95% CI)	-0.4 (-0.5,-0.4)*	
Proportions of patients (%) achieving HbA1c < 7% [b]	29%	17%
FPG (mg/dL)		
Baseline mean	166	142
Change from baseline [adjusted mean (SE)] [c]	-23(1)	-4(2)
Difference from placebo [adjusted mean] (95% CI)	-20 (-24, -15)	

SE:Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose
*Statistically significant (multiplicity adjusted one-sided p-value <0.025)
[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 24 (7% and 6% for bexagliflozin and placebo, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, region, baseline eGFR category (< 60 or ≥ 60 mL min^{-1} per 1.73m^2), baseline BMI category (< 25 or ≥ 25 kg/m^2), history of heart failure (yes or no), insulin use or not, and baseline HbA1c value.
[b] Crude proportion using imputed HbA1c values for missing data at week 24 and averaged across multiply imputed datasets
[c] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.

4.6 USE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND MODERATE RENAL IMPAIRMENT

A total of 312 patients with inadequately controlled type 2 diabetes mellitus (7.0% ≤ HbA1c ≤ 10.5%) and a baseline eGFR between 30 and 60 mL/min/1.73 m^2 received bexagliflozin or placebo in a double-blind, randomized, placebo-controlled study, C-448 (NCT02836873) to evaluate the safety and efficacy of bexagliflozin in diabetic patients with moderate renal impairment. In this study, 202 patients exposed to bexagliflozin had an eGFR between 45 and 60 mL/min/1.73 m2 and 111 patients exposed to bexagliflozin had an eGFR between 30 and 45 mL/min/1.73 m^2. The mean duration of diabetes for the study population was approximately 14 years, and the majority of patients were receiving background insulin (55.9%) and/or sulfonylurea (40.3%) therapy. Approximately 50% had a history of cardiovascular disease or heart failure. At week 24, treatment with bexagliflozin provided statistically significant reductions in HbA1c compared to placebo. The efficacy results are summarized in Table 6.[1,e] Bexagliflozin also resulted in a greater proportion of patients achieving an HbA1c <7%.

Table 6: Results at week 24 from a placebo-controlled study evaluating bexagliflozin as a therapy added to standard of care regimens for diabetic patients with stage 3 chronic kidney disease[1,e]

	Bexagliflozin N = 157	**Placebo N = 155**

	Bexagliflozin N = 157	Placebo N = 155
HbA1c (%)		
Baseline mean	8.0	7.9
Change from baseline [adjusted mean (SE)] [a]	-0.6 ((b) (4))	-0.3 ((b) (4))
Difference from placebo [adjusted mean] (95% CI)	-0.3 (-0.4, -0.1)*	
Proportions of patients (%) achieving HbA1c < 7% [b]	33%	22%
FPG (mg/dL)		
Baseline mean	156	155
Change from baseline [adjusted mean (SE)] [c]	-22 (3)	-8 (3)
Difference from placebo [adjusted mean] (95% CI)	-14 (-23, -5)	

SE:Standard Error; CI: Confidence Interval; FPG: Fasting plasma glucose
*Statistically significant (multiplicity adjusted one-sided p-value <0.025)
[a] Intention to treat population. ANCOVA was used to analyze data using imputed values for missing data at week 24 (3% and 5% for bexagliflozin and placebo, respectively) are imputed using return to baseline analysis. The ANCOVA model included treatment, treatment, region, screening anti-diabetic treatment regimen (insulin treated or other), baseline eGFR (< 45 or ≥ 45 mL min^{-1} per 1.73m^2) and baseline HbA1c value.
[b] Crude proportion using imputed HbA1c values for missing data at week 24 and averaged across multiply imputed datasets
[c] Same model as for HbA1c endpoint but with baseline FPG instead of baseline HbA1c as a covariate.

The clinical reviewer stated that the submitted clinical trial data provides evidence to support the efficacy of bexagliflozin for the proposed indication, as adjunct to diet and exercise to improve glycemic control in adults with T2DM. Data from the six phase 3 trials, which evaluated the use of bexagliflozin as monotherapy and in combination with other antihyperglycemic products, showed statistical superiority of bexagliflozin compared to placebo and non-inferioirty compared to active comparators. In addition, several trials enrolled distinct patient populations, including patients with increased CV risk and patients with renal impairment. In all trials, improvements in HbA1c were considered clinically meaningful, and the benefit of this product would be relevant to many patients with T2DM.[12,e]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were ongoing with the applicant. The following section is a summary of relevant safety information to date for bexagliflozin. The safety of bexagliflozin for use in T2DM was evaluated using a pool of one 12-week (C-449) and two 24-week placebo-controlled trials (C-419 & C-450) (see Section 4: Benefit Assessment). Bexagliflozin was used as monotherapy in two trials and as add-on therapy to metformin in one trial. In this pooled analysis, patients received placebo (N = 300) or bexagliflozin 20 mg (N = 372), once daily. The mean age of the population was 56 years and 5% were older than 75 years of age. Fifty-seven percent (57%) of the population was male and 45% were Caucasian, 38% were Asian, and 15% were Black or African American. At baseline, the mean duration of diabetes was 7.7 years, and the population had a mean hemoglobin A1c (HbA1c) of 8.2%. Established microvascular complications of diabetes at baseline included diabetic nephropathy (0.8%), retinopathy (23.8%), and peripheral neuropathy (32.9%). Baseline renal function was normal or mildly impaired in 97.8% of patients and moderately impaired in 2.2% of patients (mean eGFR 92.2 mL/min/1.73 m^2).

The safety was also evaluated in a trial (C-476) enrolling patients with type 2 diabetes mellitus who had either established cardiovascular disease or were at increased risk for cardiovascular disease (see Section 4: Benefit Assessment). Patients on standard of care therapy for diabetes management were randomized to receive placebo (N=567) or bexagliflozin (N=1132) for a minimum duration of 52 weeks (median duration 2.4 years). The mean age of the population was 64 years and 11% were older than 75

years of age. Seventy percent (70%) of the population was male and 77% were Caucasian, 10% were Asian, and 4% were Black or African American. At baseline, the mean duration of diabetes was 15 years and the population had a mean hemoglobin A1c (HbA1c) of 8.2. Baseline renal function was normal or mildly impaired in 80% of patients and moderately impaired in 20% of patients (mean eGFR 77.7 mL/min/1.73 m^2).

The overall safety profile of bexagliflozin was generally consistent with other trials conducted in the clinical program.[1] The most common adverse reactions (incidence > 5%) are female genital mycotic infections (GMI) (5.6%) and increased urination (6.6%).

Deaths

A total of 69 deaths occurred across all Phase 2b/3 trials (Broad Pool). The majority of deaths in the bexagliflozin clinical program occurred in the trial C-476, which enrolled patients with either established cardiovascular disease or multiple risk factors for cardiovascular morbidity. The clinical reviewer stated that an imbalance unfavorable to bexagliflozin in the preferred term (PT) of "cardiac arrest" was observed (1.0% versus 0.2% in the bexagliflozin and placebo groups, respectively). Narratives for the cardiac arrest events were reviewed and no apparent trend was observed, although some events contained incomplete information limiting interpretability. Overall, death data from the bexagliflozin clinical program indicates trends favorable to bexagliflozin; however, it is acknowledged that details on death events, and particularly non-cardiac death events, were limited.[12,13]

Serious Adverse Events (SAE)

The incidence of SAEs was similar between treatment arms in the Placebo-Controlled Pool, occurring in 6 (1.7%) and 5 (1.6%) subjects in the bexagliflozin and placebo groups, respectively. Regarding AEs relevant to the SGLT2 inhibitor class, there were no meaningful imbalances for serious events of pyelonephritis (0.3% and 0.2% in the bexagliflozin and placebo groups, respectively) or AKI (0.8% and 0.7% in the bexagliflozin and placebo groups, respectively). Similarly, limited SAE data was obtained in C-448 and active-controlled trials (C-423, C-480), with no meaningful imbalances in the incidence of SAEs or events by SOC between treatment groups. The clinical reviewer stated that urinary tract infections (UTI), including serious events of Urosepsis/Pyelonephritis, diabetic ketoacidosis (DKA), and GMI are considered class effects proposed for labeling. SAE data from these trials therefore does not raise new safety concerns.

Most SAEs were observed in C-476. In C-476, AEs leading to discontinuation were balanced between treatment groups (8.4% and 8.5% of subjects in the bexagliflozin and placebo groups having an AE leading to discontinuation, respectively).12 The clinical reviewer stated that as this trial enrolled patients with increased CV risk, cardiac events are expected in the enrolled population and some imbalances in individual PTs due to chance may be expected. Moreover, the Major Adverse Cardiac Events (MACE) meta-analysis did not identify a risk for MACE with bexagliflozin and provided reassuring evidence of cardiac safety.

Several imbalances unfavorable to bexagliflozin involving infection-related events were observed in C-476, including sepsis/septic shock (1.1% subjects in the bexagliflozin group versus 0.2% in placebo group), osteomyelitis (0.9% subjects in the bexagliflozin group versus 0.2% subject in the placebo group), and localized infection (1.1% subjects in the bexagliflozin group versus 0.4% subject in the placebo group), and cellulitis (0.8% subjects in the bexagliflozin group versus 0.2% subject in the placebo

group). Amputation is a serious and clinically meaningful consequence of osteomyelitis and skin infections, including cellulitis (see Section 5.1).

Similar to other SGLT2 inhibitors, such as ertugliflozin (Steglatro)[10], if approved, labeling will include the risks of ketoacidosis, lower limb amputations, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's Gangrene), and genital mycotic infections in the Warnings and Precautions section.

5.1 KETOACIDOSIS

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, have been identified in clinical trials and post-marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving SGLT2 inhibitors. In trial C-476, there were more events of confirmed diabetic ketoacidosis (DKA) in the placebo group as compared to the bexagliflozin group (bexagliflozin: 1 event (0.09%), placebo: 3 events (0.5%)). This imbalance became increasingly favorable to drug when events adjudicated as confirmed or probable DKA were pooled (bexagliflozin: 1 event (0.09%), placebo: 5 events (0.9%)).[12,13] The clinical reviewer stated that overall, the DKA monitoring, and assessment procedures appear adequate to have identified and consistently classified events. While the small number of DKA events in the clinical program limits interpretability, it is reassuring that an excess of DKA events were not observed with bexagliflozin exposure.[12]

The labeling will instruct prescribers to consider factors in the patient's history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse before initiating bexagliflozin, and to consider temporarily discontinuation of bexagliflozin for at least 3 days prior to surgery for patients who undergo scheduled surgery. The labeling also recommends considering monitoring for ketoacidosis and temporarily discontinuing bexagliflozin in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery) and ensure risk factors for ketoacidosis are resolved prior to restarting bexagliflozin. The labeling also instructs healthcare providers to educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue bexagliflozin and seek medical attention immediately if signs and symptoms occur.[1]

5.2 LOWER LIMB AMPUTATION

The data from C-476 indicated an increased risk of amputation with bexagliflozin treatment as compared to placebo (HR: 1.64 (0.70, 3.82); 8.3 versus 5.1 events per 1000 patient-years).[12] Amputations of the toe and midfoot (15 out of 23 patients with amputations receiving bexagliflozin) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (8 out of 23 patients with amputations receiving bexagliflozin). Some patients had multiple amputations. Lower limb infections, gangrene, ischemia, and osteomyelitis were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy. Similar to ertugliflozin (Steglatro)[10], labeling instructs healthcare providers to consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers, before initiating bexagliflozin. Labeling also instructs to counsel patients about the importance of routine preventative foot care, and to monitor patients receiving bexagliflozin for signs and symptoms of infection (including osteomyelitis),

new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue bexagliflozin if these complications occur.[1]

Other adverse events that bexagliflozin has in common with currently approved SGLT2 inhibitors, such as ertugliflozin (Steglatro)[10], will likely be communicated in the Warnings and Precautions section of the bexagliflozin label as well. These adverse events include: volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's Gangrene), and genital mycotic infections.[1] Similar to other SGLT2 inhibitors, if approved, labeling, including information in Patient Counseling Information, and the Medication Guide will be used to communicate the safety issues and management of toxicities associated with bexagliflozin. Similar to other SGLT2 inhibitors, labeling will also include a limitation of use statement as bexagliflozin alfa-vuxw is not recommended in type 1 diabetes mellitus patients as it may increase the risk of diabetic ketoacidosis in these patients.

6 Expected Postmarket Use

Similar to other SGLT2 inhibitors, if approved, bexagliflozin is expected to be prescribed by a wide variety of healthcare providers, including endocrinologists, primary care physicians and midlevel providers, often involved in the care of outpatient, ambulatory care diabetic patients. Adverse events of SGLT2 inhibitors have been well documented in the literature and prescribers are likely aware of the care and management of these patients.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS with this application; but proposed a non-REMS risk management plan consisting of labeling and routine pharmacovigilance.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for bexagliflozin, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Bexagliflozin is a SGLT2 inhibitor, with the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Diabetes remains the 7th leading cause of death in the US. While lifestyle modifications and metformin are the cornerstone of the initial management of T2DM, there are different families of oral and injectable drugs, available for the treatment of T2DM, which include sulfonylureas, meglitinides, insulin, thiazolidinediones and alpha-glucosidase inhibitors, GLP1 receptor agonists, DPP4 and SGLT2 inhibitors. Despite major advances in primary and secondary prevention of the past 50 years, patients with diabetes still are at increased risks of CVD relative to those without diabetes. Therefore, there remains a clear medical need to develop new therapies for the treatment of this serious and life-threatening rare disease.

Based on the efficacy and safety information currently available, the clinical reviewer stated that bexagliflozin shows clinically meaningful benefit and recommends approval of bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM with the following

Limitation of Use statement: Not recommended in patients with type 1 diabetes mellitus; it may increase the risk of diabetic ketoacidosis in these patients.[12] There were no issues identified that should be addressed by a postmarketing requirement (PMR) or commitment (PMC) aside from the pediatric study required under the Pediatric Research Equity Act (PREA) and the manufacturing PMCs described in Section 9 of the Integrated Review.[12]

DRM and DDLO have determined that if approved, a REMS is not necessary to ensure the benefits of bexagliflozin outweigh its risks. Bexagliflozin appeared efficacious in its primary outcome of significant reductions in the HbA1c at week 24, and its risks can be communicated and managed through labeling.[1,12] The clinical reviewer stated that the data from the six phase 3 trials, which evaluated the use of bexagliflozin as monotherapy and in combination with other antihyperglycemic products, showed statistical superiority of bexagliflozin compared to placebo and non-inferiority compared to active comparators. In addition, several trials enrolled distinct patient populations, including patients with increased CV risk and patients with renal impairment. In all trials, improvements in HbA1c were considered clinically meaningful, and the benefit of this product would be relevant to many patients with T2DM.[12] The most concerning adverse reactions observed with the use of bexagliflozin are risks for ketoacidosis, lower limb amputations, volume depletion, urosepsis and pyelonephritis, hypoglycemia with concomitant use with insulin and insulin secretagogues, necrotizing fasciitis of the perineum (Fournier's Gangrene), and genital mycotic infections, which are the same as in the currently approved SGLT2 inhibitors, such as ertugliflozin (Steglatro).[10] Since adverse events of SGLT2 inhibitors have been well documented in the literature, it is expected that the likely prescribers are aware of the care and management of these patients. The review team concluded that there are no new safety findings observed in the bexagliflozin clinical development program that significantly impact the overall risk profile.[12] With the exception of canagliflozin (Invokana), the SGLT2 inhibitor class does not include a Boxed Warning. Canagliflozin was initially approved in March 2013 with a boxed warning for lower limb amputaion, which was removed in August 2020. None of the SGLT2 inhibitor products required REMS for approval. The applicant did not submit a REMS with this application; but proposed a non-REMS risk management plan consisting of labeling and routine pharmacovigilance. If bexagliflozin is approved, similar to ertugliflozin (Steglatro), Warnings and Precautions in the labeling will be used to communicate the safety issues and management of toxicities associated with bexagliflozin, as well as information to be included in Patient Counseling Information, and a Medication Guide as part of labeling to inform patients regarding the potential risks.

9 Conclusion & Recommendations

DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The management of the risks associated with bexagliflozin treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 References

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[13] Division of Diabetes, Lipid Disorders, and Obesity (DDLO). Efficacy and Safety Review Presentation. Mid-Cycle Meeting, dated March 28, 2022.

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/s/

TILL OLICKAL
01/10/2023 10:02:26 AM

NAOMI S BOSTON
01/10/2023 02:27:09 PM

LAURA A ZENDEL
01/10/2023 05:56:05 PM