

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214373Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	214373
Priority or standard	Standard
Submit date(s)	10/22/2021
Received date(s)	10/22/2021
PDUFA goal date	1/22/2023
Division/office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Review completion date	1/19/2023
Established/proper name	Bexagliflozin
(Proposed) proprietary name	Brenzavvy
Pharmacologic class	Sodium-glucose cotransporter 2 (SGLT2) inhibitor
Code name	N/A
Applicant	TheracosBio LLC
Dosage form(s)/formulation(s)	Tablet
Dosing regimen	20 mg orally once daily
Applicant proposed indication(s)/ population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Proposed SNOMED indication	Diabetes mellitus type 2 (disorder) SCTID: 44054006
Regulatory action	Approval
Approved dosage (if applicable)	20 mg
Approved indication(s)/ population(s) (if applicable)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Approved SNOMED term for indication (if applicable)	Diabetes mellitus (disorder) SCTID: 73211009

Table of Contents

Table of Tables	xi
Table of Figures	xxii
Glossary	1
I. Executive Summary	4
1. Summary of Regulatory Action	4
2. Benefit-Risk Assessment.....	7
2.1. Benefit-Risk Framework	7
2.2. Conclusions Regarding Benefit-Risk	12
II. Interdisciplinary Assessment.....	14
3. Introduction	14
3.1. Review Issue List.....	14
3.1.1. Key Review Issues Relevant to Evaluation of Benefit	14
3.1.1.1. Efficacy of Bexagliflozin in Subjects With Moderate Renal Impairment	14
3.1.2. Key Review Issues Relevant to Evaluation of Risk.....	14
3.1.2.1. Increased Risk of Nontraumatic Amputation With Bexagliflozin Treatment.....	14
3.1.2.2. Safety of Bexagliflozin in Subjects With Moderate Renal Impairment	14
3.1.2.3. Safety Database Quality Concerns	15
3.2. Approach to the Review	15
4. Patient Experience Data	20
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology	21
5.1. Nonclinical Assessment of Potential Effectiveness.....	24
6. Assessment of Effectiveness	26
6.1. Dose and Dose Responsiveness.....	26
6.2. Clinical Trials Intended to Demonstrate Efficacy	28
6.2.1. Study Design	28
6.2.2. Statistical Analysis Plan.....	35
6.2.3. Results of Analyses.....	38
6.2.3.1. Demographics, Baseline Characteristics, and Disposition	38
6.2.3.2. Primary Efficacy Results, Sensitivity, and Subgroup Analyses.....	43

6.2.3.3. Key Secondary Efficacy Results	47
6.3. Key Review Issue Relevant to Evaluation of Benefit	50
6.3.1. Efficacy of Bexagliflozin in Subjects With Moderate Renal Impairment	50
7. Risk and Risk Management.....	60
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	60
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	61
7.3. Potential Safety Concerns Identified Through Postmarket Experience	62
7.4. FDA Approach to the Safety Review	62
7.4.1. Data Pooling.....	62
7.4.2. Categorization of Adverse Events.....	63
7.4.3. Data Querying	64
7.5. Adequacy of Clinical Safety Database	64
7.5.1. Exposure.....	64
7.5.2. Characteristics of the Safety Population	65
7.5.3. Exposure per FDA’s Draft Guidance Recommendations	67
7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database.....	69
7.6.1. Safety Findings and Concerns.....	69
7.6.1.1. Overall Treatment-Emergent Adverse Event Summary.....	69
7.6.1.2. Deaths	70
7.6.1.3. Serious Adverse Events	73
7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events	77
7.6.1.5. Treatment-Emergent Adverse Events.....	78
7.6.1.6. Laboratory Findings	84
7.7. Key Review Issues Relevant to Evaluation of Risk	84
7.7.1. Increased Risk of Nontraumatic Amputation With Bexagliflozin Treatment	84
7.7.2. Safety of Bexagliflozin in Subjects With Moderate Renal Impairment	89
7.7.3. Safety Database Quality Concerns.....	99
8. Therapeutic Individualization	104
8.1. Intrinsic Factors	104

8.2. Food Effect	105
8.3. Drug Interactions	105
8.3.1. DDI Potential as a Victim	107
8.3.2. DDI Potential as a Perpetrator.....	108
8.3.3. DDI Potential With Commonly Prescribed Antidiabetic Agents	108
8.4. Plans for Pediatric Drug Development	109
8.5. Pregnancy and Lactation.....	109
9. Product Quality	111
9.1. Device or Combination Product Considerations	112
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure.....	112
11. Advisory Committee Summary	112
III. Appendices.....	113
12. Summary of Regulatory History	113
12.1. General Regulatory History	113
12.2. Statistical Regulatory History	116
13. Pharmacology Toxicology: Additional Information and Assessment	121
13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application	121
13.1.1. Pharmacology.....	121
13.1.1.1. Primary Pharmacology	121
13.1.1.2. Secondary Pharmacology	121
13.1.1.3. Safety Pharmacology	121
13.1.1.4. Toxicology.....	128
13.2. Individual Reviews of Studies Submitted to the New Drug Application..	153
14. Clinical Pharmacology: Additional Information and Assessment	153
14.1. In Vitro Studies.....	153
14.1.1. Protein Binding (Study THR-1474-N-371)	153
14.1.2. Protein Binding (Study THR-1442-C-424).....	154
14.1.3. Protein Binding (Study THR-1442-C-455).....	154
14.1.4. In Vitro Metabolism in Human Liver Microsomes (Study THR- 1474-N-341).....	155
14.1.5. In Vitro Metabolism by Recombinant CYP3A (Study THR-1474- N-367)	155

14.1.6. In Vitro Metabolism by Human Liver Microsomes and Recombinant UGT (Study THR-1474-N-377)	156
14.1.7. In Vitro CYP and UGT Phenotyping by Recombinant Human CYP and UGT Enzymes (Study THR-1442-N-440)	157
14.1.8. Identification of Additional Metabolites (Study THR-1474-N-382)..	159
14.1.9. In Vivo Metabolic Profiling Study of Bexagliflozin Metabolites (Study THR-1442-N-403).....	160
14.1.10. Inhibitory Effect of Bexagliflozin on CYP450 Activities (Study THR-1474-N-346).....	160
14.1.11. Induction Effect of Bexagliflozin on CYP450 Activities (Study THR-1474-N-347).....	161
14.1.12. Inhibitory Effect of Bexagliflozin on CYP2C8 Activity (Study THR-1442-N-439).....	162
14.1.13. In Vitro Permeation of Bexagliflozin Through Caco-2 Monolayers (Study THR-1442-N-431).....	163
14.1.14. P-gp Substrate and Inhibitory Potential (Study THR-1442-N-432) .	164
14.1.15. Inhibitory Effect of Bexagliflozin on Transporters (Study THR-1442-N-441).....	164
14.1.16. Transporters Substrate and Inhibitory Potential (Study THR-1442-N-491)	165
14.2. In Vivo Studies	166
14.2.1. Single and Multiple Dose in Healthy Subjects (Trial C-328)	166
14.2.2. SAD Study in Patients With Type 2 Diabetes (Trial C-396)	169
14.2.3. SAD and MAD Study in Healthy Subjects and Patients With T2DM (Trial C-445)	172
14.2.4. Mass Balance Study (Trial C-410).....	178
14.2.5. Food Effect Study (Trial C-481)	180
14.2.6. Formulation Development (Trial CLR-002).....	181
14.2.7. Effect of Hepatic Impairment (Trial C-455)	185
14.2.8. Effect of Renal Impairment (Trial C-424)	186
14.2.9. Effect of Probenecid, Rifampin, and Verapamil on PK/PD of Bexagliflozin (Trial C-454).....	190
14.2.10. Effect of Exenatide on Bexagliflozin (Trial C-458)	191
14.2.11. Effect of Bexagliflozin on the PK of Metformin, Glimepiride or Sitagliptin (Trial C-453).....	194
14.2.12. Dose-Finding Study Using FPG (Trial C-402)	196

14.2.13. Dose-Finding Study by HbA1c (Trial C-449)	198
14.2.14. Effects on QT Prolongation (Trial C-428)	201
14.3. Pharmacometrics Review	202
14.3.1. Review Summary	202
14.3.2. Introduction	202
14.3.3. Model Development	203
14.3.4. Final Model	209
14.3.5. Reviewer's Independent Analysis	216
14.3.5.1. Introduction	216
14.3.5.2. Objectives	217
14.3.5.3. Methods	217
14.3.5.4. Results	217
14.4. Summary of Bioanalytical Method Validation and Performance	218
15. Trial Design: Additional Information and Assessment	221
15.1. Phase 3 Protocol Synopses	221
15.1.1. Clinical Protocol Synopsis for C-419 (Version 1.0, Date: July 26, 2017)	221
15.1.2. Clinical Protocol Synopsis for C-423 (Version 2.0, Date: April 06, 2017)	225
15.1.3. Clinical Protocol Synopsis for C-448 (Version 4.0, Date: October 25, 2016)	230
15.1.4. Clinical Protocol Synopsis for C-450 (Version 4.0, Date: April 04, 2017)	234
15.1.5. Clinical Protocol Synopsis for C-476 (Version 8.0, Date: October 28, 2016)	238
15.1.6. Clinical Protocol Synopsis for C-480 (Version 3.0, Date: October 27, 2016)	246
16. Efficacy: Additional Information and Assessment	252
16.1. Bexagliflozin for T2DM Clinical Program	252
16.2. Trial Design Overview	252
16.3. Statistical Analysis Plan Overview	252
16.3.1. Primary Efficacy Endpoint	252
16.3.2. Key Secondary Efficacy Endpoints	253
16.3.2.1. Labeling Considerations on the Key Secondary Efficacy Endpoints	253

16.3.2.2. Other Secondary Efficacy Endpoint: Proportion of Subject Reaching HbA1c <7% at Week 24/60.....	253
16.3.3. Analysis Set.....	254
16.3.4. Analysis Method	254
16.3.4.1. Primary Analysis Method – Regulatory Interaction History	254
16.3.4.2. Primary Analysis Method – A Return-to-Baseline Coupled ANCOVA	255
16.3.4.3. Primary Endpoint – Subgroup Analysis Methods	257
16.3.4.4. Exploration of Potential Modulation Effect of Baseline HbA1c Levels	258
16.3.4.5. Primary Endpoint – Tipping Point Sensitivity Analysis Method.....	258
16.3.4.6. Secondary Endpoint – Primary Analysis Method	259
16.3.4.7. Multiple Testing Procedures.....	259
16.4. Primary and Key Secondary Efficacy Results.....	260
16.4.1. Trial C-450	260
16.4.1.1. Design, Trial C-450	260
16.4.1.2. Statistical Analysis Plan, Trial C-450	261
16.4.1.3. Results of Analyses, Trial C-450.....	262
16.4.2. Trial C-419	270
16.4.2.1. Design, Trial C-419	270
16.4.2.2. Statistical Analysis Plan, Trial C-419	271
16.4.2.3. Results of Analyses, Trial C-419.....	271
16.4.3. Trial C-423	278
16.4.3.1. Design, Trial C-423	278
16.4.3.2. Statistical Analysis Plan, Trial C-423	279
16.4.3.3. Results of Analyses, Trial C-423.....	279
16.4.4. Trial C-480	287
16.4.4.1. Design, Trial C-480	287
16.4.4.2. Statistical Analysis Plan, Trial C-480	289
16.4.4.3. Results of Analyses, Trial C-480.....	289
16.4.5. Trial C-448	297
16.4.5.1. Design, Trial C-448	297
16.4.5.2. Statistical Analysis Plan, Trial C-448	297

16.4.5.3. Results of Analyses, Trial C-448.....	297
16.4.6. Trial C-476	306
16.4.6.1. Design, Trial C-476	306
16.4.6.2. Statistical Analysis Plan, Trial C-476	306
16.4.6.3. Results of Analyses, Trial C-476.....	306
16.5. Secondary Efficacy Endpoints Analysis Results.....	316
16.5.1. Trial C-450	316
16.5.2. Trial C-419	317
16.5.3. Trial C-423	319
16.5.4. Trial C-480	321
16.5.5. Trial C-448	323
16.5.6. Trial C-476	324
16.6. Primary Endpoint Sensitivity Analysis Results.....	327
16.6.1. Trial C-450	327
16.6.2. Trial C-419	328
16.6.3. Trial C-423	329
16.6.4. Trial C-480	330
16.6.5. Trial C-448	333
16.6.6. Trial C-476	334
17. Clinical Safety: Additional Information and Assessment	335
17.1. MACE Meta-Analysis	335
17.1.1. Data Sources.....	335
17.1.2. Data Quality	335
17.1.3. Summary of Study Design	335
17.1.4. Statistical Methodology	340
17.1.4.1. Analysis Populations and Cardiovascular Events Ascertainment	340
17.1.4.2. Analysis Methods for Cardiovascular Endpoints	341
17.1.5. Subject Disposition, Demographics and Baseline Characteristics.....	343
17.1.5.1. Subject Disposition.....	343
17.1.5.2. Demographics and Baseline Characteristics	347
17.1.6. Meta-Analysis Results and Conclusion	348
17.1.6.1. Descriptive Summary of Safety Outcomes	348

17.1.6.2. Meta-Analysis Results	348
17.1.7. Findings in Subgroup Populations	354
17.1.8. Summary and Conclusions	355
17.1.8.1. Statistical Issues	355
17.1.8.2. Collective Evidence	355
17.1.8.3. Conclusions and Recommendations	356
17.2. Applicant's Approach to the Safety Review	356
17.3. Submission-Specific Safety Issues	357
17.3.1. Fracture	357
17.3.2. Falls	362
17.3.3. Malignancy	363
17.3.4. Hypersensitivity and Rash	366
17.3.5. Hepatic Injury	368
17.3.6. DKA	370
17.3.7. Renal Events	373
17.3.8. Volume Depletion/Hypotension Events	377
17.3.9. UTI Including Pyelonephritis and Urosepsis	378
17.3.10. GMI	379
17.3.11. Hypoglycemia	380
17.3.12. Fournier's Gangrene	381
17.3.13. Revascularization Procedures	382
17.3.14. Cardiovascular Safety	382
17.4. Laboratory Findings	383
17.5. Vital Signs	403
17.6. QT	404
17.7. Safety Analyses by Demographic Subgroups	405
18. Mechanism of Action/Drug Resistance: Additional Information and Assessment	408
19. Other Drug Development Considerations: Additional Information and Assessment	408
20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)	408
21. Labeling Summary of Considerations and Key Additional Information	408

NDA 214373
Brenzavvy (bexagliflozin)

22. Postmarketing Requirements and Commitments	411
23. Financial Disclosure	412
24. References	412
25. Review Team.....	416

Table of Tables

Table 1. Administrative Application Information	i
Table 2. Benefit-Risk Framework.....	7
Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for Bexagliflozin	16
Table 4. Patient Experience Data.....	20
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics	21
Table 6. Activity and Selectivity of Bexagliflozin	24
Table 7. Blood Glucose Reduction in Rats	25
Table 8. Blood Glucose Reduction in Dogs	25
Table 9. Summary of Key Inclusion and Exclusion Criteria in Pivotal Efficacy Trials....	32
Table 10. Summary of Key Secondary Endpoints in Pivotal Efficacy Trials	35
Table 11. Baseline Demographic and Clinical Characteristics, Pivotal Efficacy Trials ...	39
Table 12. Analysis Populations and Subject Disposition, Phase 3 Efficacy Trials	42
Table 13. Primary Analysis* Results for HbA1c (%) Change From Baseline at Week 24 (Week 60 in Trial C-480).....	43
Table 14. Treatment Difference in HbA1c (%) by Baseline Demographic and Disease Factors, Trial C-476.....	46
Table 15. Key Secondary Endpoints (Shown in the Order of the Testing Hierarchy): Change From Baseline at Week 24, Return-to-Baseline Analysis Results, ITT Population	47
Table 16. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Trial C-448.....	53
Table 17. Treatment Difference in HbA1c (%) by Baseline Renal Function, Trial C- 448.....	54
Table 18. Treatment Difference in HbA1c (%) by Baseline Renal Function, ITT, Trial C-476.....	57
Table 19. Subjects Experiencing Treatment Intensification and Relaxation in Subjects by Baseline eGFR, Safety Population, Trial C-476.....	57
Table 20. Selected Labeled Safety Information for Approved SGLT2 Inhibitors	61
Table 21. Duration of On-Treatment Exposure, Safety Population, Broad Pool	65
Table 22. Duration of On-Treatment Exposure, Safety Population, Placebo- Controlled Pool	65
Table 23. Baseline Demographics and Clinical Characteristics, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448	66

Table 24. Comparison of Bexagliflozin’s Development Program to FDA’s Draft Guidance for Industry for Evaluating the Safety of New Drugs for Improving Glycemic Control.....	69
Table 25. Overview of AEs, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448.....	70
Table 26. Deaths Due to AEs by Adjudication Category, Safety Population, Trial C-476.....	71
Table 27. Deaths Due to AEs by SOC and PT as Sorted by SOC RD, Safety Population, Trial C-476	71
Table 28. SAEs by PT Reported by at Least Two Subjects in the Bexagliflozin Group With RD ≥ 0.1 , Safety Population, Trial C-476	75
Table 29. SAEs With RD ≥ 0.2 by FMQ Sorted by RD, Safety Population, Trial C-476..	76
Table 30. Subjects With AEs Leading to Treatment Discontinuation by PT Sorted by RD, Safety Population, Placebo-Controlled Pool	77
Table 31. Subjects With AEs Leading to Treatment Discontinuation by FMQ With RD ≥ 0.1 Sorted by RD, Safety Population, Trial C-476	78
Table 32. AEs Occurring in $\geq 2\%$ of Subjects in the Bexagliflozin Group and Greater and Placebo Sorted by GQ RD, Safety Population, Placebo-Controlled Pool	79
Table 33. Subjects With AEs by FMQ With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Placebo-Controlled Pool.....	80
Table 34. Subjects With Tendinopathy (FMQ) Events as Sorted by RD, Safety Population, Trial C-476	81
Table 35. FMQs With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Trial C-476.....	82
Table 36. Subjects With AEs by PT With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Trial C-476	82
Table 37. AESIs by Applicant-Derived CMQs, Safety Population, Trial C-476.....	84
Table 38. On-Study Analysis Results of Nontraumatic Amputations, Safety Population, Trial C-476	86
Table 39. On-Treatment +14 Days Analysis Results of Nontraumatic Amputations, Safety Population, Trial C-476	87
Table 40. Incidence of Nontraumatic Amputations in Subjects With Baseline Disease History, Safety Population, Trial C-476	88
Table 41. Anatomical Location of Amputation Events and Underlying Causes, Safety Population, Trial C-476	88
Table 42. Overview of AEs, Safety Population, Trial C-448	90
Table 43. Overview of AEs in Subjects With Baseline eGFR < 60 mL/min/1.73 m ² , Safety Population, Trial C-476	90
Table 44. Subjects With SAEs by PT Sorted by RD, Safety Population, Trial C-448.....	91

Table 45. Subjects With AEs Leading to Treatment Discontinuation by PT Sorted by RD, Safety Population, Trial C-448.....	92
Table 46. SAEs in Subjects With Baseline eGFR <60 mL/min/1.73 m ² by FMQ With RD >0, Safety Population, Trial C-476	92
Table 47. AEs Leading to Treatment Discontinuation in Subjects With Baseline eGFR <60 mL/min/1.73 m ² by PT as Sorted by RD, Safety Population, Trial C-476.....	93
Table 48. AEs Occurring in ≥2% of Subjects Treated With Bexagliflozin and Greater Than Placebo, Safety Population, Trial C-448	94
Table 49. Subjects With AEs by FMQ Safety Population With RD >0% as Sorted by RD, Trial C-448	95
Table 50. AEs in Subjects With Baseline eGFR <60 mL/min/1.73 m ² by FMQ With RD ≥0.5 as Sorted by RD, Safety Population, Trial C-476	97
Table 51. Patients With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial C-448.....	99
Table 52. Comparison of FMQ Analyses From ISS ADAE Versus NLP-Modified ISS ADAE Datasets, Safety Population, Trial C-476.....	101
Table 53. Nonclinical Data Supporting Labeling	110
Table 54. Summary of Regulatory History – Statistical Advice – Efficacy	118
Table 55. Safety Pharmacology Studies	121
Table 56. Pharmacokinetic Parameters of Bexagliflozin Following Single Oral Doses	123
Table 57. Composition of Radiolabel in Excreta (% of Input Label)	124
Table 58. Toxicokinetic Studies	125
Table 59. Study Information for 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study in Rats.....	129
Table 60. Observations and Results for 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study in Rats.....	129
Table 61. Study Information for 39-Week Nasogastric Intubation Toxicity and Toxicokinetics Study in Cynomolgus Monkeys	131
Table 62. Observations and Results: for 39-Week Nasogastric Intubation Toxicity and Toxicokinetics Study in Cynomolgus Monkeys	131
Table 63. Genetic Toxicology Studies.....	133
Table 64. Study Information for Oral Gavage Study of Fertility and Early Embryonic Development to Implantation With Bexagliflozin in Rats	135
Table 65. Observations and Results for Oral Gavage Study of Fertility and Early Embryonic Development to Implantation With Bexagliflozin in Rats.....	135

Table 66. Study Information for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rats	138
Table 67. Observations and Results for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rats	138
Table 68. Study Information for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rabbits	141
Table 69. Observations and Results for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rabbits	141
Table 70. Study Information for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats	144
Table 71. Observations and Results for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats, F0-Generation Dams	144
Table 72. Observations and Results for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats, F1-Generation	147
Table 73. Toxicokinetics for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats	148
Table 74. Study Information for 10-Week Toxicity Study of Bexagliflozin by Oral Administration (Gavage) in Juvenile Rats With a 4-Week Recovery Period	149
Table 75. Observations and Results for 10-Week Toxicity Study of Bexagliflozin by Oral Administration (Gavage) in Juvenile Rats With a 4-Week Recovery Period	150
Table 76. Reproductive Toxicity Safety Margins	153
Table 77. Free Fraction (Mean ± SD) of Bexagliflozin in Plasma at 20-mg Dose	154
Table 78. Distribution of Metabolites as a % of Total Metabolite Formation Following Incubations in the Presence and Absence of Human Liver Microsomes (1 mg/mL; 37°C) at 100 µM [¹⁴ C] Bexagliflozin	155
Table 79. The SIM Chromatogram Peak Response of Bexagliflozin and Its Metabolites After Incubation With CYP3A4 Isoenzyme	156
Table 80. Metabolism of Bexagliflozin in Recombinant Human CYP Enzymes	158
Table 81. Metabolism of Bexagliflozin in Recombinant Human UGT Enzymes	158
Table 82. Detected Plasma and Urine Metabolites Following Oral Administration 100 mg Bexagliflozin	160
Table 83. Summary of Inhibition Assays	161
Table 84. Impact of Bexagliflozin on Enzyme Activities of CYP1A2, 2C19 and 3A4	162
Table 85. Potential of Bexagliflozin as an Inhibitor of Human CYP2C8	163
Table 86. Papp and Efflux Ratio of Bexagliflozin and Internal Standard (×10 ⁻⁶ cm/s)	163

Table 87. Inhibitory Effect of Bexagliflozin on Drug Transporters BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2	165
Table 88. Inhibitory Effect of Bexagliflozin and Its Metabolite EGT0002149 on MATE1 and MATE2-K.....	165
Table 89. Substrate Determination for Bexagliflozin and its Metabolite EGT0002149	166
Table 90. Summary of Mean (SD) Bexagliflozin PK Parameters Following Single and Multiple Doses of EGT0001474.....	168
Table 91. Mean Bexagliflozin PK Parameters Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin) in Subjects With T2DM.....	171
Table 92. Mean UGE Values at Baseline and Different Time Intervals Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin) in Subjects With T2DM.....	171
Table 93. Effects on FPG in Subjects With T2DM	172
Table 94. Description of Treatment Plan, Trial C-445	173
Table 95. Summary of Bexagliflozin PK Parameters After Oral Administration of a Single Dose to Healthy Japanese Subjects in the Fed State.....	174
Table 96. Summary of Metabolite EGT0002149 PK Parameters After Oral Administration of a Single Dose of Bexagliflozin to Healthy Japanese Subjects in the Fed State.....	175
Table 97. Summary of UGE Rate (mg/min) After Oral Administration of a Single Dose to Healthy Japanese Subjects.....	175
Table 98. Summary of Bexagliflozin PK Parameters After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State	176
Table 99. Summary of Metabolite EGT0002149 PK Parameters After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State.....	177
Table 100. Summary of UGE Rate After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State	177
Table 101. Summary of FPG (mg/dL) After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State.....	177
Table 102. PK Parameters for [¹⁴ C] Bexagliflozin and Metabolites in Plasma.....	179
Table 103. Bexagliflozin PK Parameters Following Oral Administration Bexagliflozin Tablets, 20 mg Under Fasted Versus Fed Condition	181
Table 104. Summary PK Parameters for Bexagliflozin, Trial CLR-002 Part 1	183
Table 105. Summary PK Parameters for Bexagliflozin, Trial CLR-002 Part 2	183
Table 106. Summary UGE Parameters (mg), Trial CLR-002 Part 2.....	184

Table 107. Comparison of Total Bexagliflozin PK Parameters by Hepatic Function Group	186
Table 108. Comparison of Free Bexagliflozin PK Parameters by Hepatic Function Group	186
Table 109. PK Parameters of Bexagliflozin by Renal Function Group, PK Population	188
Table 110. Summary of 24-hr UGE (g) in T2DM Patients With Normal Renal Function, Mild, Moderate, and Severe Renal Impairment.....	189
Table 111. Bexagliflozin PK Parameters When Administered Alone or With Probenecid, Rifampin, and Verapamil.....	191
Table 112. Comparison of Bexagliflozin PK Parameters for Bexagliflozin vs. Bexagliflozin + Exenatide.....	192
Table 113. Mean Urinary Glucose Excretion	193
Table 114. Bexagliflozin PK Parameters When Taken With or Without Metformin, Glimepiride, and Sitagliptin.....	195
Table 115. PK Parameters of Metformin, Glimepiride, and Sitagliptin When Taken With or Without Bexagliflozin	195
Table 116. Primary Efficacy Analysis: ANCOVA Results on Mean Change in FPG (mg/dL) From Baseline to End of Treatment, Trial C-402, Segment 2.....	197
Table 117. Overall Summary of Treatment-Emergent Adverse Events	200
Table 118. Bexagliflozin PK Parameters Following Oral Administration of 100 mg Bexagliflozin Capsule.....	201
Table 119. Specific Comments on Applicant's Final Population PK Model	202
Table 120. Summary of Studies With PK Sampling Included in Population PK Analysis.....	204
Table 121. Summary of Baseline Demographic Covariates for PopPK Analysis by Population	206
Table 122. Covariates Tested for the Final PopPK Model	209
Table 123. Final PopPK Model Parameter Estimates.....	210
Table 124. Analysis Datasets	216
Table 125. Analysis Dataset	217
Table 126. Summary of Sample Size and Efficacy Endpoint by Treatment Groups	217
Table 127. Listing of Analyses Codes and Output Files	218
Table 128. Bioanalytical Method for Bexagliflozin (b) (4)	219
Table 129. Bioanalytical Method for Bexagliflozin, EGT0001494 and EGT0001301 (b) (4)	219
Table 130. Bioanalytical Method for EGT00021491 (b) (4)	220

Table 131. Bioanalytical Method for Bexagliflozin (b) (4)	220
Table 132. Bioanalytical Method for EGT0002149 (b) (4)	221
Table 133. Protocol History, Trial C-476	244
Table 134. Pivotal Study Milestones	255
Table 135. ANCOVA Model Covariates in Return-to-Baseline Variance Estimation by Study	256
Table 136. Primary and Key Secondary Efficacy Endpoints and Ranks in Orders.....	260
Table 137. Baseline Demographic and Clinical Characteristics, ITT, Trial C-450.....	262
Table 138. Subject Screening and Randomization, Trial C-450	263
Table 139. Subject Disposition, ITT, Trial C-450	264
Table 140. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-450	267
Table 141. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-450	267
Table 142. Baseline Demographic and Clinical Characteristics, ITT, Double-Blinded, Trial C-419.....	272
Table 143. Subject Screening and Randomization, Trial C-419	273
Table 144. Subject Disposition, ITT, Double-Blind Treatment Group, Trial C-419	274
Table 145. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-419	275
Table 146. Baseline Demographic and Clinical Characteristics, ITT, Trial C-423.....	280
Table 147. Subject Screening and Randomization, Trial C-423	281
Table 148. Subject Disposition, ITT, Trial C-423	282
Table 149. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-423	284
Table 150. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-423	285
Table 151. Baseline Demographic and Clinical Characteristics, ITT, Trial C-480.....	290
Table 152. Subject Screening and Randomization, Trial C-480	291
Table 153. Subject Disposition, ITT, Trial C-480	292
Table 154. Change From Baseline in HbA1c (%) at Week 60 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-480	294
Table 155. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 60, ITT , Return-to-Baseline Multiple Imputation, Trial C-480	295
Table 156. Baseline Demographic and Clinical Characteristics, ITT, Trial C-448.....	298

Table 157. Subject Screening and Randomization, Trial C-448	299
Table 158. Subject Disposition, ITT, Trial C-448	300
Table 159. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-448	302
Table 160. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-448	302
Table 161. Baseline Demographic and Clinical Characteristics, ITT, Trial C-476.....	307
Table 162. Subject Screening and Randomization, Trial C-476	308
Table 163. Subject Disposition, ITT, Trial C-476	309
Table 164. Change From Baseline in HbA1c (%) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476.....	311
Table 165. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-476	312
Table 166. Change From Baseline in SBP (mmHg) at Week 24, Return-to-Baseline Analysis Results, ITT, Trial C-450.....	316
Table 167. Change From Baseline in Weight (kg) at Week 24, Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m ² Subgroup, Trial C-450	316
Table 168. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-450.....	317
Table 169. Change From Baseline in SBP (mmHg) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419.....	317
Table 170. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m ² Subgroup, Trial C-419	318
Table 171. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419.....	319
Table 172. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423.....	319
Table 173. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423.....	320
Table 174. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m ² Subgroup, Trial C-423	320
Table 175. Change From Baseline in Weight (kg) at Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480.....	321
Table 176. Change From Baseline in SBP (mm Hg) at Week 60 Return-to-Baseline Analysis Results, ITT, Baseline SBP ≥ 140 mm Hg Subgroup, Trial C-480	322
Table 177. Change From Baseline in FPG (mg/dL) at Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480.....	322

Table 178. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m ² Subgroup, Trial C-448	323
Table 179. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline SBP ≥ 130 mm Hg Subgroup, Trial C-448	323
Table 180. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-448	324
Table 181. Change From Baseline in Weight (kg) at Week 48 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m ² Subgroup, Trial C-476	324
Table 182. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline SBP ≥ 140 mm Hg Subgroup, Trial C-476	325
Table 183. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476	326
Table 184. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-450	327
Table 185. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-419	328
Table 186. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-423	329
Table 187. Change From Baseline in HbA1c (%) at Week 60 Tipping Point Sensitivity Analysis, ITT, Trial C-480	330
Table 188. Change From Baseline in HbA1c (%) at Week 60 Tipping Point Sensitivity Analysis, ITT, Trial C-480	332
Table 189. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-448	333
Table 190. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-476	334
Table 191. Data Sources Used to Assess Cardiovascular Safety	335
Table 192. Summary of Trials Included in the Meta-Analysis	336
Table 193. Main Inclusion Criteria for Trials Included in the Meta-Analysis	337
Table 194. Aggregate Summary of Subject Disposition, Full Analysis Set	344
Table 195. Summary of Subject Disposition, Full Analysis Set, Trial C-476	345
Table 196. Subject Follow-Up Until Study Discontinuation, Full Analysis Set	345
Table 197. Summary of Treatment Exposure, Full Analysis Set	346
Table 198. Summary of Demographics and Baseline Characteristics, Full Analysis Set	347
Table 199. First MACE+ by Meta-Analysis Study and Treatment Group, Full Analysis Set, On-Study	348

Table 200. Primary Analysis Results of MACE+, Full Analysis Set, On-Study	348
Table 201. Analysis Results of MACE+ in Full Analysis Set, On-Study, Trial C-476 ..	349
Table 202. On-Treatment Analysis Results for MACE+, Full Analysis Set	350
Table 203. Subjects Who Experienced Adjudicated CV Death after Last Date of Study Participation, ADFA Dataset	350
Table 204. Analysis Results for 3-Component MACE, Full Analysis Set, On-Study	352
Table 205. Analysis Results for HHF or CV Death, Full Analysis Set, On-Study	352
Table 206. Analysis Results for 6-Component MACE, Full Analysis Set, On-Study	353
Table 207. Serious Fracture Events as Identified by FMQ, Safety Population, Trial C- 476	359
Table 208. Serious Fracture Events With ≥ 2 Cases in Bexagliflozin Arm, By Anatomic Location, Safety Population, Trial C-476	359
Table 209. Fall Events in Original and NLP-Modified Safety Datasets, Safety Population, Trial C-476	363
Table 210. Malignancy Events (FMQ), Safety Population, Trial C-476	365
Table 211. Rash Events (FMQ), Safety Population, Trial C-476	367
Table 212. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Broad Pool	370
Table 213. DKA Case Definitions	371
Table 214. Adjudicated DKA Cases	373
Table 215. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448	376
Table 216. AKI Events (FMQ), Safety Population, Trial C-476	377
Table 217. Dizziness, Hypotension, Syncope, and Volume Depletion Events (FMQs), Safety Population, Trial C-476	377
Table 218. Subjects With Renal and Urinary Tract Infections (FMQ), Safety Population, Trial C-476	379
Table 219. Subjects With GMI Events (Applicant CMQ), Safety Population, Trial C- 476	380
Table 220. Severe and Level 2 Hypoglycemia in Phase 3 Placebo-Controlled Trials, Safety Population, Trials C-419, C-448, C-450, and C-476	380
Table 221. Revascularization Procedures, Safety Population, Trial C-476	382
Table 222. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448	388

Table 223. Thrombosis Events by FMQ and CMQ, Safety Population, Trial C-476.....	389
Table 224. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448.....	392
Table 225. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448.....	395
Table 226. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448	401
Table 227. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Bexagliflozin and the Largest Lower Bound for Moxifloxacin, Trial C-428.....	404
Table 228. Safety Analyses by Demographic Subgroups, Safety Population, Placebo-Controlled Pool	406
Table 229. Safety Analyses by Demographic Subgroups, Safety Population, Trial C-476.....	407
Table 230. Covered Clinical Studies: C-418, C-419, C-423, C-449, C-450, C-476, C-480, C-603.....	412
Table 231. Reviewers of Integrated Assessment	416
Table 232. Additional Reviewers of Application	416
Table 233. Signatures of Reviewers	416

Table of Figures

Figure 1. Bexagliflozin Mechanism of Action	24
Figure 2. Bexagliflozin-Induced Glucosuria in Healthy Animals	25
Figure 3. Bexagliflozin Reduced HbA1c in Diabetic Mice and Rats	26
Figure 4. Change in HbA1c From Baseline at Week 12 in Patients With T2DM, Trial C-449.....	27
Figure 5. The 24-hour UGE as a Function of Dose in Healthy Subjects, Trials CLR002 and C-445	28
Figure 6. Change in FPG From Baseline on Day 28, Trial C-402.....	28
Figure 7. LS Mean Change in HbA1c (%) From Baseline as a Function of Time, ITT, Trial C-480.....	49
Figure 8. LS Mean Change in HbA1c (%) From Baseline as a Function of Time, ITT, Trial C-476.....	50
Figure 9. Mean Change From Baseline in HbA1c by Time and Treatment, ITT, Trial C-448.....	53
Figure 10. Median Reduction in FPG by Treatment and eGFR Subgroup Over Time, ITT, Trial C-448.....	55
Figure 11. Proportion of Patients Reaching HbA1c <7.0% by Treatment and eGFR Subgroup Over Time, ITT, Trial C-448.....	55
Figure 12. Mean Change From Baseline in HbA1c by Time and Treatment in Subjects With Baseline eGFR <60 mL/min/1.73 m ² (Top) and ≥60 mL/min/1.73 m ² (Bottom), ITT, Trial C-476	58
Figure 13. Median Reduction in FPG by Treatment and eGFR Subgroup Over Time, ITT, Trial C-476.....	59
Figure 14. Proportion of Subjects Reaching HbA1c <7.0% by Treatment and eGFR Subgroup Over Time, ITT, Trial C-476.....	59
Figure 15. On Study Kaplan-Meier Analysis of Time-to-First Nontraumatic Amputation, Safety Population, Trial C-476	87
Figure 16. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial C-448.....	98
Figure 17. Effect of Other Drugs on Bexagliflozin PK	106
Figure 18. Effect of Bexagliflozin on the PK of Other Drugs	106
Figure 19. Composite Metabolic Pathway for Rats, Monkeys, and Humans	124
Figure 20. Minor Metabolites of Bexagliflozin	159
Figure 21. Mean Concentration-Time Profiles for Bexagliflozin Following Single (Left) and Multiple (Right) Ascending Doses	167

Figure 22. 24-Hour Urinary Glucose Excretion (UGE) as a Function of Bexagliflozin Dose	169
Figure 23. Mean Bexagliflozin Concentration-Time Profiles Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin).....	170
Figure 24. Geometric Mean Plasma Concentrations of Bexagliflozin (Left) and Its Metabolite EGT0002149 (Right) After Oral Administration of a Single Dose of Bexagliflozin to Healthy Japanese Subjects in the Fed State	174
Figure 25. Proposed Biotransformation Pathway of [14C] Bexagliflozin in Humans	179
Figure 26. Geometric Mean Plasma Concentration Time Profiles of Bexagliflozin From All Formulations in the Fasted State (Left) and Fed State (Right), Trial CLR-002 Part 1	182
Figure 27. Geometric Mean Plasma Concentration Time Profiles of Bexagliflozin From SR5 formulation in the Fasted State (Left) and Fed State (Right), Trial CLR-002 Part 2	182
Figure 28. UGE as a Function of Dose for Capsule (Left) and Tablet Formulations (Right)	185
Figure 29. Median Plasma Concentrations of Bexagliflozin (Left) and Its Metabolite EGT0002149 (Right) Over Time in Subjects With Normal Renal Function and Subjects With Mild, Moderate, and Severe Renal Impairment	188
Figure 30. Geometric Mean ($\pm$ SE) Plasma Concentration-Time Profile of Bexagliflozin With or Without Exenatide	192
Figure 31. Change of FPG From Baseline (Mean $\pm$ SE), Trial C-402, Segment 2	197
Figure 32. Change in FPG From Baseline on Day 28	197
Figure 33. Trial Design, Trial C-449	198
Figure 34. Dose Response of HbA1c: Change From Baseline to Week 12	199
Figure 35. Change From Baseline in LSM FPG Over Time	200
Figure 36. Mean ($\pm$ SD) Bexagliflozin Plasma Concentration Curves (ng/mL)	201
Figure 37. Scheme of Base Model Structure	208
Figure 38. Final Model Structure.....	209
Figure 39. Goodness-of-Fit Plots of the Final PopPK Model.....	211
Figure 40. ETA Distributions by Continuous Covariates	212
Figure 41. ETA Distributions by Categorical Covariates	213
Figure 42. Visual Predictive Checks by Population and Dose	214
Figure 43. Effect of Covariates on Exposures at Steady-State With 20 mg Bexagliflozin.....	215
Figure 44. Simulated Exposures for Typical Study Populations at Fasted State.....	216

Figure 45. Mean Change in HbA1c From Baseline at Week 12	218
Figure 46. Intended Population, Trial C-476	241
Figure 47. Study Plan, Trial C-450	261
Figure 48. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-450	266
Figure 49. Preplanned Subgroup Analysis Results, ITT, Trial C-450	269
Figure 50. Trial C-450 Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-450	270
Figure 51. Study Plan, Trial C-419	271
Figure 52. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419	275
Figure 53. Preplanned Subgroup Analysis Results, ITT, Trial C-419	277
Figure 54. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-419	278
Figure 55. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423	284
Figure 56. Preplanned Subgroup Analysis Results, ITT, Trial C-423	287
Figure 57. Study Plan, Trial C-480	288
Figure 58. Change From Baseline in HbA1c (%) by Time and Treatment and Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480	293
Figure 59. Preplanned Subgroup Analysis Results, ITT, Trial C-480	296
Figure 60. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-448	301
Figure 61. Preplanned Subgroup Analysis Results, ITT, Trial C-448	304
Figure 62. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-448	305
Figure 63. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476	311
Figure 64. Preplanned Subgroup Analysis Results, ITT, Trial C-476	314
Figure 65. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-476	315
Figure 66. Cardiovascular Risk Eligibility Criteria for the Study Population, Trial C- 476	339
Figure 67. Kaplan-Meier Plot of Time-to-First MACE+ in, Full Analysis Set, On- Study, Trial C-476	349

Figure 68. Hazard Ratios for First Adjudicated CV Component Event, Full Analysis Set, On-Study*	353
Figure 69. Forest Plot of Hazard Ratios for MACE+ by Baseline Subgroups, Full Analysis Set, On-Study	354
Figure 70. Time-to-First Fracture (Top*) and Serious Fracture (Bottom) Event, Safety Population, Trial C-476	361
Figure 71. Time-to-Event for Nonmelanoma Skin Cancers, Safety Population, Trial C-476.....	366
Figure 72. Time-to-First Rash Event (FMQ), Safety Population, Trial C-476.....	368
Figure 73. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Broad Pool	370
Figure 74. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool	374
Figure 75. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial C-476.....	375
Figure 76. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool, Observed Data.....	384
Figure 77. Mean Laboratory (Lipids) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data.....	390
Figure 78. Mean Laboratory (Liver Biochemistry) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data	393
Figure 79. Mean Laboratory (Chemistry) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data.....	397
Figure 80. Median and Interquartile Range of Systolic and Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Placebo-Controlled Pool; Observed Data.....	403

Glossary

ADAE	analysis data model adverse events analysis dataset
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BCRP	breast cancer resistance protein
BMD	bone mineral density
BMI	body mass index
CABG	coronary artery bypass graft
CDER	Center for Drug Evaluation and Research
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CKD	chronic kidney disease
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMQ	customized Medical Dictionary for Regulatory Activities query
CPN	chronic progressive nephropathy
CrCL	creatinine clearance
CRF	case report form
CRO	clinical research organization
CV	cardiovascular
CVOT	cardiovascular outcome trials
CYP	cytochrome P450 isoenzyme
DDI	drug-drug interaction
DILI	drug-induced liver injury
DKA	diabetic ketoacidosis
ECAC	Executive Carcinogenicity Assessment Committee
ECG	electrocardiogram
ED ₅₀	half maximal effective dose
FAS	full analysis set
eGFR	estimated glomerular filtration rate
EOP2	end-of-phase 2
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FPG	fasting plasma glucose
GCP	good clinical practice
GLP	glucagon-like peptideGMI genital mycotic infection
GMR	geometric mean ratio

NDA 214373
Brenzavvy (bexagliflozin)

GQ	grouped queries
HbA1c	hemoglobin A1c
HF	heart failure
HPLC	high-performance liquid chromatography
HR	hazard ratio
IC ₅₀	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	investigational new drug
IRT-CS	Interdisciplinary Review Team for Cardiac Safety Studies
ISS	integrated summary of safety
ITT	intent-to-treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LS	least squares
LS-MS/MS	liquid chromatography mass spectrometry
LVEF	left ventricular ejection fraction
K-M	Kaplan-Meier
MACE	major adverse cardiac event
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MI-RTB	multiple imputation based on return-to-baseline
MMRM	mixed model repeated measures
MRHD	maximum recommended human dosage
NDA	new drug application
NLP	natural language processing
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal probrain natriuretic peptide
NYHA	New York Heart Association
OHA	oral hypoglycemic agent
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PAD	peripheral artery disease
PD	pharmacodynamic
PK	pharmacokinetic
PMR	postmarketing requirement
popPK	population pharmacokinetics
PP	per protocol
PT	preferred term
RD	risk difference
SAD	single ascending dose
SAE	serious adverse event
SBP	systolic blood pressure
SAP	statistical analysis plan
SGLT2	sodium-glucose cotransporter 2
SMBG	self-monitoring blood glucose

NDA 214373
Brenzavvy (bexagliflozin)

SD	standard deviation
SOC	system organ class
SPA	special protocol assessment
SR	sustained release
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
T _{lag}	lag time
T _{max}	time to maximum concentration
TQT	thorough QT
UACR	urine albumin-to-creatinine ratio
UDU	uniformity of dosage unit
UGE	urinary glucose excretion
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UTI	urinary tract infection
UV	ultraviolet

I. Executive Summary

1. Summary of Regulatory Action

The Applicant, TheracosBio LLC, has submitted a New Drug Application (NDA) for Brenzavvy (bexagliflozin) tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2DM). The recommended dosage is 20 mg orally once daily.

Bexagliflozin is a small molecule inhibitor of the sodium-glucose linked transporter 2 (sodium-glucose co-transporter-2, SGLT2), the transporter responsible for reabsorption of the majority of glucose from the renal glomerular filtrate in the renal proximal tubule. By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Bexagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. There are currently four FDA-approved SGLT2 inhibitors indicated for improved glycemic control in adults with T2DM. Bexagliflozin is a new molecular entity (NME), and the Applicant is submitting this NDA using the 505(b)(1) approval pathway.

T2DM is a serious and life-threatening condition that if left untreated leads to an increased risk of morbidity and mortality. Despite numerous available therapeutic options, a significant number of patients have difficulty achieving adequate glycemic control. Landmark clinical trials in both type 1 diabetes and type 2 diabetes demonstrated that improved glycemic control as assessed by hemoglobin A1c (HbA1c) leads to substantial reduction in the incidence of microvascular complications, including diabetic retinopathy, nephropathy, and neuropathy (Control et al. 1993; Ohkubo et al. 1995; UKPDS 1998). Improved glycemic control demonstrated by reduction of HbA1c is considered a surrogate for reduction of microvascular complications of diabetes and has served as the basis for traditional approval of drugs and biologic products for a glycemic control indication in people with diabetes (FDA 2022).

The Applicant demonstrated substantial evidence of effectiveness for the proposed indication with data from six phase 3, adequate and well-controlled investigations, including four placebo-controlled trials and two active controlled trials.

Bexagliflozin was compared to placebo in subjects with inadequately controlled T2DM as monotherapy (C-450), as add-on to metformin (C-419), and as add-on to standard of care therapies in subjects with inadequately controlled T2DM and increased cardiovascular risk (C-476) and moderate renal impairment (C-448).

The primary efficacy endpoint for glycemic control in these trials was the mean change from baseline in HbA1c. The placebo-adjusted estimate of the treatment effect in trials C-450, C-419, and C-476 (all conducted primarily in patients with normal renal function) ranged from -0.38% to -0.48%. The results were statistically significant and clinically meaningful, and collectively represent substantial evidence of effectiveness. In the active-controlled trials, bexagliflozin was statistically non-inferior to sitagliptin (C-423) and glimepiride (C-480) as an add-on to metformin, although glimepiride was only titrated up to a maximum dose of 6 mg, which is less than the maximum approved dose of 8 mg in the US. In C-423 the estimated treatment difference versus sitagliptin was 0.08 (-0.06, 0.22). In C-480 the estimated treatment versus glimepiride was

-0.03 (-0.20, 0.13). In both trials, the upper bound of the 95% confidence interval did not exceed the prespecified non-inferiority margin of 0.35. In the dedicated renal impairment trial (C-448) enrolling subjects with stage 3 chronic kidney disease (moderate renal impairment, defined as estimated glomerular filtration rate (eGFR) ≥ 30 to <60 mL/min/1.73 m²), the placebo-adjusted estimate of the treatment effect was -0.27% (95% CI: -0.44, -0.09). This result was statistically significant. In contrast, no treatment effect was observed in a subgroup analysis of subjects with eGFR <60 mL/min/1.73m² in trial C-476, the trial of patients with increased cardiovascular risk. This trial was not designed to evaluate glycemic control in patients with renal impairment; therefore, we place more weight on the demonstrated glycemic effects in the dedicated renal impairment efficacy and safety trial.

Statistically significant decreases in body weight versus placebo were observed in trials where bexagliflozin was added to standard of care therapy in subjects with renal impairment (C-448) and increased CV risk (C-476). Statistically significant reduction in systolic blood pressure (SBP) with bexagliflozin versus placebo was observed in the CV risk trial (C-476).

Safety findings were generally consistent with those of other SGLT2 inhibitor products. Consistent with other members of the SGLT2 inhibitor class, the Warnings and Precautions section of labeling will include the risk of ketoacidosis, urosepsis and pyelonephritis, Fournier's gangrene, genital mycotic infections, volume depletion, and hypoglycemia with concomitant use of insulin or an insulin secretagogue.

An increased incidence of nontraumatic amputation was observed compared to placebo in a trial of patients with increased CV risk (hazard ratio: 1.64 (0.7, 3.8)). Lower limb amputation is a recognized complication of diabetes mellitus, and an increased risk of amputation has been identified with some, but not all, members of the SGLT2 inhibitor class. A statement advising prescribers to consider factors that may increase the risk of amputation before initiating bexagliflozin and to monitor patients for infections or ulcers of lower limbs also appears appropriate to mitigate this potential risk and will be included in the Warnings and Precautions section of labeling.

Section 6 of the prescribing information will include subsections to describe imbalances unfavorable to bexagliflozin for the following adverse events: bone fracture, sepsis, rash, and dermatitis.

The Applicant conducted a program-wide meta-analysis to evaluate the cardiovascular risk of exposure to bexagliflozin. The primary endpoint was time-to-first event of a four-component composite endpoint consisting of CV death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization for unstable angina. The estimated hazard ratio of the composite endpoint associated with bexagliflozin relative to control was 0.80 (95% CI: 0.58, 1.09). Exposure to bexagliflozin is not expected to substantially increase the risk of MACE in patients with T2DM.

Key review issues in the evaluation of benefit/risk included efficacy of bexagliflozin in subjects with moderate renal impairment, increased risk of nontraumatic amputation with bexagliflozin, overall safety of bexagliflozin, and quality of the safety database. Refer to the Sections [2.2](#) (Conclusions Regarding Benefit and Risk), [3.1](#) (Review Issue List), and the linked subsections of [6](#) (Assessment of Effectiveness) and [7](#) (Risk and Risk Management) for details.

All review disciplines, the clinical division director, and the office director (signatory) support approval of the application. Refer to Sections [II](#) (Interdisciplinary Assessment) and [III](#) (Appendices) for details of the individual discipline reviews.

In summary, the application demonstrated substantial evidence of effectiveness of bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The approved dosage is 20 mg orally once daily. Bexagliflozin is not recommended for use in patients with an eGFR <30 mg/mL/1.73 m² and is contraindicated in patients on dialysis, because there is a progressive decline in urinary glucose excretion with accompanying loss of pharmacodynamic blood glucose-lowering effect with increased severity of renal impairment, as well as a reduction in urine output. As such, there will be minimal, if any, efficacy in this population always outweighed by the risks. Major safety issues are adequately communicated in labeling. Approval will include a Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) issued to assess the safety and efficacy of bexagliflozin in pediatric patients ≥ 10 to <18 years of age.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM), which affects approximately 33 million people in the United States (CDC 2022b), is a chronic medical condition characterized by insulin resistance and inadequate insulin secretion, resulting in hyperglycemia. • Patients with T2DM are at increased risk for serious microvascular (i.e., retinopathy, nephropathy, and neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications (Stratton et al. 2000; American Diabetes Association Professional Practice 2022; American Diabetes Association Professional Practice et al. 2022c; American Diabetes Association Professional Practice et al. 2022d). It is the 8th leading cause of death in the United States (CDC 2022a). • Despite known benefits of glycemic control, approximately one quarter to one half of subjects with T2DM in the United States fail to achieve recommended treatment goals (Carls et al. 2017; Khunti et al. 2018; Avramidis et al. 2020).	T2DM is a serious and life-threatening condition that if left untreated leads to an increased risk of morbidity and mortality. A significant number of patients have difficulty achieving adequate glycemic control.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There are currently 12 pharmacologic classes of antihyperglycemic medications (generally with multiple members in each class), approved to improve glycemic control in patients with T2DM (American Diabetes Association Professional Practice et al. 2022b). There are different safety concerns for each class. • Published guidelines have generally recommended initiating treatment with lifestyle interventions and metformin, with the choice of additional therapies and/or alternatives based on factors such as baseline cardiovascular (CV) and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, patient preference, and cost (American Diabetes Association Professional Practice et al. 2022b). Because T2DM is a progressive disease, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Initiation of some antihyperglycemic products are not recommended for use in patients with moderate renal impairment and/or may require dose adjustment in this patient population. • There are currently four sodium-glucose cotransporter 2 (SGLT2) inhibitor products approved in the United States (ertugliflozin, dapagliflozin, canagliflozin, empagliflozin) (Janssen 2020; AstraZeneca 2021; Merck 2021; Ingelheim 2022). • While all approved antihyperglycemic medications for T2DM have been shown to improve glycemic control, some have also been shown to improve CV and renal outcomes, including several SGLT2 inhibitor and glucagon-like peptide (GLP-1) receptor agonist products (Janssen 2020; AstraZeneca 2021; Ingelheim 2022; Lilly 2022; Nordisk 2022a; Nordisk 2022b).	Despite the many available treatment options, many patients continue to have difficulty achieving adequate glycemic control. Further, T2DM is a progressive disorder and patients typically need additional agents added as the disease progresses. Many patients with T2DM also have renal impairment, and therefore, it is important to have available treatment options for this population.

Benefit	• Six phase 3 trials that met the criteria for adequate and well-controlled investigations were submitted to establish efficacy of bexagliflozin 20 mg for the proposed indication. • These trials used HbA1c, an average measure of glycemic control over 2-3 months and an established surrogate for reduction in microvascular complications, as the key efficacy measure of effectiveness. Studies such as UKPDS indicate that a reduction in HbA1c is considered clinically meaningful because it corresponds with decreased rates of microvascular disease in proportion to the improvement in HbA1c. • Bexagliflozin was statistically superior to placebo as monotherapy, with a placebo-adjusted change from baseline in hemoglobin A1c (HbA1c) of -0.38% (-0.63%, -0.13%; $p=0.002$), and as add-on to metformin, with a placebo-adjusted change from baseline of -0.48% (-0.69%, -0.26%; $p<0.0001$). This magnitude of improvement is in line with previously approved anti-diabetics. • Bexagliflozin was also noninferior to sitagliptin [0.08% (-0.06, 0.22)] and glimepiride [-0.03% (-0.20, 0.13)], two products that are approved for the treatment of T2DM, when evaluated using a noninferiority margin of 0.35% for HbA1c. • Efficacy of bexagliflozin was evaluated in trials enrolling subjects with stage 3 chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR] 30–60 mL/min/1.73 m²) and subjects with increased CV risk. No restriction was placed on background therapy for glycemic control in these trials, with the exception of treatment with another SGLT2 inhibitor product. Glycemic control was significantly improved in both populations as compared to placebo with bexagliflozin treatment (placebo-adjusted change from baseline in HbA1c of -0.27% [-0.44%, -0.09%; $p=0.002$] and -0.44% [-0.53%, -0.35%; $p<0.0001$] in subjects with stage 3 CKD and increased CV risk, respectively). • Secondary endpoints related to change in body weight and systolic blood pressure (SBP) were evaluated. Statistically significant decreases in body weight were observed in trials where bexagliflozin was added to standard of care therapy in subjects with renal impairment (Trial C-448) and increased	• The submitted clinical trial data provides substantial evidence of effectiveness of bexagliflozin for the proposed indication, as an 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 clinically meaningful improvements in HbA1c compared to placebo and noninferiority 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. • Efficacy data support approval of dosing in patients with impaired renal function (eGFR 30-60 mL/min/1.73 m²), providing another therapeutic option for patients with both T2DM and CKD. • In certain trials, efficacy data demonstrate that bexagliflozin results in reduced body weight and/or SBP, which are other effects generally associated with the class. • The safety and efficacy of bexagliflozin in pediatric patients ≥ 10 to <18 years of age is currently unknown but will be studied.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	CV risk (Trial C-476). Statistically significant changes in SBP were also observed in Trial C-476. Uncertainties of Benefit: • The efficacy of bexagliflozin for pediatric patients with T2DM has not been established. • Pivotal trial populations underrepresented some racial subgroups (e.g., 5.7% were black). • In the trial comparing bexagliflozin to glimepiride, glimepiride was titrated to a maximum dose of 6 mg daily, not to the US approved maximum dose of 8 mg daily. The impact on noninferiority conclusions is unknown. • It is unknown if a bexagliflozin dose higher than 20 mg would lead to further improvement in efficacy and acceptable safety as a higher dose was not tested in the phase 2 or phase 3 trials.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- Safety findings were generally consistent with those of other SGLT2 inhibitor products. Compared to placebo, higher proportions of subjects experienced genital mycotic infections, urinary tract infections, vaginal pruritus, thirst, and increased urination with bexagliflozin. A higher incidence of genital mycotic infections was observed in females than males treated with bexagliflozin. - A program-wide meta-analysis was undertaken to establish the cardiovascular hazards of exposure to bexagliflozin. The primary endpoint was time-to-first adjudicated major adverse cardiac event (MACE+), a four-component composite endpoint consisting of events of CV death, nonfatal stroke, nonfatal myocardial infarction, or hospitalization for unstable angina. The estimated hazard ratio of MACE+ associated with bexagliflozin relative to control was 0.80 (95% CI: 0.58, 1.09). Exposure to bexagliflozin is not expected to unacceptably increase the risk of MACE in patients with T2DM. - An increased risk of nontraumatic amputation was observed compared to placebo in a trial enrolling patients with increased CV risk (hazard ratio: 1.64 (95% CI: 0.7, 3.8)). In addition, imbalances unfavorable to bexagliflozin were observed for events of serious fracture, sepsis, and rash/dermatitis. Uncertainties in Risk - Risks associated with bexagliflozin exposure during pregnancy or breastfeeding are uncertain. - The duration of treatment exposure and follow-up in the clinical trials was not adequate to evaluate long latency events, including cancer. - There were few events of diabetic ketoacidosis, severe hypoglycemia, Fournier's gangrene, and pyelonephritis/urosepsis, limiting the interpretability of the available data.	- No new safety findings were observed in the bexagliflozin clinical development program that significantly impact the overall risk profile. The reported AEs were generally consistent with the known safety profiles of SGLT2 inhibitor products. - In accordance with the SGLT2 inhibitor class, the <i>Warnings and Precautions</i> section in the approved bexagliflozin labeling will include the risk of ketoacidosis, urosepsis and pyelonephritis, Fournier's gangrene, genital mycotic infections, volume depletion, and hypoglycemia with concomitant use of insulin or an insulin secretagogue. As with some other members of the class, a Warnings and Precautions statement advising prescribers to consider factors that may increase the risk of amputation before initiating bexagliflozin and to monitor patients for infections or ulcers of lower limbs is also appropriate to mitigate this potential risk. - Section 6 of the prescribing information will include subsections to describe the imbalances noted for the adverse reactions of bone fracture, sepsis, rash, and dermatitis. - As with other members of the SGLT2 inhibitor class, the risks of bexagliflozin is adequately mitigated with labeling, including a Medication Guide for patients.

2.2. Conclusions Regarding Benefit-Risk

The Applicant submitted six adequate and well-controlled investigations that establish clinical benefit for bexagliflozin for improving glycemic control in adults with type 2 diabetes mellitus, including four placebo-controlled trials and two active-controlled trials.

The four placebo-controlled trials (C-419, C-448, C-450, and C-476) demonstrated superiority of bexagliflozin to placebo for the primary endpoint of change in HbA1c, from baseline to Week 24. Assessing change in HbA1c from baseline over at least 24 weeks relative to a control is the standard approach to showing benefit for a glycemic control indication for type 2 diabetes mellitus. HbA1c reflects average glucose control over the preceding 2-3 months and is an established surrogate for reduction in microvascular complications. Reductions in HbA1c were both statistically and clinically significant. Bexagliflozin was statistically superior to placebo as monotherapy, with a placebo-adjusted change from baseline in HbA1c of -0.4% (-0.6%, -0.1%; $p=0.002$) in C-450, and as add-on to metformin, with a placebo-adjusted change from baseline in HbA1c of -0.5% (-0.7%, -0.3%; $p<0.0001$) in C-419. In addition, bexagliflozin was statistically superior to placebo on change from baseline in HbA1c to Week 24 in patients with increased CV risk on standard of care therapy for glycemic control (placebo-adjusted change from baseline of -0.4% [-0.5%, -0.4%; $p<0.0001$]) in C-476. The observed treatment effect is comparable to that of some of the other approved oral agents for glycemic control in patients with T2DM. Reduction in microvascular disease in T2DM is proportional to reduction in HbA1c.

While statistically significant, glycemic efficacy was more modest in C-448, the trial of patients with moderate renal impairment (i.e., $eGFR \geq 30$ to <60 mL/min/1.73 m²), with a placebo-adjusted change from baseline in HbA1c of -0.3% (-0.4%, -0.1%; $p=0.002$).

Bexagliflozin also performed comparably to sitagliptin and glimepiride, two other approved treatments for type 2 diabetes in two active-controlled trials (C-423 and C-480). Trial C-423 compared bexagliflozin to sitagliptin at the recommended dose for patients without renal impairment (100 mg). Trial C-480 compared bexagliflozin to glimepiride titrated from 2 mg up to a maximum dose of 6 mg. In C-423 the estimated treatment difference versus sitagliptin was 0.1 (-0.1, 0.2). In C-480 the estimated treatment versus glimepiride was 0.0 (-0.2, 0.1). In both trials, the upper bound of the 95% confidence interval did not exceed the prespecified non-inferiority margin of 0.35. One limitation is that the glimepiride comparator was not titrated up to the maximum U.S. approved daily dose of 8 mg and glimepiride was not titrated after Week 6 in the 60-week trial.

Bexagliflozin use was associated with statistically significant reductions in body weight compared to placebo in both the renal impairment trial (C-448) and the increased CV risk trial (C-476). In C-476, bexagliflozin was also associated with reduction in cuff systolic blood pressure versus placebo.

Safety findings were generally consistent with those of other SGLT2 inhibitor products and can be adequately mitigated by labeling, including with a Medication Guide for patients, as has been done with the approved SGLT2 inhibitors.

Consistent with other approved products in the SGLT2 inhibitor class, the *Warnings and Precautions* section of labeling will include the risk of ketoacidosis, urosepsis and pyelonephritis, Fournier's gangrene, genital mycotic infections, volume depletion, and

hypoglycemia with concomitant use of insulin or an insulin secretagogue. In the clinical trials, a higher incidence of subjects assigned to bexagliflozin than placebo experienced one or more events of urinary tract infections, genital mycotic infections, volume depletion, and hypoglycemia. Events of ketoacidosis were observed in clinical trials with bexagliflozin. Fournier's gangrene is a rare, serious event associated with the class.

Lower limb amputation is a recognized complication of diabetes mellitus, and an increased risk of lower limb amputation has been identified with some, but not all, members of the SGLT2 inhibitor class. Data from the increased CV risk trial (C-476) indicated an increased incidence of amputation with bexagliflozin treatment as compared to placebo (HR: 1.64 (0.70, 3.82)). The risk of amputation is higher in patients with a baseline history of prior amputation, PAD, and neuropathy, compared to patients without such disease history. The majority of amputations in both groups in C-476 were below-the-knee. Description of the observed imbalance in amputation warrants inclusion in labeling.

Given the more modest treatment effect on HbA1c in patients with renal impairment in trial C-448, the safety of bexagliflozin in subjects with moderate renal impairment was considered a key review issue. Overall, considering the safety data from both the dedicated renal impairment trial (C-448) and the subgroup from the increased CV risk trial (C-476), no new safety issues were identified in subjects with stage 3 CKD, and the benefits outweigh the risks in this population.

Changes in laboratory parameters in C-448 were generally consistent with data from other trials of bexagliflozin. The magnitude of transient increases in serum creatinine and corresponding decreases in eGFR was greater in trial C-448. Communication in labeling can adequately inform prescribers regarding these changes in laboratory parameters.

In conclusion, the applicant demonstrated substantial evidence of effectiveness to support approval of the application. The benefits of treatment with bexagliflozin on glycemic control outweigh the potential risks in the indicated population when bexagliflozin is used according to the approved labeling.

II. Interdisciplinary Assessment

3. Introduction

TheracosBio LLC (hereafter referred to as the Applicant) has developed the sodium-glucose cotransporter 2 (SGLT2) inhibitor bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The SGLT2 protein is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into circulation. By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. The proposed marketed product is a blue tablet containing 20 mg of bexagliflozin. The tablet is to be taken once daily with or without food. There are currently four FDA-approved SGLT2 inhibitors indicated for improved glycemic control in adults with T2DM. Bexagliflozin is a new molecular entity (NME), and the Applicant is submitting this new drug application (NDA) using the 505(b)(1) approval pathway.

3.1. Review Issue List

The review team identified four main review issues that had a significant impact of the overall determination of approvability. In depth analyses of these key review issues can be found in Sections [6.3](#) and [7.7](#).

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

3.1.1.1. Efficacy of Bexagliflozin in Subjects With Moderate Renal Impairment

See Section [6.3.1](#).

3.1.2. Key Review Issues Relevant to Evaluation of Risk

3.1.2.1. Increased Risk of Nontraumatic Amputation With Bexagliflozin Treatment

See Section [7.7.1](#).

3.1.2.2. Safety of Bexagliflozin in Subjects With Moderate Renal Impairment

See Section [7.7.2](#).

3.1.2.3. Safety Database Quality Concerns

See Section [7.7.3](#).

3.2. Approach to the Review

Six adequate and well-controlled phase 3 trials conducted in subjects with T2DM provide substantial evidence of effectiveness for the pursued glycemic control indication (Trials C-419, C-423, C-448, C-450, C-476, and C-480; [Table 3](#)). The NDA also included a phase 2b dose-finding trial (C-449) to support dose selection and a phase 2b trial that utilized a noncommercial formulation of bexagliflozin (C-418). Other trials completed in the clinical development program either did not have a sufficient treatment duration, such that they would contribute meaningfully to the assessment of efficacy, did not enroll subjects with T2DM, or were conducted for the evaluation of bexagliflozin for the treatment of essential hypertension (e.g., C-603A, C-603B).

The safety evaluation for this Application was based on the review of pooled safety data from three placebo-controlled trials enrolling subjects who were either treatment naïve or inadequately controlled on metformin (C-419, C-449, and C-450), termed the placebo-controlled pool, and the review of phase 3 trial data from active-controlled trials (C-423 and C-480) and trials enrolling specific populations (C-448 and C-476). The placebo-controlled pool was utilized to evaluate the safety and tolerability of 20 mg bexagliflozin relative to placebo in a similar patient population and was used to inform commonly occurring adverse reactions in Section 6 of the labeling. Trial C-448, which enrolled subjects with stage 3 chronic kidney disease (CKD), and Trial C-476, which enrolled subjects with increased cardiovascular (CV) risk, were evaluated independently to assess safety in these distinct patient populations. Trial C-476 was of special interest in this safety review, as it was the largest (1,699 subjects in the safety population) and longest (median duration 2.4 years) trial in the bexagliflozin clinical program. It therefore provided the most robust assessment for various adverse events of special interest (AESIs). Analyses from C-448 and C-476 are presented independently and used to inform labeling where indicated.

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations for Bexagliflozin

Trial Identifier	Trial Population	Trial Design	Regimen, Duration, Randomization	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
C-418	Subjects with inadequately controlled T2DM who were either treatment naïve ¹ or taking one oral antihyperglycemic agent willing to discontinue treatment ²	Phase 2b, randomized, double-blind, placebo-controlled trial to compare treatment with bexagliflozin capsules to placebo in subjects with T2DM.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 96 weeks Randomization: 1:1	Primary: HbA1c at 24 weeks Secondary: ³ - FPG - Proportion of subjects with HbA1c <7% - SBP and DBP - Body weight	Planned: 300 Actual: 288	Centers: 26 Countries: 3
C-419	Subjects with T2DM inadequately controlled by metformin	Phase 3, randomized, double-blind, placebo-controlled trial to compare treatment with bexagliflozin tablets to placebo in subjects with T2DM. This trial also included a single-arm, open-label "high glycemic control group" consisting of subjects with baseline HbA1c >10.5% to ≤12%.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 24 weeks Randomization: 1:1	Primary: HbA1c at 24 weeks Secondary: ³ - FPG - SBP - Proportion of subjects with HbA1c <7% - Body weight	Planned: 300 ⁴ Actual: 317	Centers: 45 Countries: 2
C-423	Subjects with T2DM inadequately controlled by metformin	Phase 3, randomized, double-blind, active-controlled trial to compare treatment with bexagliflozin tablets to sitagliptin in subjects with T2DM.	Regimen: - Bexagliflozin, 20 mg PO QD - Sitagliptin, 100 mg PO QD Duration: 24 weeks Randomization: 1:1	Primary: HbA1c at 24 weeks Secondary: - FPG - Body Weight - SBP	Planned: 374 Actual: 386	Centers: 51 Countries: 6

NDA 214373
Brenzavvy (bexagliflozin)

Trial Identifier	Trial Population	Trial Design	Regimen, Duration, Randomization	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
C-448	Subjects with inadequately controlled T2DM and moderate renal impairment taking standard of care therapy	Phase 3, randomized, double-blind, placebo-controlled trial to compare treatment with bexagliflozin tablets to placebo in subjects with T2DM and moderate renal impairment.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 24 weeks Randomization: 1:1	Primary: HbA1c at 24 weeks Secondary: - Body Weight - SBP - HbA1c in subjects with eGFR 45-59 mL/min/1.73 m ² - HbA1c in subjects with eGFR 30-44 mL/min/1.73 m ²	Planned: 300 Actual: 312	Centers: 54 Countries: 4
C-449	Subjects with inadequately controlled T2DM who were either treatment naïve ¹ or taking one oral antihyperglycemic agent willing to discontinue treatment ⁵	Phase 2b, randomized, double-blind, placebo-controlled trial to compare treatment with 5, 10, and 20 mg bexagliflozin tablets to placebo in subjects with T2DM.	Regimen: - Bexagliflozin, 5, 10, or 20 mg PO QD - Placebo PO QD Duration: 12 weeks Randomization: 1:1:1:1	Primary: HbA1c at 12 weeks Secondary: - HbA1c over time - FPG - Proportion of subjects with HbA1c <7% - SBP and DBP - Body weight	Planned: 320 Actual: 292	Centers: 50 Countries: 2
C-450	Subjects with inadequately controlled T2DM who were either treatment naïve ¹ or taking one oral antihyperglycemic agent willing to discontinue treatment ⁵	Phase 3, randomized, double-blind, placebo-controlled trial to compare treatment with bexagliflozin tablets to placebo in subjects with T2DM.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 24 weeks Randomization: 2:1	Primary: HbA1c at 24 weeks Secondary: - SBP - Body weight	Planned: 210 Actual: 207	Centers: 25 Countries: 2

NDA 214373
Brenzavvy (bexagliflozin)

Trial Identifier	Trial Population	Trial Design	Regimen, Duration, Randomization	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
C-476	Subjects with inadequately controlled T2DM and increased CV risk on standard of care therapy	Phase 3, randomized, double-blind, placebo-controlled trial to compare treatment with bexagliflozin tablets to placebo in subjects with T2DM and increased CV risk.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 54-week minimum duration Randomization: 2:1	Primary: HbA1c at 24 weeks Secondary: - HbA1c at 24 weeks in subjects using insulin - Body weight - SBP	Planned: 1650 Actual: 1701	Centers: 176 Countries: 10
C-480	Subjects with T2DM inadequately controlled by metformin or metformin and one oral antihyperglycemic agent willing to discontinue treatment of non-metformin oral agent ⁵	Phase 3, randomized, double-blind, active-controlled trial to compare treatment with bexagliflozin tablets to glimepiride in subjects with T2DM.	Regimen: - Bexagliflozin, 20 mg PO QD - Glimepiride 2, 4, or 6 mg PO QD Duration: 96 weeks	Primary: HbA1c at 60 weeks Secondary: - Body weight - SBP - Proportion of subjects with hypo event	Planned: 420 Actual: 426	Centers: 46 Countries: 4

NDA 214373
Brenzavvy (bexagliflozin)

Trial Identifier	Trial Population	Trial Design	Regimen, Duration, Randomization	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized	No. of Centers and Countries
C-603A and C-603B	Subjects with essential HTN	Phase 2/3 crossover trial to compare treatment with bexagliflozin tablets to placebo in subjects with essential HTN. In C-603A, subjects were randomized to receive either placebo or bexagliflozin for 12 weeks. Upon completion of C-603A, subjects were enrolled in C-603B, which was a randomized withdrawal trial wherein all subjects received bexagliflozin for 12 weeks and then were randomized to bexagliflozin or placebo for an additional 12 weeks.	Regimen: - Bexagliflozin, 20 mg PO QD - Placebo PO QD Duration: 12 weeks (C-603A) and 24 weeks (C-603B) Randomization: 1:1	Part A Primary: 24-hour mean SBP at 12 weeks Part A Secondary: - Proportion of subjects with >10 mm Hg reduction in SBP Part B Primary: 24-hour mean SBP at 24 weeks Part B Secondary: - Seated SBP at 24 weeks	Planned: 680 Actual: 673	Centers: 86 Countries: 1

Source: Clinical Study Report and adsl.xpt; Generated by CDS and modified by Clinical Reviewer

¹A "treatment naïve" subject was generally defined as a subject who has taken no more than 14 days of any antihyperglycemic agent to manage their T2DM for a predefined period of time prior to enrollment (e.g., 12 weeks)

²C-418 did not employ a washout period and subjects taking one oral antihyperglycemic agent were randomized after a 2-week placebo run-in period. This trial also used a noncommercial, capsule formulation of bexagliflozin.

³Secondary endpoints C-418, C-419, and C-449 were evaluated for exploratory purposes only (i.e., hierarchical testing methodology was not carried out).

⁴An additional 50 subjects were planned for enrollment in the single-arm high glycemic control group of C-419 (34 subjects were enrolled).

⁵C-449, C-450, C-480 allowed subjects taking oral antihyperglycemic agents to enroll and undergo a 6 to 10 week treatment washout period prior to initiation of the 2 week run-in period.

Abbreviations: CV, cardiovascular; DPB, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c; hemoglobin A1c; HTN, hypertension; PO, by mouth; QD, once daily; SBP, systolic blood pressure; T2DM; type 2 diabetes mellitus.

4. Patient Experience Data

Table 4. Patient Experience Data
Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Sodium-glucose cotransporter 2 (SGLT2) inhibitor
Mechanism of action	SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Bexagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, bexagliflozin reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion.
Active moieties	Bexagliflozin (no active metabolite)
QT prolongation	At five times the maximum recommended dose (100 mg), bexagliflozin does not prolong the QTc interval to any clinically significant extent.
General Information	
Bioanalysis	Bexagliflozin concentrations in plasma were measured using validated LC-MS/MS methods.
Healthy subjects versus patients	No clinically relevant differences in bexagliflozin PK parameters between healthy volunteers and patients with T2DM.
Drug exposure following the therapeutic dosing regimen	Single dose data are presented as there is no significant accumulation following once daily dosing of bexagliflozin with the 3 mg, 10 mg, and 30 mg tablet formulation. Following oral administration of a single dose of 20 mg bexagliflozin tablet under fasted and fed conditions, the geometric mean (CV%) C_{max} was 134 (43) ng/mL and 176 (31) ng/mL, respectively, and $AUC_{0-\infty}$ was 1149 (30) ng*h/mL and 1276 (26) ng*h/mL, respectively.
Range of effective dosage(s) or exposure	20 mg QD was the only dose studied in the pivotal phase 3 studies.
Maximally tolerated dosage or exposure	Maximally tolerated dose is not known. The highest studied dose was 150 mg QD for 14 days in healthy subjects.
Dosage proportionality	Bexagliflozin PK is dose-proportional over the range of 3 mg to 90 mg.
Accumulation	No significant accumulation upon once daily dosing with accumulation ratio between 1.1 and 1.2
Time to achieve steady-state	Approximately 60 hours
Bridge between to-be-marketed and clinical trial formulations	Not needed as the to-be-marketed formulation was used in the phase 3 studies.

NDA 214373
Brenzavvy (bexagliflozin)

Characteristic	Drug Information
	Absorption
Bioavailability	Absolute bioavailability of bexagliflozin was not determined. The tablet formulation had about 16% lower AUC and 55% lower C _{max} compared to the immediate release capsule formulation that was used in early phase studies (see Section 14.2.6).
T _{max}	2-4 hours following oral administration
Food effect (fed/fasted) Geometric least square mean and 90% CI	High fat meal delayed bexagliflozin T _{max} by 1-2 hours and increased Bexagliflozin C _{max} by 31% (90% CI: 17%, 48%). There is no significant impact on bexagliflozin AUC.
	Distribution
Volume of distribution	The apparent volume of distribution is approximately 300 L in healthy subjects
Plasma protein binding	Bexagliflozin is approximately 93% bound to plasma protein. Neither renal nor hepatic impairment substantially alters protein binding
Drug as substrate of transporters	Bexagliflozin is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
	Elimination
Mass balance results	91.6% of total radioactivity was recovered, 51.1% in feces, predominantly as bexagliflozin, and 40.5% in urine, largely as the 3'-O-glucuronide metabolite.
Clearance	The apparent oral clearance is 19 L/h by population pharmacokinetic modeling.
Half-life	The apparent elimination half-life was about 12 h.
Metabolic pathway(s)	Bexagliflozin is mainly metabolized by UGT1A9 and, to a lesser extent, CYP3A.
Primary excretion pathways (% dosage)	The proportion of radioactivity recovered as bexagliflozin in urine and feces was 1.5% and 28.7%, respectively.
	Intrinsic Factors and Specific Populations
Body weight	Based on a population PK analysis, body weight does not have a clinically relevant effect on the PK of bexagliflozin.
Age	Based on a population PK analysis, age does not have a clinically relevant effect on the PK of bexagliflozin.
Renal impairment	In T2DM patients with mild (eGFR: 60-89 mL/min/1.73 m ²), moderate (eGFR: 30-59 mL/min/1.73 m ²), and severe renal impairment (eGFR: 15-29 mL/min/1.73 m ²), the AUC of bexagliflozin increased by 6.8%, 33.8% and 53.9%, respectively, compared to T2DM patients with normal renal function. The C _{max} was not affected. Consistent with the mechanism of action, the 24-hour urinary glucose excretion in T2DM patients with mild, moderate, and severe renal impairment was 17%, 60%, and 83% lower, respectively, than in T2DM patients with normal renal function. Based on safety and efficacy data in patients with moderate renal impairment, no dose adjustment is needed in patients with mild and moderate renal impairment (i.e., eGFR ≥30 mL/min/1.73 m ²). Bexagliflozin is not recommended in patients with severe renal impairment, as it is not expected to be effective in these patients (See Sections 6.3 and 8.1).
Hepatic impairment	The use of bexagliflozin has not been studied in patients with severe hepatic impairment. In subjects with moderate hepatic impairment, the AUC of bexagliflozin increased by 28.3%, and C _{max} increased by 6.3% compared to subjects with normal hepatic function. No dose adjustment is needed in patients with mild and moderate hepatic impairment.

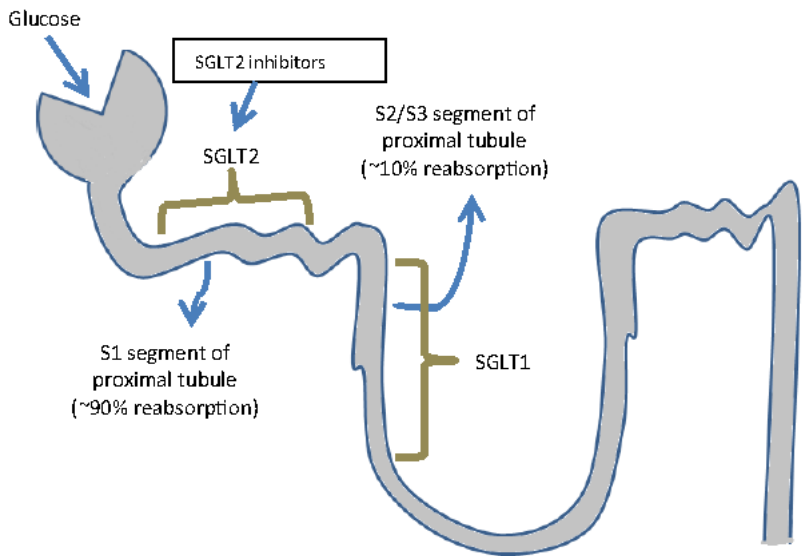
Characteristic	Drug Information
	Drug Interaction Liability (drug as perpetrator)
Inhibition/induction of metabolism	Based on in vitro studies, bexagliflozin is not expected to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 or induce CYP1A2, CYP2C19 and CYP3A4 at clinically relevant plasma concentrations.
Inhibition/induction of transporter systems	Based on in vitro studies, bexagliflozin is not expected to inhibit P-gp, BRCP and uptake transporters including BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K at clinically relevant plasma concentrations.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-∞}, area under the curve from zero to infinity; C_{max}, maximum plasma concentration; CYP; cytochrome P450 isoenzyme; LC-MS/MS, liquid chromatography mass spectrometry; PK, pharmacokinetic; QD, once daily; T2DM; type 2 diabetes mellitus; T_{max}, time to maximum concentration.

5.1. Nonclinical Assessment of Potential Effectiveness

Bexagliflozin is an inhibitor of SGLT2 indicated for the treatment of T2DM. SGLT2 is a transmembrane protein that actively cotransports extracellular sodium and hexose sugars into cells by relying on the electrochemical potential of sodium ions across the renal tubular (apical) cell membrane. Inhibition of SGLT2 prevents glucose reuptake from the renal proximal tubule, leading to glucosuria and a reduction in plasma glucose concentration.

Figure 1. Bexagliflozin Mechanism of Action



Source: (Fioretto et al. 2015)
Abbreviations: SGLT; sodium-glucose cotransporter.

Nonclinical evidence of effectiveness was obtained from in vitro studies evaluating the activity of bexagliflozin on human SGLT2, and from in vivo studies evaluating levels of glucosuria, blood glucose, and hemoglobin A1c (HbA1c) in healthy animals and/or diabetic animal models.

In vitro, bexagliflozin selectively inhibited human SGLT2 as compared to SGLT1 with a half maximal inhibitory concentration (IC₅₀) of 2 nM and 5.6 μM, respectively, representing a ~2,400-fold selectivity for SGLT2 over SGLT1 ([Table 6](#)).

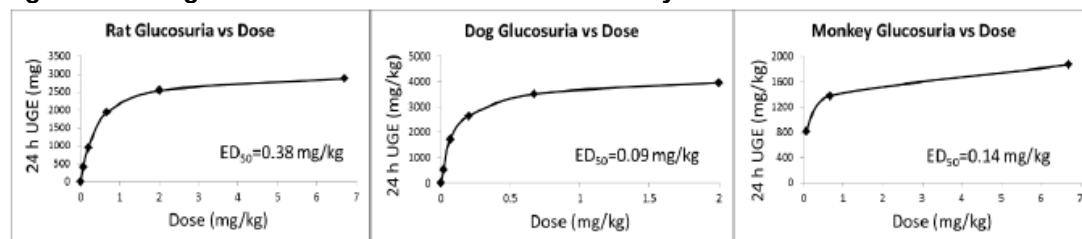
Table 6. Activity and Selectivity of Bexagliflozin

Compound	SGLT1 IC ₅₀ (μM) ¹	SGLT2 IC ₅₀ (μM) ¹	Selectivity
EGT0001442	5.6 ± 1.03	0.002 ± 0.001	2435

¹ IC₅₀ values were derived from AMG uptake experiments ± standard deviation.
Source: Applicant's submission
Abbreviations: Bexagliflozin; IC₅₀, half maximal inhibitory concentration; SGLT; sodium-glucose cotransporter.

In vivo, bexagliflozin elicited dose-dependent glucosuria in normal rats, dogs, and monkeys at exposures equivalent to the clinical dose, with a half maximal effective dose (ED₅₀) ranging between 0.14 and 0.38 mg/kg ([Figure 2](#)).

Figure 2. Bexagliflozin-Induced Glucosuria in Healthy Animals



Glucose excreted in 24 h following single dose administration of bexagliflozin. Dog and monkey excretion values are normalized per kg, rat values are expressed per animal. Data from studies THR-1474-N-349, -351 and -352.

Source: Applicant's submission

Abbreviations: ED₅₀, half maximal effective dose; UGE, urinary glucose excretion.

Secondary to glucosuria, bexagliflozin reduced plasma glucose (by area under the concentration-time curve [AUC]) in rats and dogs following an oral glucose challenge (Table 7 and Table 8).

Table 7. Blood Glucose Reduction in Rats

Group	Dose (mg/kg)	AUC _{0-2h} (mmole·min/L)	AUC _{0-2h} (% of control)
1	0	351.4±64.9	100.0
2	0.1	260.6±100.2*	74.2
3	0.3	248.4±56.5*	70.7
4	1	266.5±87.3*	75.9
5	3	227.7±61.3**	64.8
6	10	92.1±93.7**	26.2

Values of AUC (0-2h) stand for baseline-corrected values calculated using the trapezoidal rule. Values represent the mean ± SD. (n=8).

Source: Applicant's submission

Abbreviations: AUC, area under the concentration-time curve.

Table 8. Blood Glucose Reduction in Dogs

Group	Dose (mg/kg)	AUC (mmole·min/L)	Baseline Corrected AUC (mmole·min/L)
1	0	779±103	81±46
2	0.03	627±52	-46±61**
3	0.1	652±79	-6±29*
4	0.3	629±47	-18±48**
5	1.0	659±73	8±52*
6	3.0	654±37	39±44

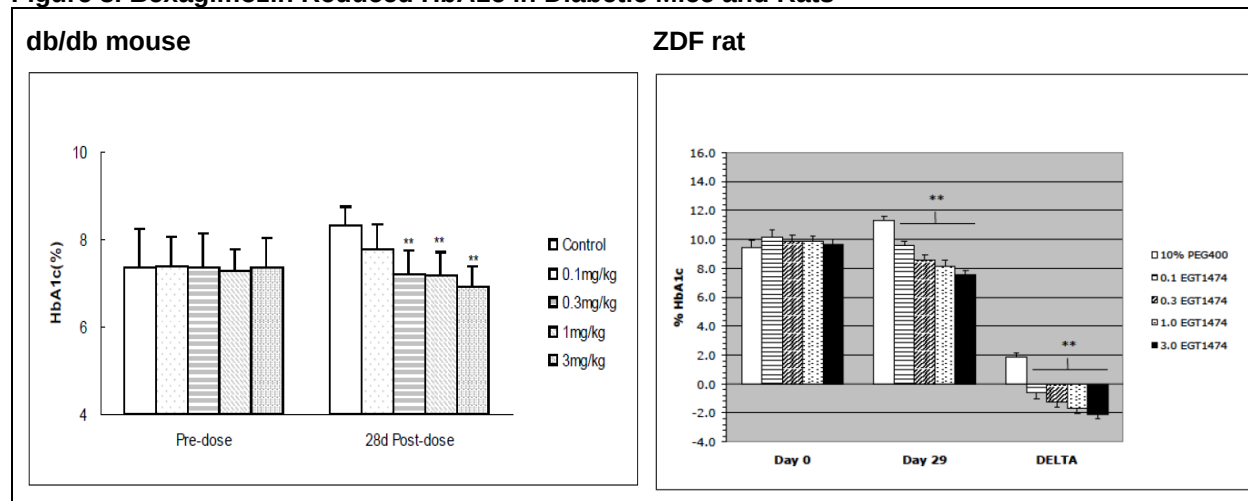
AUC (area under the curve) was calculated (0-2 h) by trapezoidal rule. (n=4)

Values represent the mean ± SD. (n=4).

Source: Applicant's submission

In diabetic mouse (db/db) and rat (ZDF) models, bexagliflozin 0.1 mg/kg to 3 mg/kg dose-dependently reduced HbA1c after four weeks of oral treatment at exposures equivalent to the clinical dose (Figure 3).

Figure 3. Bexagliflozin Reduced HbA1c in Diabetic Mice and Rats



Source: Applicant's submission
Abbreviations: HbA1c; hemoglobin A1c.

6. Assessment of Effectiveness

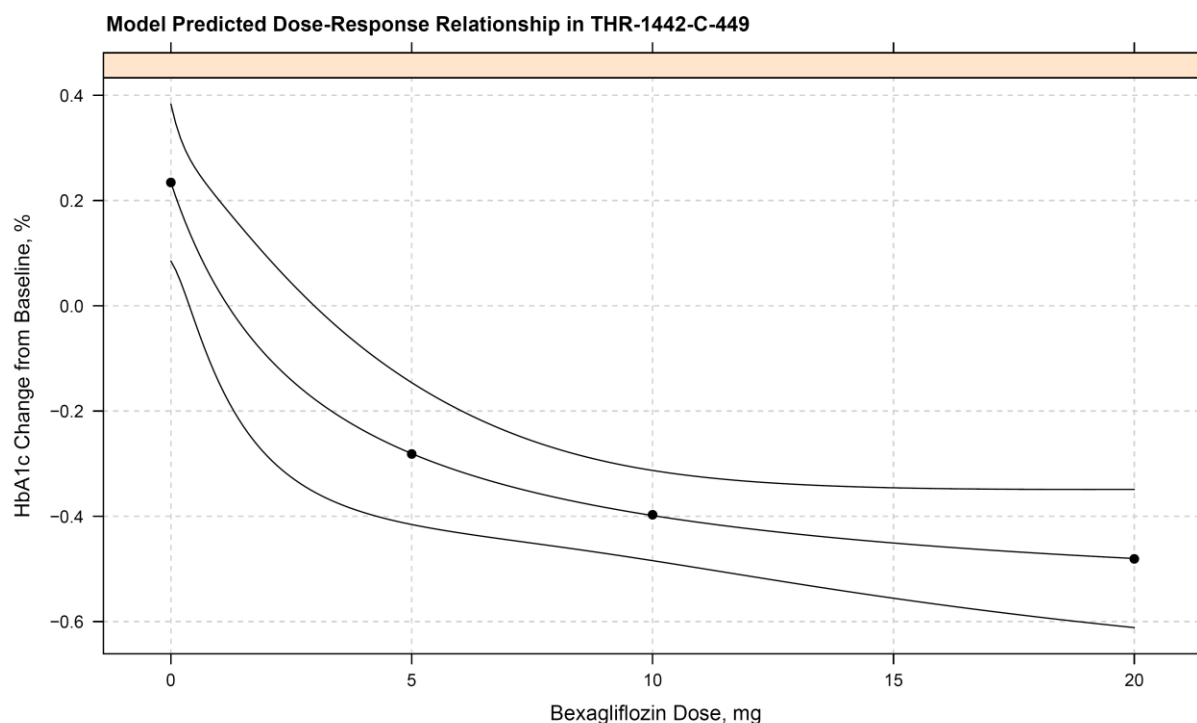
6.1. Dose and Dose Responsiveness

The Applicant's proposed dose for bexagliflozin is 20 mg once daily, taken in the morning with or without food. The proposed dosing regimen is acceptable for approval based on a favorable efficacy and safety profile.

We had recommended the evaluation of two dosage strengths in the phase 3 program (meeting minutes dated September 21, 2016); however, only a 20 mg dosage strength was evaluated. It is unclear whether a higher dosage strength could provide additional glycemic control without significant additional tolerability-related events.

The selection of the 20-mg dose was primarily based on the HbA1c reduction from baseline in T2DM subjects from a 12-week, phase 2, dose-ranging study (C-449). In the study, subjects with T2DM received placebo or bexagliflozin doses ranging from 5 to 20 mg. A dose-response relationship across bexagliflozin dosages of 5 mg to 20 mg was observed, and the unadjusted mean changes from baseline in HbA1c at Week 12 were +0.23%, -0.28%, -0.40%, and -0.48% in the placebo, 5 mg, 10 mg, and 20 mg groups, respectively (Figure 4). A maximum drug effect (E_{max}) model was fitted to the observed data with an estimated maximum mean reduction (95% CI) of -0.82% (-0.51%, -1.1%) and an estimated ED_{50} (95% CI) of 3.0 mg (0, 7.3 mg). After adjusting for placebo mean changes from baseline, 20 mg bexagliflozin was predicted to achieve 76.8% of the maximum pharmacological effect in T2DM subjects. Additionally, the placebo-adjusted least-square mean treatment differences in HbA1c at Week 12 were -0.55%, -0.68%, and -0.80% for 5 mg, 10 mg, and 20 mg, respectively (refer to Section 11.5 in the C-449 study report). The reduction in HbA1c at the proposed dose of 20 mg was considered statistically significant and clinically meaningful.

Figure 4. Change in HbA1c From Baseline at Week 12 in Patients With T2DM, Trial C-449



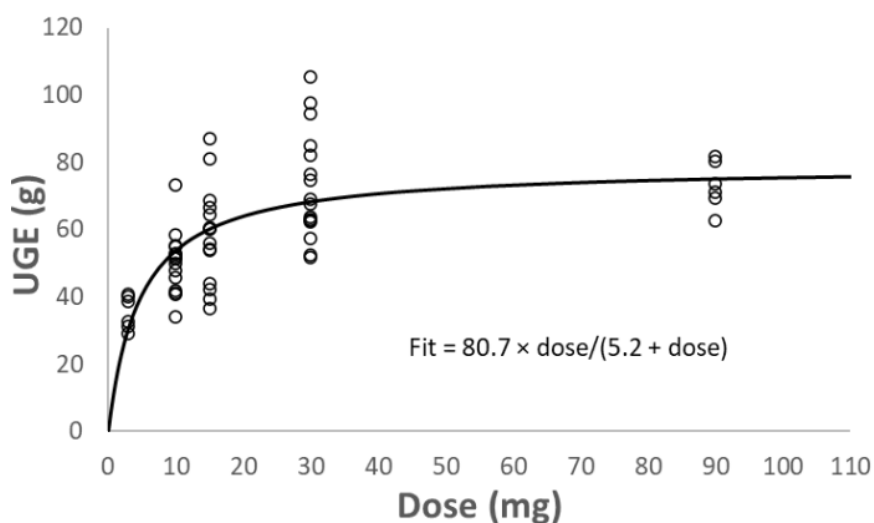
Source: Reviewer independent analysis from Study C-449 efficacy dataset with full analysis population; see Section [14.3](#) Pharmacometrics Review for details

Black dots, observed mean change from baseline of each subgroup by dosage shown; middle black line, model predictions based on parameter estimates; top and bottom black lines, upper and lower bounds of 95% confidence interval based on the parameter standard errors, respectively

Abbreviations: HbA1c; hemoglobin A1c; T2DM, type 2 diabetes mellitus.

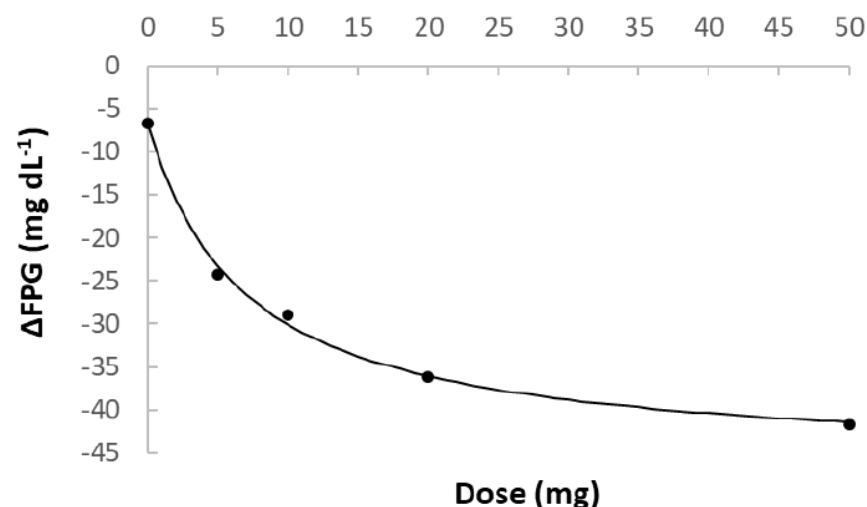
The potential effectiveness of the 20-mg dose was also supported by dose-response relationships of 24-hour urinary glucose excretion (UGE; PD effect of glucosuria) in healthy subjects and fasting plasma glucose in subjects with T2DM (C-445 and C-402). The mean change in UGE as a function of dose ranging from 5 mg to 90 mg was well fit by an $E_{\max}$ model ([Figure 5](#)). The estimated maximum UGE was 80.7 g per day (95% CI: 71.7 to 89.8) and the estimated ED_{50} was 5.2 mg (95% CI: 2.8 to 7.6). A dose of 20 mg was predicted to achieve 79% of the maximum pharmacological effect in nondiabetic subjects. The changes in fasting plasma glucose (FPG) were determined in T2DM subjects at bexagliflozin doses ranging from 5 mg to 50 mg in a 28-day study ([Figure 6](#)). Based on the fitted $E_{\max}$ model, the 20-mg dose is expected to produce ~90% of the maximum effect in lowering FPG.

Figure 5. The 24-hour UGE as a Function of Dose in Healthy Subjects, Trials CLR002 and C-445



Source: Study THR-1442-C-607 Figure S2
Abbreviations: UGE, urinary glucose excretion

Figure 6. Change in FPG From Baseline on Day 28, Trial C-402



Source: Study C-402 Table 14.2.2; Solid line is $\Delta\text{FPG} = -6.77 - 39.4 \times \text{dose} / (6.90 + \text{dose})$; capsule formulation
Abbreviations: FPG, fasting plasma glucose

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Study Design

Overview

The six phase 3 trials used to support efficacy of bexagliflozin were all multicenter, randomized, double-blinded, controlled trials that met the regulatory standards for adequate and well-controlled studies. These studies included four placebo-controlled trials and two active-

controlled trials. The placebo-controlled trials evaluated bexagliflozin as monotherapy (C-450), as add-on to metformin (C-419), as add-on to standard antihyperglycemic medications in subjects with stage 3 CKD (C-448), and as add-on to standard antihyperglycemic medications in subjects with increased CV risk (C-476). The active-controlled trials compared bexagliflozin to glimepiride (C-480) or sitagliptin (C-423) as add-on to metformin. All trials were completed at the time of this NDA review. The Applicant states that all clinical trials were conducted in compliance with good clinical practice, applicable laws, and regulations, and in accordance with the Declaration of Helsinki (1996). Protocol synopses for each trial are presented in Section [15.1](#).

Objectives

The stated primary objective of all phase 3 trials was to assess the effect of bexagliflozin relative to comparator (placebo or active) on the change in HbA1c from baseline to the primary assessment timepoint (Week 24 in C-419, C-450, C-423, C-448, and C-476, and Week 60 in C-480). Key secondary objectives differed between trials but were generally related to evaluation of the effect of bexagliflozin on body weight, systolic blood pressure (SBP), and/or FPG.

Trial Design

The following sections present an overview of noteworthy trial design features in the phase 3 clinical program.

Run-In Period

All trials included a one- or two-week, single-blind, placebo run-in period to assess compliance and uncontrolled hyperglycemia prior to randomization. At the start of the run-in period, subjects received diet and exercise counseling and were provided with a glucometer and instructions for daily use. Subjects were not eligible for randomization if more than one dose (or two doses in C-480) of run-in medication was missed. Subjects were also generally not eligible for enrollment if they experienced uncontrolled hyperglycemia during the run-in period (e.g., FPG ≥ 250 mg/dL on two or more consecutive days, signs and symptoms of uncontrolled hyperglycemia).

Study Treatments

Of the six phase 3, pivotal trials, four trials were placebo-controlled (C-419, C-450, C-448, C-476) and two trials were active-controlled (C-480 utilized glimepiride and C-423 utilized sitagliptin as the active-comparator treatments). All trials evaluated bexagliflozin 20 mg utilizing the to-be-commercialized tablet formulation.

Dose Modification of Study Treatments

As the Applicant only proposes to commercialize one dosage strength (20 mg) of bexagliflozin, no dose modification for bexagliflozin occurred in any trial.

In C-423, subjects assigned to the active comparator group received sitagliptin 100 mg.

In C-480, optimal titration of glimepiride was required, and a titration algorithm was detailed in the study protocol. Briefly, subjects who successfully completed the run-in period were randomized to receive either bexagliflozin tablets with placebo glimepiride capsules (Group 1) or placebo bexagliflozin tablets and active glimepiride capsules (Group 2). Subjects were to receive a starting dose of 2 mg glimepiride or placebo glimepiride at randomization. At Weeks 2, 4, and

6, subjects had in-clinic visits for the assessment of glimepiride up-titration and safety evaluation. Glimepiride doses were increased if a subject met the following two criteria:

- (1) $\geq 50\%$ of documented fasting self-monitoring blood glucose (SMBG) measurements > 110 mg/dL
- (2) No severe or documented symptomatic hypoglycemia events (defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dL)

Subjects were advised to contact the clinical site in the case of persistent hyperglycemia (more than three consecutive daily fasting SMBG measures ≥ 270 mg/dL) such that glimepiride doses could be increased earlier than the next scheduled study visit. After Week 6 of treatment, no further increases in glimepiride were to occur, and rescue medication could be prescribed by the investigator if deemed necessary for the well-being of the subject. As C-480 was double-blinded, subjects assigned to receive placebo glimepiride received mock titrations at Weeks 2, 4, and 6 based on the noted glycemic criteria.

In all trials that allowed background antihyperglycemic therapy (C-419, C-423, C-448, C-476, C-480), dosing was to remain stable over the course of the trial unless a change was deemed necessary for the well-being of the subject (see “Rescue Medication” below). Protocols stated that changes to dosage and administration that occurred during trials should be documented.

Stratification

Stratification factors varied by trial as summarized below:

- C-419: HbA1c ≤ 8.5 or not; United States or Japan clinical site
- C-423: HbA1c ≤ 8.5 or not
- C-448: HbA1c ≤ 8.5 or not; baseline insulin use or not; estimated glomerular filtration rate (eGFR) 30 to 44 or 45 to 59 mL/min/1.73 m²
- C-450: HbA1c ≤ 8.5 or not; treatment-naïve or not
- C-476: HbA1c ≤ 9.5 or not; body mass index (BMI) < 25 kg/m² or not; eGFR < 60 mL/min/1.73 m² or not; history of heart failure (HF) or not
- C-480: HbA1c ≤ 8.5 or not; metformin use only or metformin use +1 additional antihyperglycemic agent; eGFR ≥ 90 mL/min/1.73 m² or not

Inclusion/Exclusion Criteria

Key inclusion and exclusion criteria for the pivotal, phase 3, efficacy trials are presented in

NDA 214373
Brenzavvy (bexagliflozin)

[Table 9.](#)

APPEARS THIS WAY ON ORIGINAL

Table 9. Summary of Key Inclusion and Exclusion Criteria in Pivotal Efficacy Trials

Trials	Trial C-450 Monotherapy	Trial C-419 Add-On Met	Trial C-448 CKD	Trial C-476 High CV Risk	Trial C-423 vs. Sitagliptin	Trial C-480 vs. Glimepiride
Inclusion						
Male or Female with T2DM	X	X	X	X	X	X
≥18 years old*	X	X	X		X	X
≥40 years old				X		
Treatment naïve or taking one oral antihyperglycemic willing to under a 6-week washout	X					
On stable metformin dose ≥1,500 mg/day as sole antihyperglycemic medication ^{±,β}		X			X	X
Taking stable doses of antihyperglycemic medications (excluding SGLT2 inhibitors)			X	X		
HbA1c ≥7.0% to ≤10.5% at screening and/or randomization	X		X			X
HbA1c ≥7.5% to ≤10.5% at screening and/or randomization**		X				
HbA1c ≥7.0% to ≤11.0% at randomization ^π				X	X	
On stable doses of medications for HTN and/or dyslipidemia (if applicable)	X	X			X	
eGFR ≥30 to <60 mL/min/1.73 m ²			X			
BMI ≤45 kg/m ²	X	X	X		X	X
Increased CV Risk ^κ				X		
Exclusion						
T1DM, maturity-onset diabetes of the young (MODY)	X	X	X	X	X	X
Female subjects pregnant or breastfeeding	X	X	X	X	X	X
History of UTI or GMI within 6 weeks of screening or a history of ≥3 events requiring treatment within 6 months of screening	X	X	X	X	X	X
Hemoglobinopathy impacting HbA1c measurement	X	X	X	X	X	X
Symptomatic hypoglycemia >1 episode/week			X	X		
ALT and/or AST ≥2.5xULN or total bilirubin ≥1.5xULN	X	X	X	X	X	X
Uncontrolled HTN [#]	X	X	X		X	X
eGFR <60 mL/min/1.73 m ²	X	X			X	X
eGFR <45 mL/min/1.73 m ²				X		
Cancer, active or in remission for <3 years (NMSC and in situ carcinoma of the cervix excluded)			X	X	X	X
NYHA Class IV HF, MI, unstable angina, stroke, or hospitalization for HF within 3 months of screening%	X	X	X	X	X	X

NDA 214373
Brenzavvy (bexagliflozin)

Trials	Trial C-450 Monotherapy	Trial C-419 Add-On Met	Trial C-448 CKD	Trial C-476 High CV Risk	Trial C-423 vs. Sitagliptin	Trial C-480 vs. Glimepiride
Scheduled for PCI, CABG, or any surgical procedure				X		
Diagnosis of peripartum or chemotherapy-induced cardiomyopathy within prior 12 months				X		
Symptomatic bradycardia or 2nd or 3rd degree AV block without a pacemaker				X		
Implantation of a cardiac resynchronization therapy (CRT) device within prior 3 or intent to implant a CRT device within 6 months				X		

Source: Generated by Clinical Reviewer from phase 3 protocols

*In Trials C-419 and C-448 subjects were eligible if ≥20 years old

** In Trial C-419 subjects were also eligible for enrollment into an uncontrolled high-glycemic group if screening HbA1c was >10.5% and ≤12%

±In Trial C-419, subjects at Japanese sites were eligible for enrollment if on stable doses of metformin ≥1,000 mg/day

β Subjects in Trial C-480 were considered eligible if they were taking stable doses of metformin ≥1,500 mg/day or if they were taking ≥1,500 mg/day of metformin plus one additional antihyperglycemic agent and willing to undergo a 6-week washout prior to randomization

¥Increased CV risk was defined as either having a history of atherosclerotic vascular disease, a history of NYHA class II or class III heart failure, and/or age ≥55 years with two or more additional CV risk factors (see protocol synopsis in Section 15.1.5 for additional information).

Definitions for uncontrolled HTN differed between trials, ranging from SBP >160 to 180 mm Hg and/or DBP >110 mm Hg

π The initial protocol for Trial C-476 specified inclusion criteria for HbA1c to be 7.5 to 11% but was updated to 7 to 11% in Version 7.

%NYHA Class IV was not an exclusion criterion in Trial C-480

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CABG, coronary artery bypass graft; CV cardiovascular; eGFR, estimated glomerular filtration rate; GMI, genital mycotic infections; HbA1c; hemoglobin A1c; HF, heart failure; HTN, hypertension; MI, myocardial infarction; NMSC, non-melanoma skin cancer; PCI; percutaneous coronary intervention; T2DM, type 2 diabetes mellitus; SGLT; sodium-glucose cotransporter; ULN, upper limit of normal; UTI, urinary tract infections.

Rescue Medication

Subjects were to receive counseling regarding appropriate diet and exercise to aid in glycemic control throughout all phase 3 trials. In addition, subjects were advised to take daily fasting SMBG measurements. Rescue medication was recommended if, after diet and exercise counseling, subjects had uncontrolled hyperglycemia. While specific rescue criteria differed by trial,¹ criteria were generally as follows:

- (1) More than three consecutive, daily fasting SMBG measures of ≥ 270 mg/dL from baseline to Week 6, ≥ 240 mg/dL from Week 6 to Week 12, or ≥ 200 mg/dL from Week 12 to end of treatment.
- (2) Fasting SMBG values ≥ 250 mg/dL and associated with clinical signs or symptoms of hyperglycemia (e.g., weight loss, blurred vision, increased thirst, increased urination, or fatigue), and the signs or symptoms are severe.

In C-476, subjects were to be managed with diet and exercise counseling or rescue medication (if above criteria were met) for the first 24 weeks. After the primary endpoint measurement at Week 24, changes to the medical therapy for hyperglycemia could occur at investigator discretion based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM.

Study Endpoints

The primary endpoint in all phase 3 trials was change from baseline in HbA1c to the prespecified timepoint at Week 24 (except C-480, at Week 60). HbA1c is a surrogate endpoint for microvascular disease risk reduction and is a validated surrogate endpoint (FDA 2022) to support glycemic control indications in patients with diabetes. In the bexagliflozin clinical program, HbA1c was measured using a high-performance liquid chromatography (HPLC) method certified to be Level 1 by the National Glycohemoglobin Standardization Program (NGSP) and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.

A summary of secondary endpoints as described in the statistical analysis plan (SAP) for each trial is presented in [Table 10](#). To control for type I error, a hierarchical testing approach was carried out for the testing of secondary endpoints. No formal hypothesis testing occurred for secondary efficacy endpoints in C-419 and it is thus excluded from [Table 10](#). Secondary endpoints evaluated for exploratory purposes in C-419 included changes in FPG, SBP, body weight, and proportion of subjects with HbA1c $\leq 7\%$ over time.

¹ C-419 and C-423 also recommended rescue treatment if HbA1c was $>8.0\%$ between weeks 12-24. C-450 did not specify a minimum fasting SMBG values or specify “severe” signs and symptoms for rescue criteria to be met for criterion #2. In C-476, two consecutive, daily, fasting SMBG values above the noted thresholds could prompt rescue treatment. C-476 also did not include rescue criteria regarding clinical signs and symptoms of hyperglycemia.

Table 10. Summary of Key Secondary Endpoints in Pivotal Efficacy Trials

Trial C-423 vs. Sitagliptin	Trial C-448 CKD	Trial C-450 Monotherapy	Trial C-476 High CV Risk	Trial C-480 vs. Glimepiride
1. Change in FPG from baseline at Week 24	1. Change from baseline to Week 24 in body weight in subjects with baseline BMI ≥ 25 kg/m ²	1. Change in SBP from baseline to Week 24	1. Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes	1. Change from baseline to Week 60 in body weight in subjects with baseline BMI ≥ 25 kg/m ²
2. Change in body weight in subjects with baseline BMI ≥ 25 kg/m ² at Week 24	2. Change from baseline to Week 24 in SBP in subjects with baseline SBP ≥ 130 mm Hg from baseline	2. Change in body weight from baseline to Week 24 in subjects with a BMI ≥ 25 kg/m ²	2. Change in body weight from baseline to Week 48 in subjects with a BMI ≥ 25 kg/m ²	2. Change from baseline to Week 60 in SBP in subjects with baseline SBP ≥ 140 mm Hg
3. Change in SBP from baseline at Week 24	3. Change from baseline to Week 24 in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m ²		3. Change in SBP from baseline to Week 24 in subjects with baseline SBP ≥ 140 mm Hg	3. Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks
	4. Change from baseline to Week 24 in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m ²			4. Change from baseline to Week 60 in HbA1c

Source: Compiled by Clinical Reviewer

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; SBP, systolic blood pressure.

6.2.2. Statistical Analysis Plan

This section provides a brief description of key SAP elements. Please see Section [12.2](#) for a detailed description of the SAP and its development history.

Analysis Set for Efficacy

The intent-to-treat (ITT) analysis set included all subjects who were randomized and was preplanned to serve as the primary set for the efficacy analyses. All analyses of the ITT analysis set were based on the randomization assignment.

Primary Analysis Method for the Primary and Key Secondary Efficacy Endpoints

During the IND stage, the Applicant first proposed an LOCF analysis, and then an MMRM method for the primary analysis of the primary or secondary endpoints with missing data. FDA continuously advised against the LOCF, and the MMRM approach that does not appropriately address missing data, as it treats the behavior of missing data for those subjects who are off-treatment to be the same as that of observed data for those subjects who are on-treatment in the same treatment group. The Applicant's prespecified primary estimand for the bexagliflozin T2DM HbA1c studies is the treatment policy estimand, which is FDA's preferred estimand. An appropriate statistical method that aligns with the treatment policy estimand in handling missing data is the retrieved- dropout-based pattern mixture multiple imputation method (MI-RD). To

estimate the treatment policy estimand, efficacy data should be collected and utilized in analyses on all randomized treated subjects regardless of treatment adherence, rescue status, or other post baseline status. Missing data should be imputed in a fashion consistent with what the measurement would have been, had it been measured.

Disagreeing with the proposed MMRM approach in the Applicant's preNDA meeting package (meeting date December 5, 2019), FDA recommended that where there are a sufficient number of retrieved dropouts (subjects who discontinued treatment before the final assessment window but still had an efficacy measurement in the final assessment window). FDA prefers a multiple imputation approach that models the missing final assessment of nonretrieved dropouts (subjects who discontinued treatment before the final assessment window and did not have a measurement in this assessment window) based on known measurements from the retrieved dropouts. The Applicant's pivotal trials were all completed and unblinded (database locked at on November 22, 2019) at the time of the preNDA meeting. Clinical study reports (CSRs) had been finalized before the FDA's specific recommendation of retrieved drop-out approach or return-to-baseline approach (if insufficient retrieved dropouts) analysis advice was delivered. Across the six HbA1c studies, an insufficient number of retrieved dropouts rendered the MI-RD approach analysis not feasible. Following the FDA's recommendation at a preNDA meeting, the Applicant used the multiple imputation based on return-to-baseline approach (MI-RTB) in handling missing data as post-hoc analyses. As analysis methods have been continuously recommended by FDA to estimate the appropriate treatment effect for evaluation of efficacy, these post-hoc analyses were acceptable.

A three-step MI-RTB plus analysis of covariance (ANCOVA) approach was adopted by the Applicant as the primary analysis method for both the primary and key secondary efficacy endpoints; the same method was used by the FDA statistical reviewer in this NDA review. The three steps are:

- (1) MI-RTB to impute missing data: based on the baseline of the subject for an endpoint, with variance estimated from an ANCOVA model of nonmissing Week 24 (Week 60 for Study C-480) HbA1c for the treatment arms. The ANCOVA model will include the same variables as the primary analysis model. The variance, σ^2 , for the Week 24 (Week 60 for Study C-480) data for each treatment arm will be used as the variance in an imputation model $X_{Week\ 24\ or\ 60} \sim N(X_{baseline}, \sigma^2)$ to impute the missing Week 24 (Week 60 for Study C-480) data.
- (2) ANCOVA model analysis: for each iteration of the multiply imputed full dataset, the primary and secondary endpoints were analyzed using an ANCOVA model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate. The least squares (LS) mean differences between bexagliflozin 20 mg and a comparator in each study, with the associated two-sided 95% CIs were estimated from the ANCOVA model.
- (3) Rubin's rule to combine the results: Rubin's rule was applied to combine and synthesize the results from step 2 to estimate an overall treatment effect and corresponding variability.

Noninferiority Margin for the Active-Controlled Trials

For the active-controlled trials C-423 and C-480, a noninferiority margin of 0.35% was preplanned by the Applicant and agreed upon by the FDA review team at the clinical development stage. See the Applicant's justifications for the margin selection in Section [12.2](#).

Multiple Testing Procedures

In each of the six pivotal studies, the study SAP prespecified a hierarchical testing sequence of primary endpoint and key secondary endpoints to control for study-wise type I error due to multiplicity. For each endpoint in the sequence, a two-sided statistical test was to be conducted at the 5.0% significance level. In each study, if the primary endpoint met the statistical significance, then the key secondary endpoints were to be tested sequentially in the order as listed in [Table 10](#) and [Table 136](#) [Section [16](#)].

Tipping Point Sensitivity Analyses for the Primary Efficacy Endpoints

For each of the four superiority trials (C-450, C-419, C-448, and C-476), a two-dimensional delta-based tipping point analysis was carried out to assess the robustness of inferences from the primary analysis method to deviations from its underlying assumptions, targeting the same primary estimand.

For each of the two active-controlled trials (C-423 and C-480), the FDA statistical reviewer performed a one-dimensional tipping point analysis: based on the RTB-MI imputed datasets, penalizing the missing outcomes on the bexagliflozin arm by applying a delta of size equal to the null hypothesis of the noninferiority test (i.e., the noninferiority margin of 0.35%) while keeping the MI-RTB imputed active-control arm missing outcomes unchanged.

Subgroup Analyses

For each of the preplanned subgrouping factors (age, gender, race, region and baseline HbA1c for all studies, see Section [16](#) preplanned subgroups of each individual study), a by-subgroup analysis was firstly performed for each subgroup level using the primary analysis method (with modifications on covariates when necessary) to derive a sample estimate of the subgroup treatment effect; subsequently, a Bayesian hierarchical model was used to derive a shrinkage estimate of the subgroup treatment effect using the sample estimates. Forests plots are used to present both the "sample" and "shrinkage" estimates and corresponding confidence intervals.

To investigate for potential effect modification of baseline HbA1c levels, an additional exploratory simple linear regression analysis treating baseline HbA1c as a continuous variable was carried out for each of the four placebo-controlled studies. The response variable was the change from baseline in HbA1c at Week 24, the predictor variables included treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction. The size and the significance level of the interaction term (difference in by-arm baseline HbA1c slopes) from this model fitting is an indicator of the potential modification effect.

6.2.3. Results of Analyses

6.2.3.1. Demographics, Baseline Characteristics, and Disposition

6.2.3.1.1. Demographics and Baseline Characteristics

Relevant demographics and baseline clinical characteristics of the pivotal efficacy trials are shown in [Table 11](#). Characteristics between drug and comparator groups were generally balanced in all trials. Trials enrolling subjects who were either treatment-naïve or inadequately controlled on metformin (i.e., C-419, C-423, C-450, C-480) were generally similar, with a mean age of approximately 55 to 60 years and an average diabetes duration of approximately 9 years. In contrast, subjects enrolled in C-448 and C-476 were older (average age of approximately 65 to 70 years) with a longer duration of diabetes (approximately 15 years) with a significant amount of baseline insulin use (approximately 50 to 55%). Proportions of male and female subjects varied by trial. Trial C-476, which evaluated subjects with increased risk for MACE, enrolled a majority of male subjects (approximately 70%). The majority of subjects in most trials were White, although C-419 and C-448 enrolled approximately 50% and 39% of Asian subjects, respectively. All trials predominantly enrolled non-Hispanic/Latino subjects.

Table 11. Baseline Demographic and Clinical Characteristics, Pivotal Efficacy Trials

Characteristic	Trial C-419 Add-On Met		Trial C-423 vs. Sitagliptin		Trial C-450 Monotherapy		Trial C-480 vs. Glimepiride		Trial C-448 CKD		Trial C-476 High CV Risk	
	Bexa N=158	Placebo N=159	Bexa N=191	Sita N=193	Bexa N=138	Placebo N=69	Bexa N=213	Glim N=213	Bexa N=157	Placebo N=155	Bexa N=1133	Placebo N=567
Sex, n (%)												
Male	100 (63)	94 (59)	71 (37)	67 (35)	66 (48)	34 (49)	118 (55)	130 (61)	92 (59)	104 (67)	792 (70)	390 (69)
Female	58 (37)	65 (41)	120 (63)	126 (65)	72 (52)	35 (51)	95 (45)	83 (39)	65 (41)	51 (33)	341 (30)	177 (31)
Age, years												
Mean (SD)	56 (10)	56 (11)	59 (10)	60 (10)	56 (10)	55 (11)	59 (9)	60 (10)	69 (8)	70 (8)	64 (8)	65 (8)
Median	56	56	61	61	56	55	61	60	70	70	65	65
(min, max)	(30, 79)	(28, 81)	(36, 79)	(23, 83)	(26, 79)	(33, 81)	(33, 87)	(28, 86)	(39, 88)	(47, 85)	(39, 91)	(40, 92)
Age groups (years), n (%)												
<65	127 (80)	124 (78)	130 (68)	129 (67)	112 (81)	58 (84)	150 (70)	146 (69)	38 (24)	37 (24)	562 (50)	276 (49)
≥65	31 (20)	35 (22)	61 (32)	64 (33)	26 (19)	11 (16)	63 (30)	67 (31)	119 (76)	118 (76)	571 (50)	291 (51)
≥75	6 (4)	7 (4)	6 (3)	8 (4)	4 (3)	4 (6)	7 (3)	16 (8)	40 (25)	50 (32)	113 (10)	67 (12)
Race, n (%)												
White	51 (32)	48 (30)	158 (83)	156 (81)	96 (70)	58 (84)	198 (93)	204 (96)	83 (53)	88 (57)	879 (78)	430 (76)
Asian	78 (49)	79 (50)	27 (14)	35 (18)	15 (11)	5 (7)	9 (4)	4 (2)	61 (39)	59 (38)	108 (10)	55 (10)
Black/African American	26 (16)	29 (18)	6 (3)	2 (1)	25 (18)	6 (9)	5 (2)	4 (2)	9 (6)	6 (4)	46 (4)	28 (5)
Other	3 (<1)	3 (<1)	0 (0)	0 (0)	2 (<1)	0 (<1)	1 (<1)	1 (<1)	4 (<1)	2 (<1)	100 (10)	54 (10)
Ethnicity, n (%)												
Hispanic or Latino	35 (22)	32 (20)	3 (2)	7 (4)	67 (49)	40 (58)	46 (22)	47 (22)	7 (4)	17 (11)	166 (15)	93 (16)
Non-Hispanic or Latino	123 (78)	127 (80)	188 (98)	186 (96)	71 (51)	29 (42)	167 (78)	166 (78)	149 (95)	138 (89)	967 (85)	474 (84)
Not reported	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Country of participation, n (%)												
United States	83 (53)	83 (52)	15 (8)	21 (11)	117 (85)	57 (83)	65 (31)	63 (30)	53 (34)	50 (32)	397 (35)	205 (36)
Non-US	75 (47)	76 (48)	176 (92)	172 (89)	21 (15)	12 (17)	148 (69)	150 (70)	99 (63)	105 (67)	548 (48)	276 (49)
BMI, kg/m ²												
Mean (SD)	29.7 (6.4)	30.0 (6.3)	32.1 (6.1)	31.4 (5.3)	32.8 (5.7)	30.5 (4.6)	31.4 (4.9)	32.2 (5.2)	30.3 (6.0)	30.1 (5.8)	32.8 (6.1)	32.2 (5.8)
Median	28.9	29.1	31.3	30.5	31.8	29.8	31.1	31.5	29.5	28.8	32.0	31.6
(min, max)	(17.4, 45.4)	(19.1, 44.9)	(20.5, 46.7)	(18.6, 44.9)	(20.4, 46.0)	(23.4, 44.1)	(18.3, 44.5)	(19.8, 46.3)	(19.0, 44.9)	(20.1, 44.6)	(19.6, 61.6)	(21.2, 65.2)
BMI Group, n(%)												
<25	39 (25)	35 (22)	22 (12)	19 (10)	9 (7)	7 (10)	12 (6)	11 (5)	32 (20)	33 (21)	86 (8)	45 (8)
≥25	119 (75)	124 (78)	169 (88)	174 (90)	128 (93)	62 (90)	201 (94)	202 (95)	125 (80)	122 (79)	1047 (92)	522 (92)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

NDA 214373
Brenzavvy (bexagliflozin)

Trial C-419 Add-On Met			Trial C-423 vs. Sitagliptin		Trial C-450 Monotherapy		Trial C-480 vs. Glimepiride		Trial C-448 CKD		Trial C-476 High CV Risk	
Duration of T2DM, years												
Mean (SD)	9.3 (6.6)	8.9 (5.9)	8.2 (5.7)	9.4 (5.7)	9.3 (6.6)	8.9 (5.9)	9.3 (5.9)	8.0 (5.5)	15.5 (9.2)	16.3 (9.0)	14.9 (8.6)	15.2 (9.3)
Median (min, max)	8.0 (0.2, 33.1)	8.0 (0.2, 31.1)	7.4 (0.2, 33.9)	8.8 (0.2, 29.8)	8.0 (0.2, 33.1)	8.0 (0.2, 31.1)	8.5 (0.3, 32.9)	6.9 (0.2, 32.3)	15.2 (0.0, 50.2)	17.0 (0.0, 47.3)	14.3 (0.4, 57.4)	13.7 (0.3, 53.7)
Baseline Insulin, n (%)												
Insulin treated	NA	NA	NA	NA	NA	NA	NA	NA	86 (55)	88 (57)	610 (54)	292 (51)
Not insulin treated	NA	NA	NA	NA	NA	NA	NA	NA	71 (45)	67 (43)	523 (46)	275 (49)
Baseline HbA1c, (%)												
Mean (SD)	8.7 (0.9)	8.6 (0.8)	7.9 (0.8)	8.0 (0.9)	8.7 (0.9)	8.6 (0.8)	8.0 (0.8)	8.0 (0.7)	8.0 (0.8)	7.9 (0.8)	8.3 (0.9)	8.3 (0.9)
Median (min, max)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)	7.7 (6.7, 10.3)	7.8 (6.3, 10.8)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)	7.9 (6.7, 10.5)	7.9 (6.2, 10.1)	7.8 (6.7, 10.4)	7.8 (5.9, 10.4)	8.2 (5.8, 11.0)	8.2 (5.5, 11.4)
HbA1c Group, n (%)												
≤8.5%	83 (53)	82 (52)	144 (75)	145 (75)	107 (78)	55 (80)	155 (73)	159 (75)	124 (79)	123 (79)	716 (63)	362 (64)
>8.5%	75 (47)	77 (48)	47 (25)	48 (25)	31 (22)	14 (20)	58 (27)	54 (25)	33 (21)	32 (21)	417 (37)	205 (36)
eGFR (mL/min/1.73 m ²)												
Mean (SD)	89.0 (19.4)	91.5 (21.2)	88.7 (17.3)	87.1 (18.3)	93.4 (19.0)	97.3 (24.2)	91.8 (17.9)	91.1 (18.2)	45.4 (8.6)	44.8 (8.1)	77.5 (19.9)	78.0 (20.3)
Median (min, max)	85 (58, 143)	88 (60, 179)	87.5 (54.6, 163.6)	85.0 (48.3, 148.6)	93 (57, 164)	93 (58, 181)	90 (55, 146)	89 (53, 163)	46.3 (26.3, 73.3)	45.0 (25.7, 63.9)	75.6 (25.2, 158.1)	75.6 (35.6, 155.7)
eGFR Group, mL/min/1.73 m ²												
Missing ^β	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)
<30	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)	4 (3)	1 (<1)	0 (0)
≥30 to <45	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	70 (45)	73 (47)	33 (3)	17 (3)
≥45 to <60	2 (1)	0 (0)	7 (4)	6 (3)	3 (2)	2 (3)	6 (3)	6 (3)	77 (49)	74 (48)	191 (17)	92 (16)
≥60 to <90	87 (55)	86 (54)	100 (52)	106 (55)	59 (43)	29 (42)	99 (46)	103 (48)	7 (4)	4 (3)	623 (55)	313 (55)
>90	69 (44)	73 (46)	84 (44)	81 (42)	76 (55)	38 (55)	108 (51)	102 (48)	0 (0)	0 (0)	285 (25)	145 (26)
SBP, mm Hg												
Mean (SD)	128.8 (14.4)	129.7 (15.1)	135.0 (12.2)	135.7 (14.3)	131.0 (14.4)	125.6 (13.8)	133.3 (14.9)	134.2 (14.4)	135.9 (14.2)	137.6 (14.7)	134.2 (16.2)	133.7 (16.2)

Source: Generated by statistical reviewer

*In Study C-480, two subjects had baseline eGFR value missing.

^β Subject eligibility was determined based on screening eGFR measurements. This Table presents baseline eGFR measurements. Variability between screening and baseline eGFR measurements generally accounts for the enrollment of subjects who did not meet the eligibility criteria (e.g., enrollment of subjects with eGFR ≥60 mL/min/1.73 m² in C-448, enrollment of subjects with eGFR <45 mL/min/1.73 m² in C-476, etc.).

Abbreviations: Bexa, bexagliflozin; BMI, body mass index; eGFR, estimated glomerular filtration rate; Glim, glimepiride; HbA1c, hemoglobin A1c; Met, metformin; N, number of subjects in treatment arm; n, number of subjects in subgroup; SBP, systolic blood pressure; Sita, sitagliptin; T2DM, type 2 diabetes mellitus

6.2.3.1.2. Disposition

Analysis populations and subject disposition from the efficacy trials is summarized in [Table 12](#). Screened subjects were eligible for randomization if study-specific inclusion/exclusion criteria were met and if the subject successfully completed the run-in period. The most common reasons subjects were not eligible for randomization varied by trial but included having screening HbA1c <7% and not meeting the eligibility criteria for renal function.

Approximately 90 to 95% of the subjects completed each study ([Table 12](#)). The trials with the least completers were C-419 and C-480, with about 90% of subjects in both trials completing treatment in the bexagliflozin and placebo groups, respectively. While these trials had fewer completers as compared to other trials in the clinical program, the completion rate is considered acceptable, and it is reassuring that no imbalances in completers between treatment groups was observed. While data are limited, there were no discernable trends in reasons for study discontinuation between treatment arms and study. Imbalances in subjects lost to follow-up were observed in some trials (e.g., seven and one subjects in the bexagliflozin and placebo groups were lost to follow up, respectively, in C-450); however, this finding was not observed consistently, thus limiting interpretability. See Section [16.4](#) for additional information on disposition for each trial.

Table 12. Analysis Populations and Subject Disposition, Phase 3 Efficacy Trials

	Trial C-419* Add-On Met		Trial C-423 vs. Sitagliptin		Trial C-448 CKD		Trial C-450 Monotherapy		Trial C-476 ^β High CV Risk		Trial C-480 ^β vs. Glimepiride	
Screened, Disposition, n (%)	521		563		490		466		3270		812	
	Bexa	Placebo	Bexa	Sita	Bexa	Placebo	Bexa	Placebo	Bexa	Placebo	Bexa	Glim
Randomized	158 (100)	159 (100)	192 (100)	194 (100)	157 (100)	155 (100)	140 (100)	70 (100)	1134 (100)	567 (100)	214 (100)	213 (100)
ITT Population	158 (100)	159 (100)	191 (99)*	193 (99)*	157 (100)	155 (100)	138 (99)*	69 (99)*	1133 (100)	567 (100)	213 (100)*	213 (100)
PP Population	151 (96)	156 (98)	188 (98)	191 (98)	154 (98)	150 (97)	131 (94)	67 (96)	1072 (95)	548 (97)	196 (92)	194 (91)
Safety Population	158 (100)	159 (100)	191 (99)	193 (99)	157 (100)	155 (100)	138 (99)	69 (99)	1132 (100)	567 (100)	213 (100)	213 (100)
Completed	141 (89)	142 (89)	180 (94)	189 (97)	152 (97)	144 (93)	123 (88)	64 (91)	1089 (96)	542 (96)	193 (90)	192 (90)
Discontinued Study	17 (11)	17 (11)	11 (6)	4 (2)	5 (3)	11 (7)	15 (11)	5 (7)	44 (4)	25 (4)	20 (9)	21 (10)
Protocol Violation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (<1)	1 (<1)	1 (<1)	0 (0)
AE	3 (2)	2 (1)	5 (3)	1 (1)	1 (1)	4 (3)	0 (0)	0 (0)	9 (1)	3 (1)	2 (1)	5 (2)
Consent withdrawal	9 (6)	5 (3)	4 (2)	2 (1)	2 (1)	2 (1)	6 (4)	1 (1)	17 (1)	13 (2)	10 (5)	9 (4)
Lost to Follow Up	5 (3)	9 (6)	0 (0)	1 (1)	1 (1)	3 (2)	7 (5)	1 (1)	8 (1)	1 (<1)	6 (3)	5 (2)
Withdrawal by Investigator	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (<1)	0 (0)	0 (0)	0 (0)
Withdrawal by Sponsor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	7 (1)	7 (1)	0 (0)	0 (0)
Other ^{††}	0 (0)	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	2 (1)	1 (1)	1 (<1)	0 (0)	1 (<1)	2 (1)

Source: Compiled from Statistical Review with modifications where indicated (see ^β)

*The single-arm high glycemic group of C-419 is excluded from this table.

^{††}Other reasons include pregnancy, entry criteria not met, and failure in follow up.

^βThe disposition information presented in this Table is based on the variables COMPLFL (Completers Population Flag) and DCSREAS (Reason for Discontinuation from Study) variables for each trial in the ADSL dataset. As the duration of subject participation varied in C-476 and C-480, the data presented in this table are disposition information at the time of the primary endpoint measurement (i.e., 24 and 60 weeks in C-476 and C-480, respectively) reported by the Applicant.

* Trials C-423, C-450, C-476, and C-480 excluded a small number of randomized subjects from the ITT population. In C-423, two subjects were excluded from the ITT populations due to site closure. In C-450, three randomized subjects were excluded in the ITT population due to GCP violations. Subjects 450 (b) (6) and 450 (b) (6) were the same person who enrolled in two clinical sites (b) (6) and (b) (6). Subject 450 (b) (6) enrolled in another bexagliflozin clinical Trial C-480 (this subject was also excluded from the ITT population of C-480). In C-476, one randomized subject was excluded from the ITT population due to a GCP violation.

Abbreviations: AE, adverse event; Bexa, bexagliflozin; GCP, good clinical practice; ITT, intent-to-treat; ITT Population, all randomized subjects; Met, metformin; PP Population, per-protocol subjects; Safety Population, randomized and had taken at least one dose

6.2.3.2. Primary Efficacy Results, Sensitivity, and Subgroup Analyses

6.2.3.2.1. Primary Efficacy Results

[Table 13](#) summarizes FDA's primary analysis results for the six pivotal efficacy studies in the bexagliflozin clinical development program. Additional detailed information on the efficacy analysis can be found in [Section 16](#).

Superiority of bexagliflozin to placebo was demonstrated for the primary endpoint of change in HbA1c from baseline to Week 24 for the four placebo-controlled trials (C-419, C-448, C-450, and C-476). Reductions in HbA1c were both statistically and clinically significant. Bexagliflozin was statistically superior to placebo as monotherapy, with a placebo-adjusted change from baseline of -0.38% (-0.63%, -0.13%; $p=0.002$) in C-450, and as add-on to metformin, with a placebo-adjusted change from baseline of -0.48% (-0.69%, -0.26%; $p<0.0001$). In addition, bexagliflozin was statistically superior to placebo from baseline to Week 24 in subjects with increased CV risk on standard of care therapy for glycemic control (placebo-adjusted change from baseline of -0.44% [-0.53%, -0.35%; $p<0.0001$]). While statistically significant, glycemic efficacy was more modest in C-448, enrolling patients with moderate renal impairment (i.e., $eGFR \geq 30$ to <60 mL/min/1.73 m²), with a placebo-adjusted change from baseline of -0.27% (-0.44%, -0.09%; $p=0.002$). Efficacy in this patient population is discussed in additional detail in [Section 6.3.1](#).

Noninferiority was achieved for the two active-controlled trials (C-423 and C-480). Trial C-423 compared bexagliflozin to sitagliptin at the recommended dose for patients without renal impairment (100 mg). Trial C-480 compared bexagliflozin to glimepiride 2, 4, or 6 mg (see [Section 6.2](#) for additional details regarding how glimepiride was titrated in this study). Of note, the maximal approved dose of glimepiride in the US is 8 mg, and 81% of subjects in the glimepiride group received up-titration to 6 mg, suggesting that additional up-titration could have occurred if an 8 mg dosage strength had been incorporated into this trial. The impact of additional glimepiride titration (i.e., up to 8 mg) on the overall results of this trial is unclear.

Table 13. Primary Analysis* Results for HbA1c (%) Change From Baseline at Week 24 (Week 60 in Trial C-480)

Trial	Trial C-419 Add-On Met	Trial C-423 vs. Sitagliptin	Trial C-448 CKD	Trial C-450 Monotherapy	Trial C-476 High CV Risk	Trial C-480 vs. Glimepiride
Comparator	Placebo	Sitagliptin	Placebo	Placebo	Placebo	Glimepiride
Add-on	Metformin	Metformin	SOC	None	SOC	Metformin
N (Bexa/Ctrl)	158/159	191/193	157/155	138/69	1133/567	213/213
Missing data n(%) (Bexa/Ctrl)	16(10)/15(9)	11(6)/3(2)	5 (3)/7(5)	12(9)/5(7)	79(7)/34(6)	20(9)/22 (10)
LS mean at baseline (SE)						
Comparator	8.57 (0.79)	8.03 (0.92)	7.95 (0.81)	7.97 (0.76)	8.33 (0.94)	7.98 (0.70)
Bexagliflozin	8.66 (0.87)	7.94 (0.81)	8.01 (0.79)	8.05 (0.82)	8.32 (0.90)	8.04 (0.77)
LS mean change from baseline (SE) ^a						
Comparator	-0.54 (0.08)	-0.85 (0.05)	-0.30 (0.07)	-0.09 (0.10)	-0.36 (0.04)	-0.61 (0.06)
Bexagliflozin	-1.01 (0.08)	-0.77 (0.05)	-0.56 (0.06)	-0.46 (0.07)	-0.79 (0.03)	-0.65 (0.06)
Comparator-adjusted treatment effect with 95% CI ^a						
Bexagliflozin	-0.48 (-0.69, -0.26)	0.08 (-0.06, 0.22)	-0.27 (-0.44, -0.09)	-0.38 (-0.63, -0.13)	-0.44 (-0.53, -0.35)	-0.03 (-0.20, 0.13)

Trial	Trial C-419 Add-On Met	Trial C-423 vs. Sitagliptin	Trial C-448 CKD	Trial C-450 Monotherapy	Trial C-476 High CV Risk	Trial C-480 vs. Glimepiride
One-sided p-value / NI margin ^b	p-value <0.0001	NI margin 0.35	p-value 0.002	p-value 0.002	p-value <0.0001	NI margin 0.35

Source: Compiled by statistical reviewer from [Table 140](#), [Table 145](#), [Table 149](#), [Table 154](#), [Table 159](#), and [Table 164](#).

*All analyses used the Intention to Treat (ITT) Analysis Set that included all subjects who were randomized.

^aBased on ANCOVA model using imputed values for missing data based on the return-to-baseline approach. Fixed effects in the model varied across the studies.

^bFor the superiority studies, one-sided p-values are reported; for the noninferiority studies, predefined NI margins are listed.

Abbreviations: Bexa, bexagliflozin; CI, confidence interval; Ctrl, control; LS, least squares; Met, metformin; SE, standard error; SOC, standard of care

To date, no trials have been conducted to directly compare the efficacy of bexagliflozin to another approved SGLT2 inhibitor. Cross-trial comparison of data suggest that the efficacy of bexagliflozin may be more modest than other approved SGLT2 inhibitors. For example, when comparing data from monotherapy trials presented in Section 14 of the USPI, placebo-adjusted change from baseline in HbA1c from baseline to 24 to 26 weeks was 0.7% for ertugliflozin 15 mg, 0.7% for dapagliflozin 10 mg, 1.2% for canagliflozin 300 mg, and 0.9% for empagliflozin 25 mg as compared to 0.4% for bexagliflozin 20 mg (Janssen 2020; AstraZeneca 2021; Merck 2021; Ingelheim 2022). However, cross-trial comparisons should be approached with caution as differing trial designs and patient populations may influence the data observed in any given trial. In addition, FDA's approach to the preferred statistical analysis of trials to determine the most appropriate estimate of the treatment effect closer to realistic effectiveness has evolved over time, further limiting meaningful conclusions from cross-trial comparisons. (e.g., use of LOCF versus return to baseline for missing data imputation based on the most relevant assumption of missing data considering reasons of the missing data). Furthermore, other SGLT2 inhibitor programs evaluated two dosage strengths in phase 3 as compared to bexagliflozin which only evaluated a 20 mg dosage strength. It is unclear whether additional glycemic efficacy could be achieved with a higher bexagliflozin dose without an unacceptable increase in tolerability events. Ultimately, it is unclear at this time if, and to what extent, bexagliflozin may be less efficacious than other approved products.

6.2.3.2.2. Sensitivity Analysis of the Primary Endpoint

For each of the superiority trials, tipping points were determined at the values of delta combinations where the statistical significance of treatment effect is lost; none of these derived delta combinations were clinically plausible (see result tables in Section [16.6](#)). For each of the noninferiority trials, penalizing the missing outcomes on the bexagliflozin arm by applying a delta of 0.35% while keeping the MI-RTB imputed active-control arm missing outcomes unchanged, did not change the conclusion of noninferiority. These sensitivity analyses and results support the robustness of the conclusions based on primary analysis of HbA1c changes across the six pivotal trials.

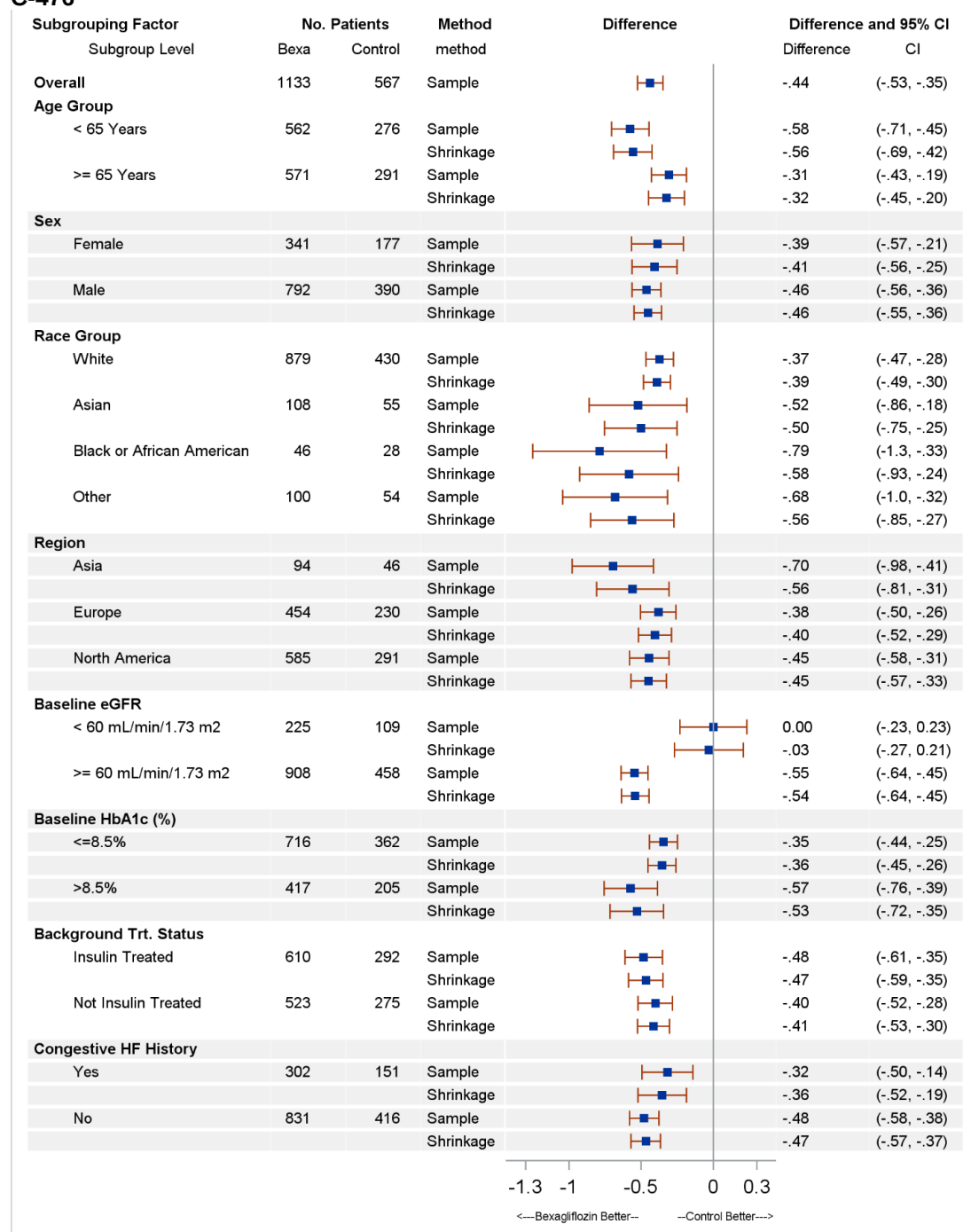
6.2.3.2.3. Subgroup Analysis of the Primary Endpoint

Subgroup analyses of the primary endpoint were conducted for all trials and are presented individually in Section [16.4](#). Subgroup analysis results were generally consistent across trials to demonstrate homogeneity of the favorable result for bexagliflozin, although limited data in

certain subgroups impeded interpretability in some cases. Shrinkage estimates show narrower credible intervals than confidence intervals of sample estimates. The point estimate of the Shrinkage estimates are closer to the point estimate for the overall treatment difference compared to the sample estimates. No notable differences were detected using shrinkage estimates in all trials.

The subgroup analysis from C-476 is presented here as a representative analysis because C-476 was the largest trial (ITT N=1700) and thus, provided more data contributing to each subgroup. As shown in [Table 14](#), the treatment effect of bexagliflozin showed similar results to the overall population in all subgroups evaluated with the exception of a subgroup of subjects with renal impairment (i.e., baseline eGFR <60 mL/min/1.73 m²). Efficacy in subjects with moderate renal impairment is discussed further in Section [6.3.1](#).

Table 14. Treatment Difference in HbA1c (%) by Baseline Demographic and Disease Factors, Trial C-476



Source: statistical reviewer's analysis

Abbreviations: Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure.

Additional analyses to investigate the potential modification effect of baseline HbA1c levels as a continuous variable were carried out for each of the four placebo-controlled studies. Section [16.4](#) [Figure 50](#), [Figure 54](#), [Figure 62](#), and [Figure 65](#) show scatter plots of change from baseline in HbA1c at Week 24 versus baseline HbA1c levels, overlaid with the estimated by-arm group

regression lines for C-450, C-419, C-448 and C-476, respectively. In all treatment arms of each study, the higher baseline HbA1c showed the larger HbA1c reduction from baseline.

6.2.3.3. Key Secondary Efficacy Results

As the primary endpoint was significant in each trial, statistical testing was performed for the key secondary endpoints based on testing hierarchy in each trial. [Table 15](#) presents the analysis results for the key secondary endpoints of pivotal efficacy trials. If the key secondary endpoint was not significant (one-sided p-value ≥ 0.025) in the order, then the formal testing was stopped and p-values are shown as nominal value for descriptive purpose. For example, in C-450, bexagliflozin use was associated with numerical reductions in SBP and body mass compared with placebo, but these differences did not reach statistical significance at Week 24.

Table 15. Key Secondary Endpoints (Shown in the Order of the Testing Hierarchy): Change From Baseline at Week 24, Return-to-Baseline Analysis Results, ITT Population

Endpoint (Unit)	Treatment	N	Baseline [Mean (SD)]	Change From Baseline [LS Mean (SE)] ^a	LS Mean Difference*	LCL	UCL	P-Value ^e
Trial C-450 (monotherapy)								
SBP (mm Hg)	Placebo	69	125.64 (13.84)	1.03 (1.47)				
	Bexagliflozin	138	131.02 (14.35)	-0.72 (1.02)	-1.75	-5.26	1.77	0.16
Weight ^b (kg)	Placebo	62	86.94 (19.36)	-0.76 (0.41)				
	Bexagliflozin	128	92.51 (19.55)	-1.46 (0.29)	-0.70	-1.69	0.30	0.85
Trial C-423 (add-on to metformin)								
FPG (mg/dL)	Sitagliptin	193	181 (46)	-26 (2.2)				
	Bexagliflozin	191	175 (42)	-31 (2.2)	-5	-11	1	0.05
Weight ^b (kg)	Sitagliptin	174	92.42 (17.58)	-0.77 (0.22)				
	Bexagliflozin	169	93.64 (19.39)	-3.02 (0.23)	-2.25	-2.88	-1.62	<0.0001
SBP (mm Hg)	Sitagliptin	193	135.66 (14.31)	-1.55 (0.85)				
	Bexagliflozin	191	135.01 (12.17)	-3.82 (0.86)	-2.27	-4.56	0.10	0.03
Trial C-480 ^f (add-on to metformin)								
Weight ^b (kg)	Glimepiride	202	91.68 (16.80)	0.58 (0.29)				
	Bexagliflozin	201	89.67 (18.22)	-3.44 (0.29)	-4.01	-4.82	-3.21	<0.0001*
SBP ^c (mm Hg)	Glimepiride	75	149.23 (8.38)	-6.24 (1.48)				
	Bexagliflozin	78	148.50 (7.32)	-12.99 (1.45)	-6.75	-10.83	-2.67	<0.001*

Endpoint (Unit)	Treatment	N	Baseline [Mean (SD)]	Change From Baseline [LS Mean (SE)] ^a	LS Mean Difference*	LCL	UCL	P-Value ^e
Hypoglycemic event over 96 wks				0.15 (95% CI: 0.10, 0.22)				
Event n (%)	Glimepiride	212	44 (20.8)					
	Bexagliflozin	213	7 (3.3)	0.02 (95% CI: 0.01, 0.05)	OR: 0.12	0.05	0.28	<0.0001*
Trial C-448 (add-on to SOC in subjects with moderate renal impairment)								
Weight ^b (kg)	Placebo	122	88.90 (18.96)	-0.43 (0.27)				
	Bexagliflozin	125	88.81 (18.57)	-2.14 (0.26)	-1.71	-2.44	-0.97	<0.0001*
SBP ^d (mm Hg)	Placebo	113	144.33 (10.58)	-6.92 (1.45)				
	Bexagliflozin	107	143.23 (10.46)	-9.40 (1.48)	-2.48	-6.55	1.58	0.12
HbA1c with eGFR 45 to 59 mL/min/1.73 m ²	Placebo	78	7.57 (0.81)	-0.42 (0.09)				
	Bexagliflozin	83	7.37 (0.86)	-0.61 (0.09)	-0.19	-0.43	0.05	0.06
HbA1c with eGFR 30 to 44 mL/min/1.73 m ²	Placebo	77	7.75 (1.02)	-0.18 (0.09)				
	Bexagliflozin	74	7.75 (0.80)	-0.51 (0.09)	-0.33	-0.59	-0.07	0.007
Trial C-476 (add on to SOC in subjects with elevated CV risk)								
HbA1c in subjects on insulin (%)	Placebo	292	8.41(0.91)	-0.15 (0.10)				
	Bexagliflozin	610	8.43(0.88)	-0.63 (0.09)	-0.48	-0.61	-0.35	<0.0001*
Weight ^b (kg)	Placebo	522	94.86 (19.02)	-0.32 (0.17)				
	Bexagliflozin	1047	97.00 (19.80)	-2.66 (0.13)	-2.34	-2.76	-1.92	<0.0001*
SBP ^c (mm Hg)	Placebo	215	150.08 (8.453)	-6.57 (1.07)				
	Bexagliflozin	448	149.83 (9.21)	-9.24 (0.75)	-2.66	-5.23	-0.10	0.02*

Source: Compiled by statistical reviewer from Tables in Section [16.5](#).

*Statistically significant p-values based on hierarchical testing order for each study

^a Based on ANCOVA model using imputed values for missing data based on the return-to-baseline approach. Fixed effects in the model varied across the studies.

^b In patients with baseline BMI ≥ 25 kg/m². Weight was assessed at Week 24 except C-476 (Week 48) and C-480 (Week 60).

^c In patients with baseline SBP ≥ 140 mm Hg.

^d In patients with baseline SBP ≥ 130 mm Hg.

^e The p-values are all one-sided p-values.

^f The key secondary endpoints in Trial C-480 were assessed at Week 60.

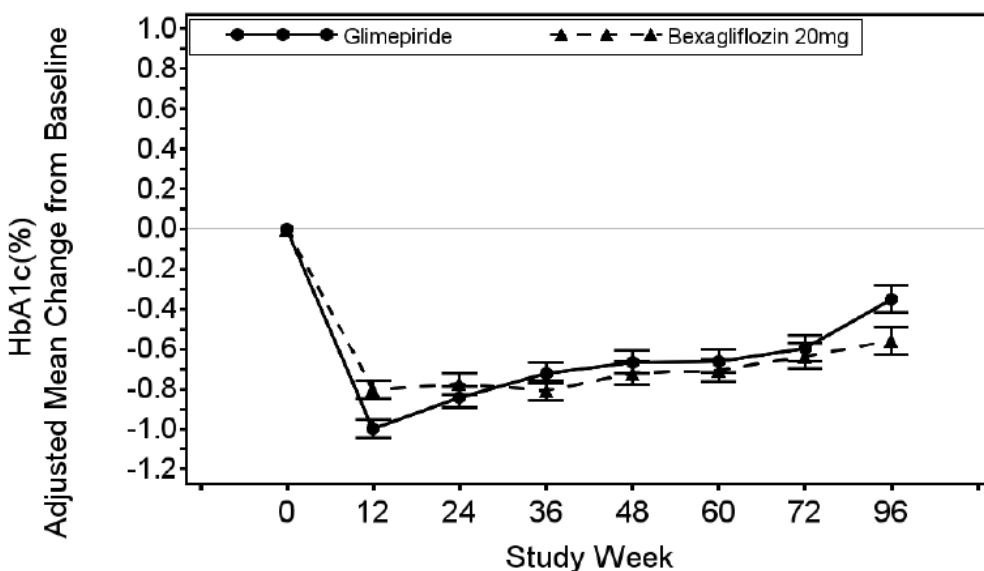
Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; kg, kilogram; LCL, lower confidence limit; LS, least squares; mm Hg, milliliter of mercury; SBP, systolic blood pressure; SD, standard deviation; SBP, systolic blood pressure; SE, standard error; SOC, standard of care; UCL, upper confidence limit.

6.2.3.3.1. Change in HbA1c (%) From Baseline Over Time

As discussed above, most trials evaluated the primary endpoint of change in HbA1c from baseline to 24 weeks, with active-controlled trial C-480 evaluating change from baseline in HbA1c at 60 weeks. While the primary endpoint was evaluated at Week 60 in C-480 the total trial duration was 96 weeks. Likewise, while the primary endpoint was evaluated at Week 24 in C-476, the trial duration was driven by the accrual of major adverse cardiac events (MACE+), and the average treatment duration was 2.4 years. These trials provide supportive information of changes in HbA1c (%) from baseline to longer time points for bexagliflozin.

Figure 7 and Figure 8 are presented for exploratory purposes to show changes in HbA1c (%) from baseline over time using observed data only without consideration of missing data imputation. As shown in Figure 7, in C-480, maximal HbA1c reduction occurred at week 12 followed by decreases in effect over time for both drugs. C-476 provides additional long-term data for changes in HbA1c from baseline up to 168 weeks, although data at later timepoints are limited (Figure 8). As shown in Figure 8, reduction in HbA1c is maintained from baseline to approximately week 36, with a decline in treatment effect over time. However, all timepoints show a greater treatment effect in the bexagliflozin group as compared to the placebo group.

Figure 7. LS Mean Change in HbA1c (%) From Baseline as a Function of Time, ITT, Trial C-480



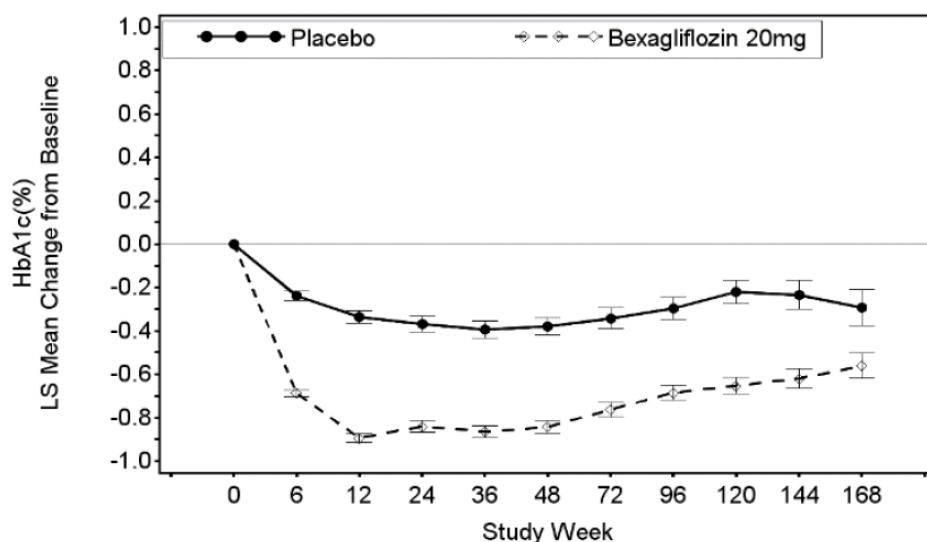
Sample Size per Time Point

Glimepiride	213	204	199	197	195	191	188	182
Bexa. 20 mg	213	208	203	197	196	193	191	185

Source: CSR for C-480; Applicant's Analysis

Abbreviations: Bexa, bexagliflozin ; ITT, intention-to-treat ; HbA1c, hemoglobin A1c; LS, least squares.

Figure 8. LS Mean Change in HbA1c (%) From Baseline as a Function of Time, ITT, Trial C-476



Sample Size per Time Point

Placebo	567	553	544	531	511	496	469	426	364	196	99
Bexa. 20 mg	1133	1111	1075	1046	1017	992	965	874	768	445	218

Source: CSR for C-476; Applicant's Analysis

Abbreviations: Bexa, bexagliflozin ; ITT, intention-to-treat ; HbA1c, hemoglobin A1c; LS, least squares.

6.3. Key Review Issue Relevant to Evaluation of Benefit

6.3.1. Efficacy of Bexagliflozin in Subjects With Moderate Renal Impairment

Background/Issue

SGLT2 inhibitor products were not initially recommended for use in patients with moderate renal impairment due to diminished glycemic efficacy and safety concerns (e.g., increases in serum creatinine/decreases in eGFR upon treatment initiation, acute kidney injury) leading to an unfavorable benefit-risk assessment in this patient population. However, additional information has been obtained regarding the safety and efficacy of SGLT2 inhibitors in patients with moderate renal impairment, including the evaluation of these products in dedicated renal impairment studies and long-term cardiovascular outcome trials (CVOTs). These trials have supported expanded labeling for the use of SGLT2 inhibitors to improve glycemic control in patients with moderate renal impairment. Currently, dosing and administration recommendations for patients with renal impairment are product-specific based on the available clinical data. At this time of this NDA review, ertugliflozin and dapagliflozin are not recommended for use to improve glycemic control in patients with T2DM and an eGFR <45 mL/min/1.73 m², and canagliflozin and empagliflozin are not recommended for use to improve glycemic control in patients T2DM and an eGFR <30 mL/min/1.73 m² because studies to support efficacy in patients with this level of renal impairment were not conducted or did not show statistically robust results.

In the bexagliflozin clinical program, C-448 was a dedicated renal impairment trial enrolling patients with eGFR ≥ 30 to < 60 mL/min/1.73 m². In addition, subjects were eligible for enrollment in C-476 with eGFR ≥ 45 mL/min/1.73 m². Subjects with moderate and severe renal impairment (eGFR < 60 mL/min/1.73 m²) were excluded from all other trials in the bexagliflozin clinical program and therefore Trials C-448 and C-476 are the only trials with sufficient information to inform safety and efficacy in this patient population. While glycemic efficacy was observed in C-448, efficacy was not observed in the subset of subjects with moderate renal impairment in C-476, raising uncertainties about the efficacy of bexagliflozin in this patient population. The efficacy of bexagliflozin in patients with moderate renal impairment is therefore a key review issue.

Assessment

Overview

The assessment of renal efficacy focused on two trials: C-448, a dedicated renal impairment trial enrolling patients with eGFR between ≥ 30 and < 60 mL/min/1.73 m² (i.e., stage 3a and 3b CKD), and C-476, a trial enrolling subjects with increased CV risk that enrolled subjects with eGFR ≥ 45 mL/min/1.73 m² (i.e., stage 3a CKD). In C-476, treatment was stratified by eGFR category (eGFR < 60 or ≥ 60 mL/min/1.73 m²), and approximately 20% of subjects in each treatment arm had eGFR < 60 mL/min/1.73 m². Baseline demographics for C-448 and C-476 are presented in [Table 11](#). All other trials excluded subjects with a screening eGFR < 60 mL/min/1.73 m² and were therefore not considered due to limited data. Renal efficacy data from C-448 and C-476 are discussed independently below.

Trial C-448 in Patients With Moderate Renal Impairment

C-448 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of bexagliflozin 20 mg versus placebo in subjects with T2DM, moderate renal impairment, and inadequate glycemic control. The study population included subjects with T2DM, an HbA1c of 7.0 to 10.5% (inclusive), and stage 3 CKD as defined by an eGFR ≥ 30 and < 60 mL/min/1.73 m² at the screening visit and at one additional time of measurement between 1 and 12 months prior to screening, which could be obtained from available medical records. Subjects were excluded if there was a $> 20\%$ change in eGFR between the historical value and the screening visit. Subjects on any antihyperglycemic regimen were eligible for enrollment (with the exception of taking an SGLT2 inhibitor). At the time of screening, the doses and frequency of all antihyperglycemic medications were to have been stable for at least 8 weeks. See

APPEARS THIS WAY ON ORIGINAL

[Table 9](#) for additional information on inclusion/exclusion criteria for this trial.

All eligible subjects entered a one-week single-blind, placebo run-in period to allow for optimization of compliance with diet and exercise recommendations. Subjects who were compliant in taking run-in medication were eligible for randomization. Randomization was stratified by HbA1c (7.0 to 8.5% or 8.6 to 10.5%), baseline insulin use, and eGFR (30 to 44 mL/min/1.73 m² or 45 to 59 mL/min/1.73 m²) at the screening visit.

Out of 490 screened subjects, 312 were randomized to either the bexagliflozin arm (n=157) or the placebo arm (n=155). All randomized subjects (ITT) took at least one dose of investigational product (safety population), and thus the ITT and safety analysis populations were the same. As shown in [Table 11](#), subjects enrolled in C-448 had a mean age of 69.6 (39 to 88) years, a mean diabetes duration of 15.9 (0 to 50.2) years, and a mean baseline HbA1c of 8.0% (SD =0.8). Mean baseline eGFR was 45.1 mL/min/1.73 m². The majority of subjects were male (63%), White (55%), and non-Hispanic/Latino (92%). Approximately 56% of subjects used insulin as part of their regimen for glycemic control.

The results of the primary efficacy analysis (i.e., placebo-subtracted change in HbA1c from baseline to Week 24), are presented in [Table 159](#) and reproduced in [Table 16](#) below.

Bexagliflozin demonstrated a modest, but statistically and clinically significant reduction in HbA1c as compared to placebo (LS mean difference: -0.27%; 95% CI: -0.44%, -0.09%). In accordance with these results, fewer subjects received rescue treatment for uncontrolled hyperglycemia in the bexagliflozin group (9 subjects (5.7%)) as compared to the placebo group (17 subjects (11.0%)), and rescue medication was prescribed to subjects in the bexagliflozin group at a later mean date in the treatment period as compared to subjects in the placebo group (mean time-to-first rescue medication of 84.3 versus 72.3 days in the bexagliflozin and placebo groups, respectively; Applicant's analysis). As demonstrated in [Figure 9](#), the bexagliflozin group consistently had a larger mean change in HbA1c over time as compared to placebo.

More modest glycemic efficacy of SGLT2 inhibitor products in patients with moderate renal impairment is expected based on the mechanism of action of the drug class and has been characterized with other approved products. As discussed above (Section [6.2.3.2.1](#)), it is difficult to draw meaningful conclusions from cross-trial comparisons as differences in study designs and analysis methods may impact trial results. However, the reduction in HbA1c with bexagliflozin treatment in C-448 is generally consistent with data available from other members of class. For example, in a double-blind, 26-week, placebo-controlled trial enrolling 269 subjects with T2DM and moderate renal impairment (eGFR 30 to 50 mL/min/1.73 m²), canagliflozin 100 mg and 300 mg demonstrated placebo-adjusted changes in HbA1c of -0.30% (95% CI: -0.53%; -0.07%) and -0.40% (95% CI: -0.64%; -0.17%), respectively (Janssen 2020). In VERTIS CV enrolling subjects with T2DM and CVD, ertugliflozin demonstrated a placebo-adjusted change in HbA1c of -0.28% (95% CI: -0.4, -0.15) in a subgroup of subjects with baseline eGFR of 45 to 59 mL/min/1.73 m² (see clinical review in DARRTS dated September 16, 2021).

Table 16. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Trial C-448

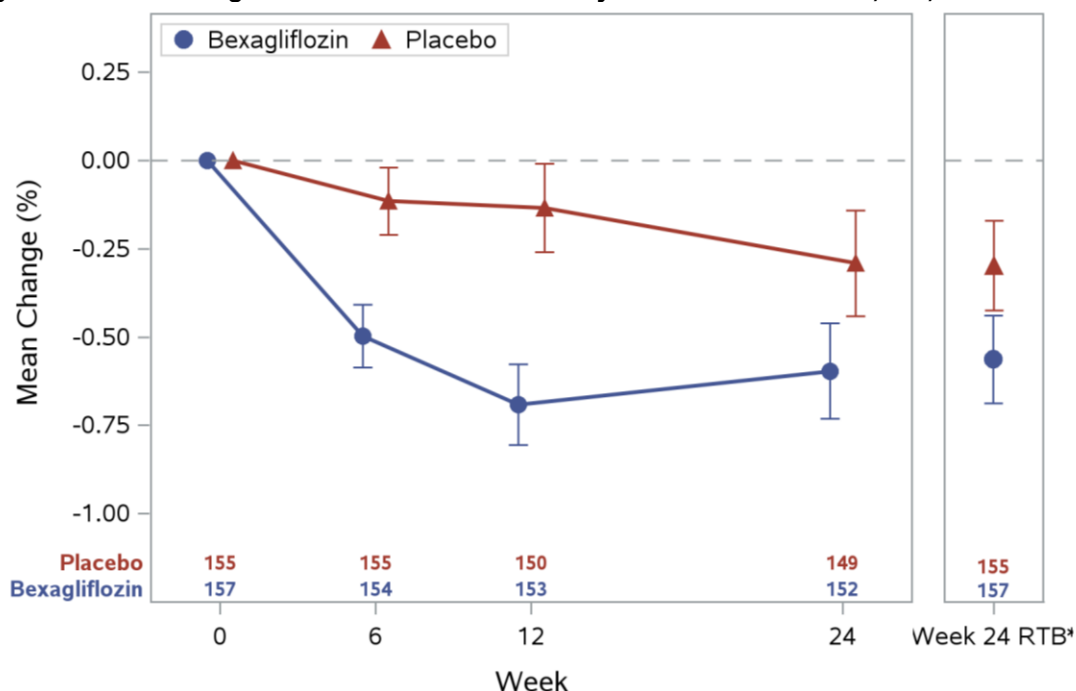
Variable	Bexagliflozin 20 mg (N=157)	Placebo (N=155)
Baseline HbA1c, mean (SD)	8.01 (0.786)	7.95 (0.812)
Change from baseline, LS mean (SE)	-0.56 (0.064)	-0.30 (0.065)
Difference from placebo, LS Mean (95% CI)	-0.27 (-0.44, -0.09)	
One-sided p-value	0.0017	
Patients achieving HbA1c <7%, n (%) [1]	52 (33.1)	34 (21.9)

Source: FDA statistical reviewer

[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

Abbreviation: HbA1c, hemoglobin A1c ; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile SD, standard deviation; SE, standard error.

Figure 9. Mean Change From Baseline in HbA1c by Time and Treatment, ITT, Trial C-448



Source: statistical reviewer's analysis

Note: Change from baseline in HbA1c at Weeks 0, 6, 12 and 24 are using observed data. The rightmost panel shows the changes in HbA1c using observed and imputed values based on RTB analysis. Vertical lines represent 95% CIs. *Data were analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening, anti-diabetic treatment regimens, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group LSMS in change from baseline in HbA1c was estimated by the ANCOVA Model

Abbreviations: ANCOVA, analysis of covariance; HbA1c, hemoglobin A1c; RTB, return to baseline.

As displayed in [Table 10](#) the secondary endpoints in C-448 included change in body weight in subjects with baseline BMI ≥ 25 kg/m², change in SBP in subjects with baseline SBP ≥ 130 mm Hg, change in HbA1c over time in subjects with stage 3a CKD (eGFR 45 to 59 mL/min/1.73 m²), and change in HbA1c over time in subjects with stage 3b CKD (eGFR 30 to 44 mL/min/1.73 m²) (endpoints are listed in the hierarchical testing order). Statistical significance of the effect of bexagliflozin compared to placebo on the effect of SBP was not met, and therefore no additional testing of secondary endpoints could proceed. Therefore, change in HbA1c in eGFR subgroups was evaluated only for descriptive purposes.

Glycemic efficacy by CKD subgroup is shown in [Table 17](#). A greater treatment effect in HbA1c was observed in the stage 3b CKD subgroup (-0.33%; 95% CI: -0.59, -0.07) as compared to the stage 3a CKD subgroup (-0.19; 95% CI: -0.43, 0.05). The treatment effect in the stage 3a subgroup numerically favored bexagliflozin (-0.19%), but nominal statistical significance was not achieved (p=0.06).

These findings are counterintuitive, as greater glycemic efficacy would be expected in subjects with better renal function given the mechanism of action of the drug. Mean changes in HbA1c from baseline in the placebo group between subgroups appears to contribute, at least in part, to the findings noted above, with the stage 3a placebo group having a -0.42% mean decrease in HbA1c as compared to the stage 3b placebo group which had a -0.18% decrease in HbA1c from baseline. Importantly, C-448 was not powered to detect differences in glycemic control between bexagliflozin and placebo in each subgroup of renal function; all of these descriptive findings are for exploratory purposes only.

Table 17. Treatment Difference in HbA1c (%) by Baseline Renal Function, Trial C-448

Variable	Baseline eGFR Level			
	CKD Stage 3b 30 - 44 mL/min/1.73 m ²		CKD Stage 3a 45 - 59 mL/min/1.73 m ²	
	Bexagliflozin		Bexagliflozin	
	20 mg (N=74)	Placebo (N=77)	20 mg (N=83)	Placebo (N=78)
Baseline HbA1c, mean (SD)	7.43 (0.80)	7.75 (1.02)	7.37 (0.86)	7.57 (0.81)
Change from baseline at Week 24, LS mean (SE)	-0.51 (0.09)	-0.18 (0.09)	-0.61 (0.09)	-0.42 (0.09)
Difference				
Difference from placebo, LS means (95% CI)	-0.33 (-0.59, -0.07)		-0.19 (-0.43, 0.05)	
One-sided p-value	0.0070		0.0622	
P-value for interaction test (treatment by baseline renal function)			0.45	

Source: FDA statistical reviewer

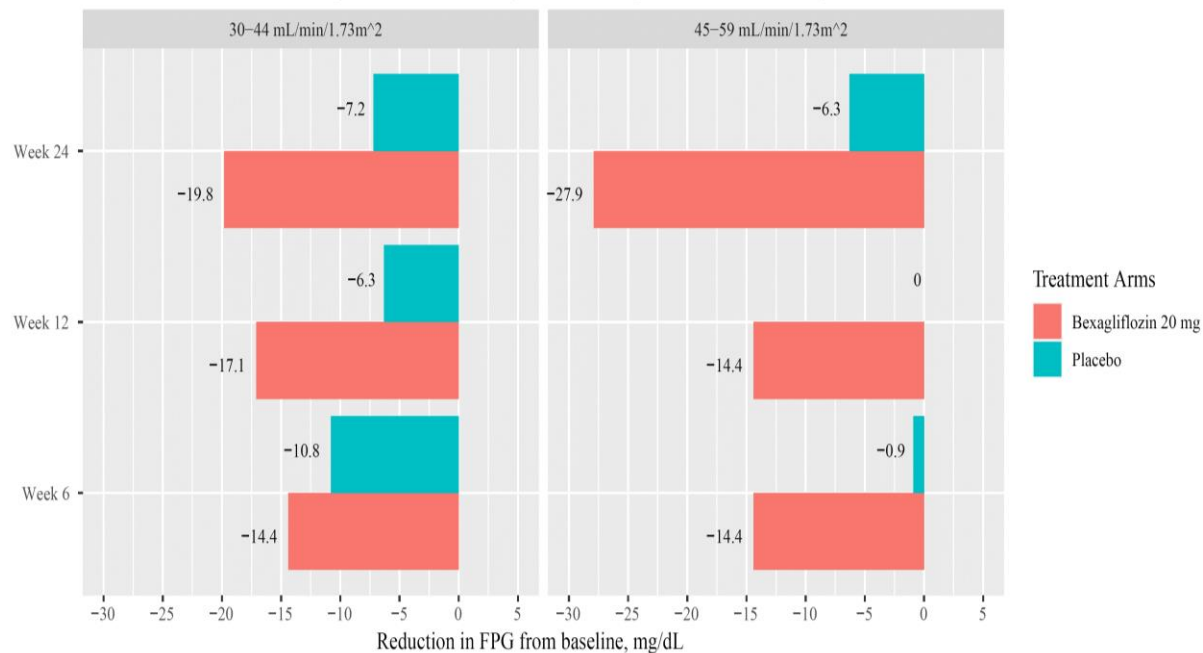
Note: For each subgroup, LS mean differences versus placebo at Week 24 were assessed using the same return-to-baseline coupled ANCOVA model as for the primary endpoint.

Abbreviations: ANCOVA, analysis of covariance; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c ; LS, least square; SE, standard error.

To further investigate glycemic efficacy in subjects with renal impairment, additional supportive endpoints related to glycemic control were assessed in an exploratory manner by the review team. As shown in [Figure 10](#), greater decreases in median FPG were observed in both stage 3a and 3b CKD bexagliflozin subgroups as compared to placebo subgroups over time. A larger decrease compared to placebo was observed in the stage 3a CKD bexagliflozin subgroup as compared to the stage 3b CKD subgroup at Week 24. Given reduction in median FPG in subjects with stage 3a exposed to bexagliflozin, it is unclear why the effect of HbA1c was more modest than in stage 3b.

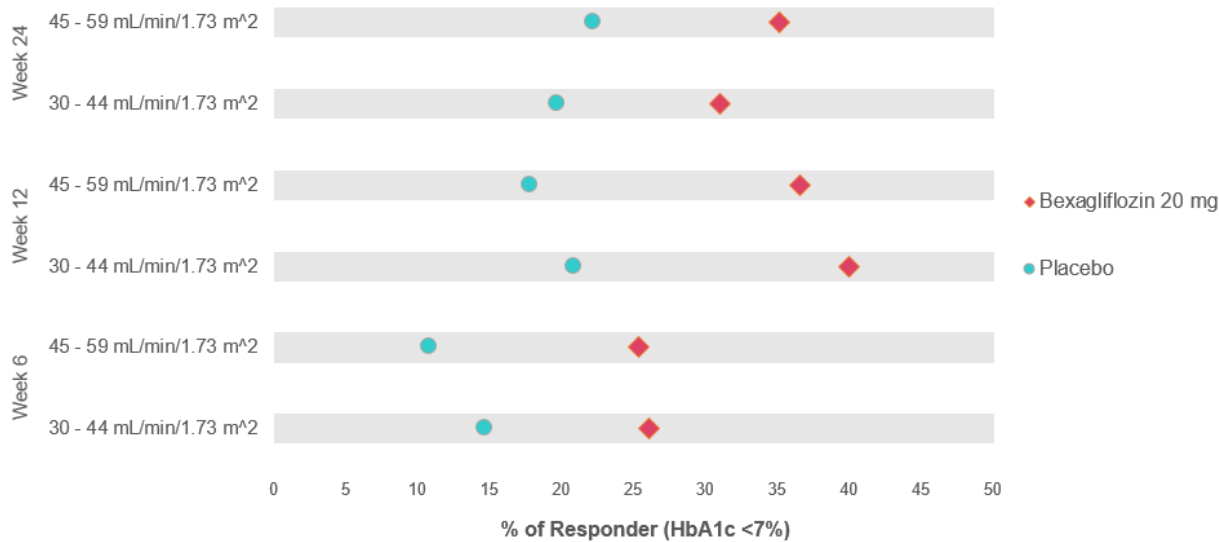
A higher proportion of subjects with stage 3a CKD in the bexagliflozin group met the glycemic control target (i.e., HbA1c <7%) as compared to subjects with stage 3b CKD at Week 24, although differences in baseline HbA1c between subgroups limits the interpretability of these data (e.g., 7.57% versus 7.37% in the placebo and bexagliflozin Stage 3a CKD subgroups, respectively) ([Figure 11](#)). Overall, findings from these supportive measures support the efficacy of bexagliflozin in patients with T2DM and moderate renal impairment in C-448.

Figure 10. Median Reduction in FPG by Treatment and eGFR Subgroup Over Time, ITT, Trial C-448



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; ITT, intention-to-treat.

Figure 11. Proportion of Patients Reaching HbA1c <7.0% by Treatment and eGFR Subgroup Over Time, ITT, Trial C-448



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat.

Trial C-476 in Patients With Increased CV Risk

Subjects with eGFR ≥ 45 mL/min/1.73 m² were eligible for enrollment in C-476, allowing for an efficacy evaluation in a subgroup of subjects with stage 3a CKD in this trial. Unlike C-448, an historical eGFR measurement was not utilized to confirm stability of renal function over time,

and some patients with baseline eGFR <45 mL/min/ 1.73 m² were enrolled in C-476 due to variability between screening and baseline eGFR measurements (this also occurred in C-448, albeit to a lesser extent; [Table 11](#)). For the subgroup analysis presented in this review, a cutoff of eGFR <60 mL/min/ 1.73 m² was utilized to identify subjects with renal impairment in C-476. Of the subjects in C-476 with baseline eGFR <60 mL/min/ 1.73 m², approximately 15% of subjects in each treatment group had baseline eGFR <45 mL/min/ 1.73 m². The mean (SD) eGFR value in subjects with eGFR <45 mL/min/ 1.73 m² was 41 (4) mL/min/ 1.73 m².

Although efficacy in subjects with renal impairment was a prespecified subgroup, the Applicant did not include this subgroup in their hierarchical testing plan, and therefore the analyses below are presented descriptively. As shown in [Table 18](#), glycemic efficacy was not observed in subjects with eGFR <60 mL/min/ 1.73 m² in C-476, with bexagliflozin demonstrating a mean treatment difference (vs. placebo) in HbA1c of 0.0% (95% CI: -0.23, 0.23). Change from baseline in HbA1c over time by treatment group and baseline renal function is shown in [Figure 12](#). In subjects with eGFR <60 mL/min/ 1.73 m² maximal glycemic reduction in the bexagliflozin occurred at week 12, followed by a decline in efficacy at week 24.

The Applicant proposes several reasons that may account for this finding. The Applicant notes that, although the mean change from baseline of HbA1c in the bexagliflozin arm of this subgroup was more modest (-0.50%) compared to the mean change for bexagliflozin arm with normal renal function or mild renal impairment (-0.87%), the mean change from baseline in the placebo arm was larger in the subgroup with eGFR <60 mL/min/ 1.73 m² (-0.50%) as compared to the subgroup with eGFR ≥ 60 mL/min/ 1.73 m² (-0.32%). Furthermore, in subjects with eGFR <60 mL/min/ 1.73 m², over twice as many subjects in the placebo arm required treatment intensification as compared to the bexagliflozin group, and over twice as many subjects in the bexagliflozin group had documented relaxation of concomitantly prescribed antihyperglycemic agents as compared to the placebo group ([Table 19](#)). The Applicant states that these factors indicate a degree of investigator intervention that did not occur in C-448, thereby explaining the discrepant results between trials.

The rationales proposed by the Applicant do not provide compelling justification for the lack of treatment effect in subjects with eGFR <60 mL/min/ 1.73 m² in C-476. For example, while more subjects in the placebo group received treatment intensification as compared to the bexagliflozin group, this occurred to approximately equal extents in both subgroups ([Table 19](#)). In addition, these data are difficult to interpret since the degree of treatment intensification/relaxation is unclear. The Applicant also posits that differences in placebo effect between subgroup accounts, at least in part, for the lack of glycemic efficacy in subjects with eGFR <60 mL/min/ 1.73 m². This argument is not very compelling because in a randomized, controlled trial, the placebo arm should reflect what would have happened in the drug arm absent the drug.

Table 18. Treatment Difference in HbA1c (%) by Baseline Renal Function, ITT, Trial C-476

Variable	Baseline eGFR Level			
	<60 mL/min/1.73 m ²		≥60 mL/min/1.73 m ²	
	Bexagliflozin 20 mg (N=225)	Placebo (N=109)	Bexagliflozin 20 mg (N=908)	Placebo (N=458)
Baseline HbA1c, mean (SD)	8.31 (0.89)	8.30 (0.91)	8.32 (0.90)	8.34 (0.95)
Change from baseline at Week 24, LS mean (SE)	-0.50 (0.07)	-0.50 (0.10)	-0.87 (0.03)	-0.32 (0.04)
Difference				
Difference from placebo, LS means (95% CI)		0.00 (-0.23, 0.23)		-0.55 (-0.64, -0.45)
One-sided p-value		0.5003		<0.0001
P-value for interaction test (treatment by baseline renal function)		<0.0001		

Source: FDA statistical reviewer

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; SE, standard error.

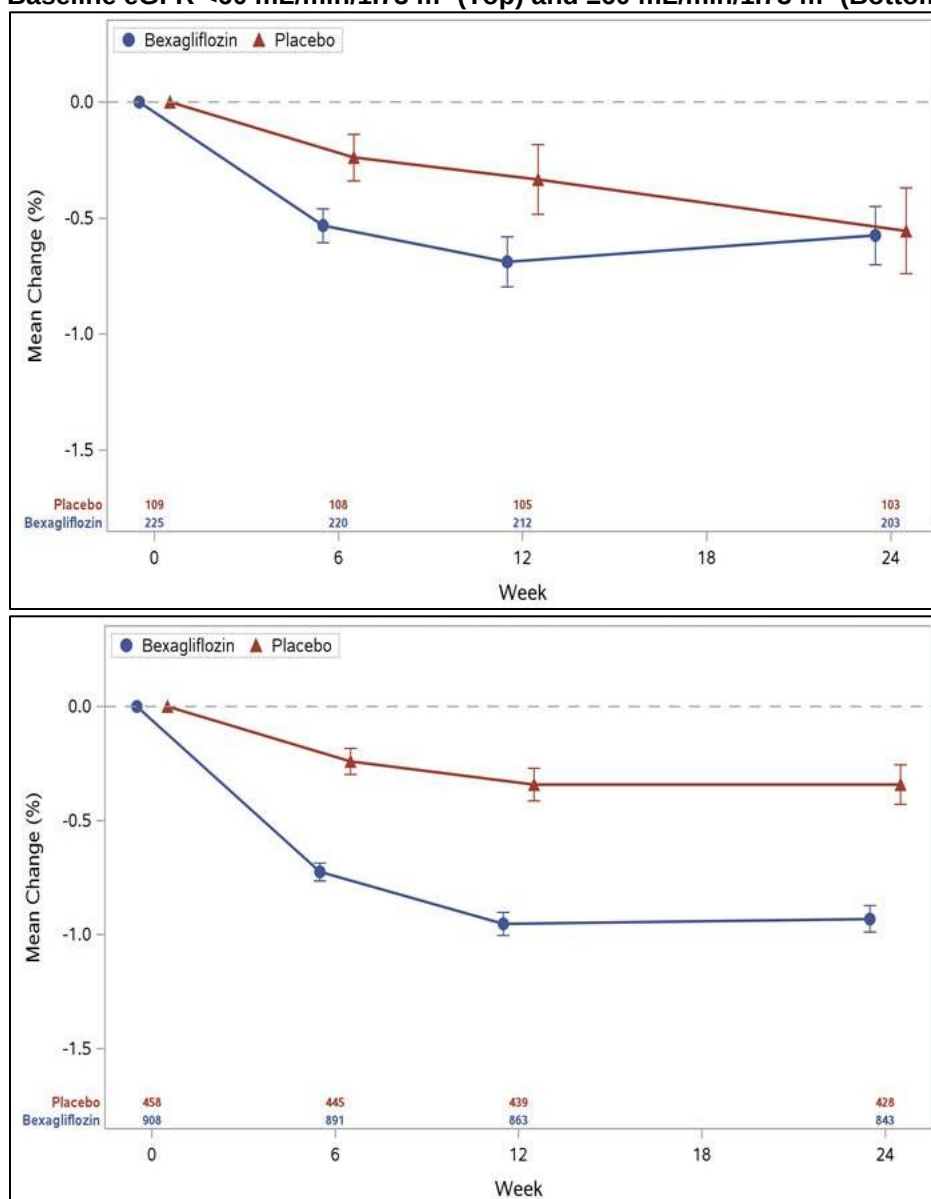
Table 19. Subjects Experiencing Treatment Intensification and Relaxation in Subjects by Baseline eGFR, Safety Population, Trial C-476

Treatment Arm	<60 mL/min/1.73 m ²		≥60 mL/min/1.73 m ²	
	Bexagliflozin 20 mg N=225	Placebo N=109	Bexagliflozin 20 mg N=907	Placebo N=458
Hypoglycemic Therapy Intensified	18 (8.9)	20 (19.4)	62 (6.8)	91 (19.9)
Hypoglycemic Therapy Relaxed	24 (11.8)	5 (4.9)	89 (9.8)	24 (5.2)

Source: adtte.xpt and adsl.xpt; Software: R; Generated by CDS

Abbreviations: eGFR, estimated glomerular filtration rate

Figure 12. Mean Change From Baseline in HbA1c by Time and Treatment in Subjects With Baseline eGFR <60 mL/min/1.73 m² (Top) and ≥60 mL/min/1.73 m² (Bottom), ITT, Trial C-476



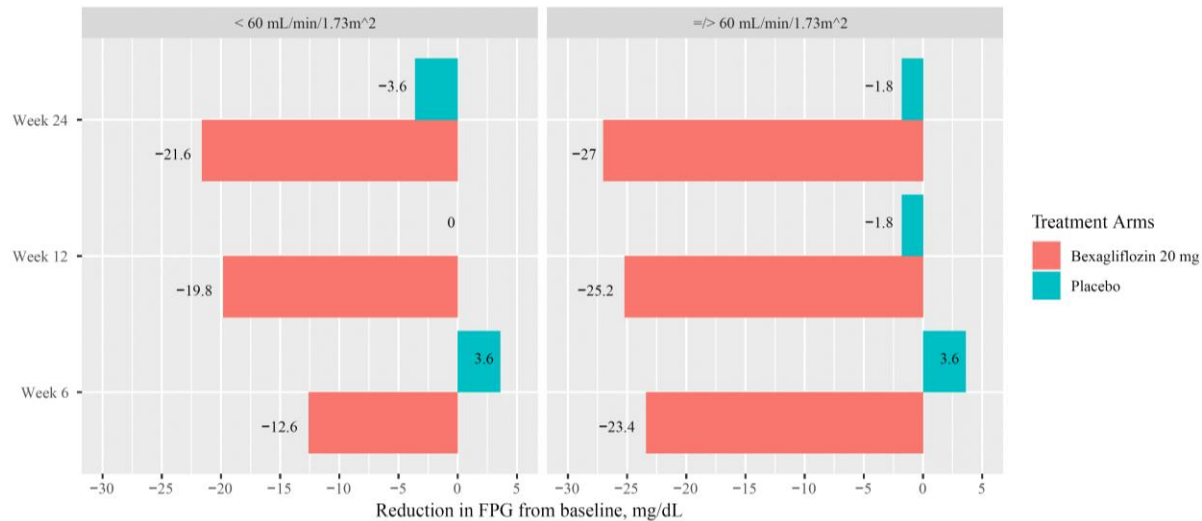
Source: Statistical Reviewer's Analysis

Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intention-to-treat.

To further investigate glycemic efficacy in subjects with renal impairment in C-476, additional glycemic control measures were assessed in an exploratory manner by the review team. As shown in [Figure 12](#), bexagliflozin was nominally statistically superior to placebo at weeks 6 and 12 in the subgroup of patients with eGFR <60 mL/min/1.73 m², despite showing no treatment effect at week 24. As shown in [Figure 13](#), greater decreases in FPG were observed in the bexagliflozin group as compared to placebo in subjects with baseline eGFR <60 mL/min/1.73 m² across Weeks 6, 12, and 24. In addition, as shown in [Figure 14](#), a higher proportion of subjects in the bexagliflozin group with baseline eGFR <60 mL/min/1.73 m² met glycemic control targets as compared to subjects on placebo at Weeks 6 and 12; however, a lower responder rate in the bexagliflozin group was observed when compared to the placebo group at Week 24 in this

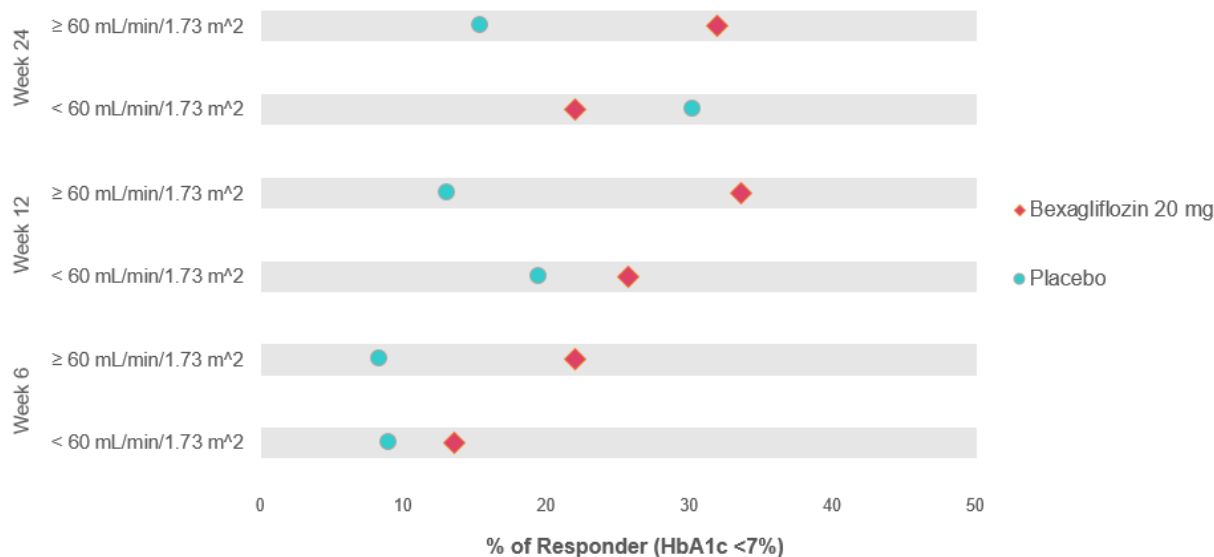
subpopulation. Notably, the responder rate in placebo group with baseline eGFR <60 mL/min/1.73 m² was approximately twice that of the placebo group with baseline eGFR ≥60 mL/min/1.73 m² (30% versus 15%, respectively). While efficacy appears more modest in subjects with reduced renal function compared to patients with normal or moderately impaired renal function in Trial C-476, overall, these supportive analyses generally appear to support the efficacy of bexagliflozin in this patient population.

Figure 13. Median Reduction in FPG by Treatment and eGFR Subgroup Over Time, ITT, Trial C-476



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; ITT, intention-to-treat.

Figure 14. Proportion of Subjects Reaching HbA1c <7.0% by Treatment and eGFR Subgroup Over Time, ITT, Trial C-476



Source: Clinical Pharmacology Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat

Conclusion

A dedicated renal impairment trial (C-448) demonstrated statistically significant and clinically meaningful reductions in HbA1c in subjects with T2DM and moderate renal impairment. Despite this, efficacy was not observed in a subgroup analysis of subjects with baseline eGFR <60 mL/min/1.73 m² in C-476. While the Applicant has proposed explanations for these results, the underlying reason for the data observed is ultimately unclear. Trial C-476 was not designed to assess glycemic efficacy in subjects with renal impairment. Hence, all of the descriptive findings presented herein are for exploratory purposes only. In contrast, C-448 was an adequate and well-controlled study designed to assess glycemic efficacy in subjects with renal impairment, thus providing more conclusive evidence of the glycemic lowering effect of bexagliflozin in this patient population. In addition, while modest, the efficacy observed in C-448 was generally in accordance with the efficacy observed with other SGLT2 inhibitors, which also demonstrate more modest efficacy in this patient population.

As discussed in detail in Section [7.7.2](#), the safety of bexagliflozin in subjects with moderate renal impairment is generally similar to the overall population, and no safety findings were observed that significantly impact the benefit-risk assessment. Subjects enrolled in C-448 (i.e., subjects with T2DM failing standard of care therapy with renal impairment) represent a patient population who could benefit from therapies that could further improve glycemic control. Taken together, the data presented support the efficacy of bexagliflozin in this patient population. Labeling in “8.6 Renal Impairment” and “14 Clinical Studies” is proposed to describe the results obtained in the bexagliflozin clinical development program.

Dissent

Not applicable.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Bexagliflozin was evaluated in a comprehensive program of nonclinical safety studies that included secondary (off-target) pharmacology studies, in vitro and in vivo (rats and monkeys) safety pharmacology studies, general toxicology studies (up to 6 months in rats and 9 months in monkeys), genetic toxicology studies (Ames, in vitro chromosomal aberration, and in vivo rat micronucleus assays), a full battery of reproductive toxicity studies in rats and rabbits, a juvenile animal study in rats, and 2-year (lifetime) carcinogenicity studies in mice and rats.

In the chronic (39-week) monkey study, minimal to slight kidney cortical tubular cell vacuolation, characterized by cytoplasmic microvacuoles adjacent to the basement membrane, was observed at all bexagliflozin dose levels. This finding is considered secondary to bexagliflozin-induced glucosuria but was not considered toxicologically significant based on the absence of significant adverse effects on renal function. In the chronic (26-week) rat study, a low incidence of minimal to slight stomach erosion/ulcer was observed in all treated male groups, without dose dependency, and in high dose females. These findings might be treatment related

because similar findings were also reported in rats with other SGLT2 inhibitors. However, the clinical importance of stomach erosion is limited considering the low incidence and severity in rats and absence of similar findings in nonrodent species as well as in humans based on the extensive clinical experience with the drug class. In both monkeys and rats, the no observed adverse effect level (NOAEL) was the highest dose tested, which corresponded to 78 and 89 times the clinical dose of 20 mg, respectively, based on AUC.

Bexagliflozin produced no adverse effects on fertility in rats, on embryofetal toxicity in rats or rabbits, or on pre- and postnatal development in rats at clinically relevant exposures. In juvenile rats administered bexagliflozin during a period of renal development corresponding to the late second and third trimesters of human pregnancy, adverse renal pelvic and tubular dilatation was observed at the end of dosing and throughout the 4-week recovery period at exposures ≥ 11 times the MRHD. These findings are secondary to bexagliflozin's pharmacodynamic activity (see details in Section 5.1) and have been seen with all the drugs in the class. Based on the juvenile animal data, bexagliflozin is not recommended for use during the second and third trimester of pregnancy.

Bexagliflozin produced no evidence of carcinogenic potential in mice or rats when administered for a lifetime. The duration of the male rat study was inadequate to allow rigorous statistical evaluation of carcinogenic potential, due to early mortality that resulted in premature study termination at Week 88. However, the available information, including the absence of imbalances for preneoplastic findings and tumors in male rats, suggests that repeating the carcinogenicity study in male rats at lower doses would be unlikely to provide additional useful information. See details in Sections 13.1.1.4.2 and 13.1.1.4.3.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

There are currently four SGLT2 inhibitor drugs approved in the US: canagliflozin (approved 2013, NDA 204042), empagliflozin (approved 2014, NDA 204629), dapagliflozin (approved 2014, NDA 202293), and ertugliflozin (approved 2017, NDA 209803). Selected safety information as represented in the US prescribing information for each drug is shown in [Table 20](#).

Table 20. Selected Labeled Safety Information for Approved SGLT2 Inhibitors

Labeled Safety Information	Cana	Empa	Dapa	Ertu
Warnings and precautions				
GMI	X	X	X	X
Fournier's gangrene	X	X	X	X
Urosepsis/pyelonephritis	X	X	X	X
Ketoacidosis	X	X	X	X
Volume depletion	X	X	X	X
Hypoglycemia with insulin/secretagogue	X	X	X	X
Hypersensitivity	X	X	X [†]	X [†]
Lower limb amputation	X			X
Bone fracture	X			
Adverse reactions $\geq 5\%^*$				
Female GMI	X	X	X	X
UTI	X	X	X	
Increased urination	X			

Labeled Safety Information	Cana	Empa	Dapa	Ertu
Other labeled events:				
AKI	X	X	X	X
Falls	X			
Renal cell carcinoma	X			

Source: Adapted from USPIs for Jardiance, Farxiga, Invokana, and Steglatro as of October 2021 (Janssen 2020; AstraZeneca 2021; Merck 2021; Ingelheim 2022)

* Dapagliflozin also is labeled for nasopharyngitis

† Dapagliflozin and ertugliflozin do not have listed Warnings and Precautions for hypersensitivity reactions but are contraindicated in patients with a history of serious hypersensitivity to the drug and/or any excipients

Abbreviations: AKI, acute kidney injury; Cana, canagliflozin; Dapa, dapagliflozin; Empa, empagliflozin; Ertu, ertugliflozin; GMI, genital mycotic infections, SGLT, sodium-glucose cotransporter 2; UTI, urinary tract infection.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Not applicable; bexagliflozin is not currently marketed in any country.

7.4. FDA Approach to the Safety Review

7.4.1. Data Pooling

The FDA's safety evaluation for this application was based on the review of pooled safety data from three placebo-controlled trials enrolling subjects, who were either treatment naïve or inadequately controlled on metformin (C-419, C-449, and C-450), termed the placebo-controlled pool, and the review of individual phase 3 trial data from active-controlled trials (C-423 and C-480) and trials enrolling specific populations (C-448 and C-476). The Applicant's approach to the safety review is discussed in Section [17.2](#).

The placebo-controlled pool was utilized to evaluate the safety and tolerability of 20 mg bexagliflozin relative to placebo across multiple trials in a similar patient population. This pool excluded the uncontrolled, high-glycemic group (i.e., baseline HbA1c >10.5%) from C-419, as well as the 5 and 10 mg bexagliflozin dosage strengths evaluated in C-449 that are not proposed for marketing. This pool was used to inform common adverse reaction information presented in Section 6 of the labeling.

Not all of the placebo-controlled trials were included in the placebo-controlled pool, as C-448 (enrolling subjects with moderate renal impairment) and C-476 (enrolling subjects with increased CV risk) evaluated distinct patient populations as compared to trials C-419, C-449, and C-450. In addition, trial C-476 was by far the largest (1,699 subjects in the safety population) and longest (median duration of 2.4 years) trial in the safety program, and therefore pooling of this trial with other trials in the clinical development program would have skewed the results of the safety analysis towards this trial. Additional reasons to exclude C-476 from pooled analyses also include higher background rates of AEs in C-476 compared to other trials that may dilute imbalances observed in other trials, potential attenuation of imbalances due to the long observation period, and potential introduction of bias such as ascertainment bias due to differential dropout rates between treatment groups over time. For these reasons, safety data from C-448 and C-476 are presented independently where appropriate. Active-controlled trials were also reviewed and presented where appropriate, but not pooled with other placebo-

controlled trials to inform product labeling. Lastly, a “broad pool,” which pooled all phase 2b/3 trials (C-418, C-419, C-423, C-449, C-450, C-476, C-480, C-603A), was used to assess more infrequent adverse events and inform overall exposure. As the broad pool consisted of trials of significantly different study designs, patient populations, and drug formulation, safety analyses with this pool were used for exploratory purposes only. See Section [17.2](#) for additional information regarding this pool, including data handling considerations.

Safety data from phase 1/2a trials were excluded from the safety review conducted to inform product labeling as trials were generally short (e.g., 1 to 14 day) PK/PD studies that did not utilize the to-be-marketed formulation of bexagliflozin and/or did not enroll subjects with T2DM. Relevant phase 1 trials to this safety review, including C-428 conducted to assess the impact of bexagliflozin on cardiac repolarization, are discussed where relevant.

7.4.2. Categorization of Adverse Events

This section summarizes relevant information and methods utilized for the definition, categorization, assessment, and adjudication of safety data.

- **Medical Dictionary for Regulatory Activities (MedDRA) coding and mapping:** All adverse events were coded according to MedDRA using the current version at the time of trial reporting. For the purposes of the integrated safety analysis, the Applicant mapped adverse events (AEs) from all trials to MedDRA version 22.0. The CoreDF Report was utilized to ensure adequate mapping of verbatim terms to preferred terms (PTs).
- **AE:** The Applicant defined an AE as any untoward medical occurrence in a subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE could therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered related to the medicinal product use.
- **Serious adverse event (SAE):** A serious AE was defined as any untoward medical occurrence that at any dose resulted in the following: death, a life-threatening experience, in-patient hospitalization, or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly. Important medical events would also be considered an SAE when (based on appropriate medical judgement) the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition of SAE.
- **Safety population and treatment-emergent adverse events (TEAEs):** The safety population was defined as all randomized subjects who received at least one dose of investigational product. A TEAE was defined as an AE that begins after the first dose date or an existing AE that worsens after the first dose date. The Applicant’s TEAE definition was deemed adequate, and only TEAEs were considered in this review.²
- **MACE and fatal events:** An independent clinical endpoint committee (CEC), based out of the Clinical Endpoint Center at Brigham and Women’s Hospital (Boston, MA),

² The Applicant’s ISS SAP defines a TEAE as an event occurring within 28 days of the last dose taken; however, a 28-day window was not applied in the Applicant’s analysis. The Applicant confirmed (SD0018) that this was an error in their ISS SAP, and that their analysis did not utilize a 28-day window.

performed blinded adjudication of CV events that contributed to the MACE+ meta-analysis. The CEC members included medical experts in the field of cardiovascular disease. The CEC received and reviewed the following events for adjudication: all deaths, suspected nonfatal myocardial infarction (MI), suspected hospitalization for unstable angina, suspected transient ischemic attack and stroke, suspected hospitalization for heart failure, and coronary revascularization procedures. The CEC also reviewed a listing of SAEs on a monthly basis to identify MACE events potentially not identified/reported by the investigator. The CEC's manual of operations (i.e., adjudication charter) was reviewed and deemed adequate to classify events appropriately, consistently, and in an unbiased manner. Deaths were classified as CV death, non-CV death, or death of unknown cause. CV deaths were subclassified as either fatal MI, pump failure, sudden death, presumed sudden death, presumed CV death, fatal stroke, fatal pulmonary embolism (PE), death related to CV procedure, or other CV death. There was no classification or judgement by adjudicators on the investigator-reported PT for any event type.

- **Diabetic ketoacidosis (DKA):** DKA events were adjudicated by an endocrinologist according to the Applicant's DKA adjudication charter. See Section [17.3.6](#) for additional information on the DKA monitoring plan and case definitions used in the clinical program.

7.4.3. Data Querying

Several methods to query the data were employed in this safety review, including the use of FDA Medical Queries (FMQs), custom MedDRA queries (CMQs) developed by the Applicant, and grouped queries (GQs) developed by the clinical reviewer. All FMQ analyses utilized the "narrow" queries from FMQ release Version 2.0. Additional information on the PTs considered for each GQ is provided in the caption of the associated table.

7.5. Adequacy of Clinical Safety Database

7.5.1. Exposure

When pooling all phase 2b/3 trials conducted in the clinical development program of bexagliflozin for improved glycemic control and the placebo-controlled portion of a trial for the treatment of essential hypertension (i.e., the broad pool; see Section [17.2](#) for details), 2,578 subjects were exposed to bexagliflozin for 3,482 patient-years (on-treatment) ([Table 21](#)). There were 1,294 subjects exposed to bexagliflozin for ≥ 1 year, and 791 patients exposed for ≥ 2 years, with longer duration exposure primarily occurring in C-476. Given that all trials included a follow-up period, on-trial exposure was longer, with 3,824 patient-years of on-trial exposure in the broad pool. See Section [7.5.3](#) for a discussion on how the total exposure met current divisional guidance recommendations.

Table 21. Duration of On-Treatment Exposure, Safety Population, Broad Pool

Parameter	Bexa 20 mg N=2578 n (%)	Placebo N=1478 n (%)	Active Comparator N=406 n (%)
Duration of exposure, weeks			
Mean (SD)	70.5 (56)	60.2 (54.9)	56.5 (36)
Median (Q1, Q3)	56.4 (23.7, 119.7)	24.1 (12.3, 111)	24.9 (24, 96)
Min, max	0.1, 197	0.1, 194	0.3, 101
Total exposure (person-years)	3482.0	1702.2	438.3
Patients treated, by duration, n (%)			
≥1 day	2578 (100)	1476 (99.9)	405 (99.8)
≥6 weeks	2519 (97.7)	1452 (98.2)	400 (98.5)
≥12 weeks	2383 (92.4)	1335 (90.3)	397 (97.8)
≥18 weeks	2030 (78.7)	1021 (69.1)	391 (96.3)
≥24 weeks	1845 (71.6)	909 (61.5)	343 (84.5)
≥36 weeks	1340 (52)	628 (42.5)	194 (47.8)
≥52 weeks	1294 (50.2)	598 (40.5)	188 (46.3)
≥78 weeks	1240 (48.1)	570 (38.6)	181 (44.6)
≥104 weeks	791 (30.7)	387 (26.2)	0 (0)
≥130 weeks	466 (18.1)	217 (14.7)	0 (0)

Source: adex.xpt and adsl.xpt; Software: R; Generated by CDS
Abbreviations: Bexa, bexagliflozin; Q, quartile.

Duration of exposure in the placebo-controlled pool is shown in [Table 22](#). In this pool, 372 subjects were exposed to bexagliflozin for 145 patient-years (on-treatment).

While exposure in the placebo-controlled pool is somewhat limited, this pool is mainly used to inform commonly occurring (i.e., occurring at a $\geq 2\%$ frequency) adverse reactions for Section 6 of the labeling, and the amount of exposure in this pool is considered adequate for this purpose.

Table 22. Duration of On-Treatment Exposure, Safety Population, Placebo-Controlled Pool

Parameter	Bexa 20 mg N=372	Placebo N=300
Duration of treatment, weeks		
Mean (SD)	20.4 (6.3)	20.1 (6.3)
Median (Q1, Q3)	24 (12.7, 24.1)	24 (12.4, 24)
Min, Max	0.1, 27.9	0.1, 28.4
Total exposure (person years)	145.2	115.8
Patients treated, by duration, n (%)		
≥2 weeks	370 (99.5)	296 (98.7)
≥6 weeks	359 (96.5)	293 (97.7)
≥12 weeks	336 (90.3)	265 (88.3)
≥24 weeks	201 (54.0)	163 (54.3)
≥26 weeks	4 (1.1)	2 (0.7)

Source: adex.xpt and adsl.xpt; Software: R; Generated by CDS
Abbreviations: Bexa, bexagliflozin; Q, quartile.

7.5.2. Characteristics of the Safety Population

Baseline characteristics of subjects from trials that comprise the placebo-controlled pool, C-448, and C-476, are presented in [Table 23](#). The placebo-controlled pool consisted of 672 subjects with T2DM. 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. Baseline renal function was normal or mildly impaired in 98% of subjects and moderately impaired in 2% of subjects (mean eGFR of 92.2 mL/min/1.73 m²). Baseline characteristics of active-controlled trials C-423 and C-480 were generally similar to the placebo-controlled pool (data not shown).

C-448 (renal impairment trial) and C-476 (increased CV risk trial) enrolled distinct populations, with subjects in these trials being generally older, having a longer duration of diabetes, and worse renal function as compared to subjects in the placebo-controlled pool and active-controlled trials (Table 23). For example, the mean age of subjects enrolled in C-448 and C-476 was 64 and 69 years old, respectively, compared to a mean of 56 years in the placebo-controlled pool. Over half of subjects in C-476 and C-448 used insulin as a part of their diabetes management at baseline, indicating more advanced disease, as compared to no subject using insulin at baseline in the placebo-controlled pool.

Table 23. Baseline Demographics and Clinical Characteristics, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Characteristic	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Sex, n (%)						
Female	156 (41.9)	130 (43.3)	341 (30.1)	177 (31.2)	65 (41.4)	51 (32.9)
Male	216 (58.1)	170 (56.7)	791 (69.9)	390 (68.8)	92 (58.6)	104 (67.1)
Age, years						
Mean (SD)	56.6 (10.3)	56.2 (11)	64.4 (7.9)	64.6 (8)	69.3 (8.4)	69.9 (8.3)
Median (min, max)	57 (26, 80)	57 (28, 81)	65 (39, 91)	65 (40, 92)	70 (39, 88)	70 (47, 85)
Age group, years, n (%)						
Age <65 years	288 (77.4)	231 (77.0)	561 (49.6)	276 (48.7)	38 (24.2)	37 (23.9)
Age ≥65 years	84 (22.6)	69 (23.0)	571 (50.4)	291 (51.3)	119 (75.8)	118 (76.1)
Age group ≥75, years, n (%)						
≥75 years	15 (4.0)	17 (5.7)	113 (10.0)	67 (11.8)	40 (25.5)	50 (32.3)
Race, n (%)						
American Indian/Alaska Native	1 (0.3)	1 (0.3)	98 (8.7)	54 (9.5)	0 (0)	0 (0)
Asian	134 (36.0)	121 (40.3)	107 (9.5)	55 (9.7)	61 (38.9)	59 (38.1)
Black/African American	59 (15.9)	43 (14.3)	46 (4.1)	28 (4.9)	9 (5.7)	6 (3.9)
Multiple	2 (0.5)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Native Hawaiian/Pacific Islander	2 (0.5)	0 (0)	0 (0)	0 (0)	2 (1.3)	0 (0)
Other	1 (0.3)	0 (0)	2 (0.2)	0 (0)	2 (1.3)	2 (1.3)
White	173 (46.5)	133 (44.3)	879 (77.7)	430 (75.8)	83 (52.9)	88 (56.8)
Ethnicity, n (%)						
Hispanic or Latino	117 (31.5)	86 (28.7)	166 (14.7)	93 (16.4)	7 (4.5)	17 (11.0)
Not Hispanic or Latino	255 (68.5)	213 (71.0)	966 (85.3)	474 (83.6)	149 (94.9)	138 (89.0)
Unknown	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.6)	0 (0)

Characteristic	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Country of participation, n (%)						
US	237 (63.7)	176 (58.7)	397 (35.1)	205 (36.2)	53 (33.8)	50 (32.3)
Non US	135 (36.2)	124 (41.3)	735 (64.9)	362 (63.8)	104 (66.2)	105 (67.7)
BMI, kg/m ²						
Mean (SD)	30.5 (6.2)	29.7 (5.8)	32.8 (6.1)	32.2 (5.8)	30.3 (6)	30.1 (5.8)
Median	29.7	29.1	32	31.6	29.5	28.8
(min, max)	(17, 46)	(18, 45)	(20, 62)	(21, 65)	(19, 45)	(20, 45)
Duration of T2DM, years						
Mean (SD)	7.6 (6.6)	7.8 (5.8)	14.9 (8.6)	15.2 (9.3)	15.5 (9.2)	16.3 (9)
Median	5.8	6.5	14.3	13.7	15.2	17
(min, max)	(0, 40.3)	(0, 31.1)	(0.4, 57.4)	(0.3, 53.7)	(0, 50.2)	(0, 47.3)
Baseline insulin, n (%)						
Insulin treated	0 (0)	0 (0)	610 (53.9)	292 (51.5)	86 (54.8)	88 (56.8)
Not insulin treated	372 (100)	300 (100)	522 (46.1)	275 (48.5)	71 (45.2)	67 (43.2)
Baseline HbA1c, n (%)						
Mean (SD)	8.2 (0.9)	8.2 (0.8)	8.3 (0.9)	8.3 (0.9)	8.0 (0.8)	7.9 (0.8)
Median	8.1	8	8.2	8.2	7.8	7.8
(min, max)	(7, 10.5)	(7, 10.5)	(5.8, 11)	(5.5, 11.4)	(6.7, 10.4)	(5.9, 10.4)
HbA1c group, n (%)						
≤8.5%	272 (73.1)	217 (72.3)	715 (63.2)	362 (63.8)	124 (79.0)	123 (79.4)
>8.5%	100 (26.9)	83 (27.7)	417 (36.8)	205 (36.2)	33 (21.0)	32 (20.6)
eGFR, mL/min/1.73 m ²						
Mean (SD)	91.6 (24)	92.9 (23.1)	77.5 (19.9)	78 (20.3)	45.4 (8.6)	44.8 (8.1)
Median	88.8	88.3	75.6	75.6	46.3	45
(min, max)	(51, 267)	(52, 181)	(25, 158)	(36, 156)	(26, 73)	(26, 64)
eGFR group, mL/min/1.73 m ²						
≥90	179 (48.1)	140 (46.7)	285 (25.2)	145 (25.6)	0 (0)	0 (0)
≥60 to <90	183 (49.2)	155 (51.7)	622 (54.9)	313 (55.2)	7 (4.5)	4 (2.6)
≥45 to <60	10 (2.7)	5 (1.7)	191 (16.9)	92 (16.2)	76 (48.4)	74 (47.7)
≥30 to <45	0 (0)	0 (0)	33 (2.9)	17 (3.0)	71 (45.2)	73 (47.1)
<30	0 (0)	0 (0)	1 (0.09)	0 (0)	3 (1.9)	4 (2.6)
UACR group						
Macroalbuminuria	3 (0.8)	3 (1.0)	98 (8.7)	45 (7.9)	31 (19.7)	47 (30.3)
Microalbuminuria	41 (11.0)	26 (8.7)	341 (30.1)	158 (27.9)	64 (40.8)	53 (34.2)
Normal	128 (34.4)	72 (24.0)	693 (61.2)	364 (64.2)	62 (39.5)	55 (35.5)
Missing	200 (53.8)	199 (66.3)	0 (0)	0 (0)	0 (0)	0 (0)

Source: adsl.xpt and abdl.xpt; Software: R; Generated by CDS

UACR Groups: Normal: <30 mg/g, Microalbuminuria: ≥30 to <300 mg/g, Macroalbuminuria: ≥300 mg/g

Abbreviations: Bexa, bexagliflozin; BMI, body mass index; eGFR, estimated glomerular filtration; HbA1c, hemoglobin A1C; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

7.5.3. Exposure per FDA's Draft Guidance Recommendations

The extent to which the clinical program meets the recommendations set forth in the draft guidance document *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving*

Glycemic Control Guidance for Industry (March 2020) is shown in [Table 24](#) and discussed below:

Total Exposure and Exposure Duration: There were 3,482 patient-years of on-treatment exposure and 3,824 patient-years of on-trial exposure in the broad pool. On-trial exposure was longer due to follow-up periods in each trial (AEs that occurred during the follow-up period were considered treatment-emergent and thus considered in this safety review). Therefore, the guidance recommendation to have at least 4,000 patient-years of exposure was not met. In addition, while the program did not meet the guidance recommendations for 1-year exposure duration, it exceeded the recommendations for 2-year exposure durations.

Older adults: The clinical program exceeded the recommendation to evaluate at least 600 subjects >65 years of age.

Established CV Disease: The clinical program exceeded the recommendation to evaluate at least 600 subjects with established CV disease. In C-476, there were 703 subjects assigned to bexagliflozin in group 1 (consisting of subjects with a history of atherosclerotic vascular disease) and 166 patients assigned to bexagliflozin in group 2 (consisting of subjects with a history New York Heart Association [NYHA] class II/III HF), for a total of 869 subjects with established CV disease exposed to bexagliflozin. As exposure in C-476 exceeded the guidance recommendation, the Applicant did not undertake a program-wide evaluation of exposure for this category.

Renal Impairment: The clinical program did not meet the recommendation to evaluate at least 500 subjects with stage 3/4 CKD exposed to drug. There were 375 subjects in C-448 and C-476 with baseline eGFR <60 mL/min/1.73 m² exposed to bexagliflozin ([Table 11](#)). While all other trials excluded subjects with eGFR <60 mL/min/1.73 m², a small number of subjects in these trials were enrolled with baseline eGFR <60 mL/min/1.73 m² due to variability in measurements between screening and baseline. Given that baseline eGFR was variable between screening and baseline, these subjects were not considered in the evaluation of exposure for this population.

With the new guidance, the Division has moved away “from a narrow focus on evaluating cardiovascular safety” and toward an approach that would yield a robust evaluation for a broad range of safety concerns (Chong et al. 2020). In lieu of a requisite minimum number of events and a degree of risk to be excluded, adequate enrollment of a broad population with enough exposure to generate a robust safety database was sought. The bexagliflozin clinical program was completed prior to issuance of the draft guidance in March 2020. Furthermore, at the time the clinical program was under development, a prior draft guidance document (Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes dated December 2008; now withdrawn (December 2008)) was in effect, and the Applicant’s clinical program was completed in accordance with the recommendations in the 2008 guidance. Despite not meeting all criteria recommended in the 2020 draft guidance for each category, the total exposure and exposure durations observed in the clinical program for bexagliflozin are adequate given that 1) they are sufficient to characterize commonly occurring AEs, 2) the additional exposure needed to meet the guidance recommendations is not of sufficient quantity such that it is likely to characterize safety signals that may occur at a low frequency, and 3) the safety profile of SGLT2 inhibitors is generally well established, and the safety review supports a similar safety profile to other SGLT2 inhibitor products. On balance, given that the program enrolled higher numbers for older adults and those with established CV

disease (see below) and exceeded the recommended number of patients with exposure greater than 2 years, the total exposure was deemed adequate.

The amount of exposure in subjects with renal impairment is considered adequate as bexagliflozin will not be recommended for use in patients with eGFR <30 mL/min/1.73 m². In addition, the amount of exposure in C-448 is generally comparable to renal impairment trials that have been used to inform the safety and efficacy of other SGLT2 inhibitors in this patient population (e.g., dapagliflozin/DERIVE N=160 exposed subjects, empagliflozin/1245.36 N=188 exposed subjects, canagliflozin/DIA3004 N=179 exposed subjects).

Table 24. Comparison of Bexagliflozin’s Development Program to FDA’s Draft Guidance for Industry for Evaluating the Safety of New Drugs for Improving Glycemic Control

Recommendation	Bexagliflozin Development Program
≥4,000 patient-years exposure in phase 3 clinical trials	3,482 patient-years* [±]
≥1,500 patients exposed to drug for at least 1 year	1,294 subjects [±]
≥500 patients exposed to drug for at least 2 years	791 subjects [±]
≥500 patients with stage 3/4 CKD exposed to the drug	375 subjects ^β
≥600 patients with established CV disease exposed to drug	>869 subjects [¥]
≥600 patients older than 65 years of age exposed to drug	955 subjects [±]

Source: Compiled by Clinical Reviewer from CDS and Applicant analyses.

* On-treatment exposure.

± As calculated from Broad Pool.

β Subjects with baseline eGFR <60 mL/min/1.73 m² in C-448 and C-476.

¥ A program-wide analysis for the number of patients with established CV disease did not occur as 869 subjects with CV disease were enrolled in C-476 alone.

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular.

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

There were no clinically meaningful imbalances in the overall incidence of subjects experiencing AEs in the placebo-controlled pool, C-476, or C-448 ([Table 25](#)), nor in active-controlled trials (data not shown). While some event categories shown in [Table 25](#) demonstrated imbalances unfavorable to bexagliflozin (e.g., AEs leading to discontinuation in the placebo-controlled pool, SAEs in Trial C-448), limited data in these categories impedes interpretability. No meaningful imbalances were observed for AEs leading to discontinuation, AEs leading to drug interruption, or SAEs in C-476, which had the most data to support meaningful conclusions. Overall, there do not appear to be concerning trends.

Table 25. Overview of AEs, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Event Category	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372 n (%)	Placebo N=300 n (%)	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)
SAE	6 (1.7)	5 (1.6)	373 (33.0)	208 (36.7)	11 (7.0)	9 (5.8)
AE leading to permanent discontinuation of study drug	8 (2.2)	3 (0.9)	95 (8.4)	48 (8.5)	4 (2.5)	8 (5.2)
AE leading to interruption of study drug	3 (0.8)	3 (0.9)	173 (15.3)	82 (14.5)	9 (5.7)	5 (3.2)
AE	175 (46.5)	143 (48.6)	1006 (88.9)	524 (92.4)	109 (69.4)	105 (67.7)
Death	0 (0)	1 (0.4)	39 (3.4)	26 (4.6)	0 (0)	0 (0)
Severe	8 (2.2)	8 (3)	211 (18.6)	110 (19.4)	12 (7.6)	8 (5.2)
Moderate	34 (9)	41 (13.8)	444 (39.2)	231 (40.7)	31 (19.7)	31 (20.0)
Mild	133 (35.3)	93 (31.2)	312 (27.6)	157 (27.7)	66 (42.0)	66 (42.6)

Source: adae.xpt; Software: R; Generated by CDS

Percentages for the Placebo-Controlled Pool based on study-size adjusted proportions.

Abbreviations: AE, adverse event; Bexa, bexagliflozin; SAE, severe adverse event.

7.6.1.2. Deaths

There were 69 deaths across all phase 2b/3 trials (broad pool). The majority of deaths in the bexagliflozin clinical program occurred in C-476 (65 deaths), which enrolled patients with either established cardiovascular disease or multiple risk factors for cardiovascular morbidity ([Table 26](#) and [Table 27](#)). Deaths were limited in other phase 2/3 trials, with no deaths occurring in C-419, C-448, C-449, or C-603. Single events of fatal cardiac arrest and sigmoid adenocarcinoma occurred in the bexagliflozin groups of C-418 and C-423, respectively, and events of fatal cardiomyopathy and small cell undifferentiated lung carcinoma occurred in the placebo and glimepiride groups of C-450 and C-480, respectively.

In C-476 there were proportionally fewer deaths in the bexagliflozin group (3.4%) as compared to the placebo group (4.6%) ([Table 26](#)). As expected, the majority of deaths were related to cardiac events. As discussed in [Section 7.4.2](#), an independent CEC reviewed all deaths that occurred in the clinical program regardless of whether they were indicated as CV-related or not by the investigator, and classified the event as either a CV death, non-CV death, or death of unknown cause. Deaths of unknown cause were considered CV deaths for the purpose of the MACE analysis and are presented in accordance with this practice in [Table 26](#). In line with conclusions from the MACE+ meta-analysis, there were proportionally fewer adjudicated CV deaths in the bexagliflozin group (26 events, 2.3%) as compared to the placebo group (18 events, 3.2%). In addition, there were no meaningful imbalances in subcategories of CV death (e.g., sudden deaths, deaths of unknown cause, pump failure, etc.); although events in each category were limited.

An imbalance unfavorable to bexagliflozin in the PT of “cardiac arrest” was observed (1.0% versus 0.2% in the bexagliflozin and placebo groups, respectively), as shown in [Table 26](#). Narratives for the cardiac arrest events were reviewed and no apparent trend was observed, although some events contained incomplete information limiting interpretability. The majority of adjudicated CV deaths were classified as sudden deaths in both treatment groups, with more

sudden deaths occurring in the placebo group (Table 26). The CEC did not comment on the PT associated with the event, and several events with the PT of “cardiac arrest” were adjudicated not to be CV related by the CEC. Overall, the reason for the noted imbalance in investigator-assigned PT is unclear; however, the overall favorable drug effect on CV death in C-476 and the MACE+ meta-analysis is reassuring.

There were proportionally fewer deaths that were adjudicated to be non-CV deaths in the bexagliflozin group (13 events (1.1%)) versus the placebo groups (8 events (1.4%)) (Table 26). There were also no meaningful imbalances in any PTs for noncardiac deaths or concerning trends at the system organ class (SOC) level (Table 27), although data were limited.

Lastly, to assess deaths that may have occurred after subjects were lost to follow-up or withdrew consent, the Applicant attempted to determine the vital status (i.e., living or deceased) for all subjects randomized in C-476. Vital status was obtained for all but four subjects. Results from this analysis show that there were 82 deaths in C-476, 48 (4.2%) occurring in subjects randomized to receive bexagliflozin and 34 (6.0%) occurring in subjects randomized to receive placebo.

Overall, death data from the bexagliflozin clinical program indicate trends favorable to bexagliflozin; however, it is acknowledged that death events, and particularly noncardiac death events, were limited.

Table 26. Deaths Due to AEs by Adjudication Category, Safety Population, Trial C-476

Adjudication Category	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
All deaths due to AEs	39 (3.4)	26 (4.6)	-1.1 (-3.2, 0.9)
Adjudicated CV deaths	26 (2.3)	18 (3.2)	-0.9 (-2.6, 0.8)
Sudden death	12 (1.1)	10 (1.8)	-0.7 (-1.9, 0.5)
Deaths of unknown cause	6 (0.5)	2 (0.4)	0.2 (-0.5, 0.8)
Presumed CV death	4 (0.4)	2 (0.4)	0.0 (-0.6, 0.6)
Pump failure	1 (0.1)	1 (0.2)	-0.1 (-0.5, 0.3)
Fatal MI	1 (0.1)	0 (0)	0.1 (-0.1, 0.3)
Presumed sudden death	1 (0.1)	1 (0.2)	-0.1 (-0.5, 0.3)
Other CV death	1 (0.1)	1 (0.2)	-0.1 (-0.5, 0.3)
Fatal stroke	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Adjudicated non-CV deaths	13 (1.1)	8 (1.4)	-0.3 (-1.4, 0.9)

Source: Compiled by Clinical Reviewer from adjudication records and SD0023

Abbreviations: AE, adverse event; Bexa, bexagliflozin; CV, cardiovascular; MI, myocardial infarction.

Table 27. Deaths Due to AEs by SOC and PT as Sorted by SOC RD, Safety Population, Trial C-476

System Organ Class Preferred Term	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
All deaths due to AEs	39 (3.4)	26 (4.6)	-1.1 (-3.2, 0.9)
General disorders and administration site conditions	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Death	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Sudden cardiac death	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Metabolism and nutrition disorders	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Diabetic complication	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Metabolic acidosis ^Q	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)

System Organ Class Preferred Term	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Hepatobiliary disorders*	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cholangitis	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Injury, poisoning and procedural complications	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Post procedural complication	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Blood and lymphatic system disorders	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Blood loss anemia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Vascular disorders	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Thrombosis	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Arteriosclerosis	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Respiratory, thoracic, and mediastinal disorders	4 (0.4)	3 (0.5)	-0.2 (-0.9, 0.5)
Respiratory distress	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Acute respiratory failure	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Respiratory failure	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Aspiration	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Infections and infestations	2 (0.2)	2 (0.4)	-0.2 (-0.7, 0.4)
Gangrene	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Septic shock	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cellulitis	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Pneumonia	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Nervous system disorders	0 (0)	2 (0.4)	-0.4 (-0.8, 0.1)
Central nervous system hemorrhage	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Syncope	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	2 (0.2)	4 (0.7)	-0.5 (-1.3, 0.2)
Adenocarcinoma gastric	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Bile duct cancer	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Metastatic renal cell carcinoma	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Non-small cell lung cancer	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Pancreatic carcinoma	0 (0)	3 (0.5)	-0.5 (-1.1, 0.1)
Cardiac disorders	22 (1.9)	14 (2.5)	-0.5 (-2.0, 1.0)
Cardiac arrest	11 (1.0)	1 (0.2)	0.8 (0.1, 1.5)
Acute left ventricular failure	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cardiac failure acute	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cardiac failure chronic	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cardiomyopathy	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Cardio-respiratory arrest	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Acute myocardial infarction	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Cardiac failure	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Arrhythmia	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Myocardial infarction	2 (0.2)	2 (0.4)	-0.2 (-0.7, 0.4)
Ventricular fibrillation	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Coronary artery disease	1 (0.09)	2 (0.4)	-0.3 (-0.8, 0.3)
Cardiac failure congestive	0 (0)	2 (0.4)	-0.4 (-0.8, 0.1)
Cardiopulmonary failure	0 (0)	2 (0.4)	-0.4 (-0.8, 0.1)

Source: adae.xpt; Software: R; Generated by CDS

* See Section 17.3.5 Hepatic Injury, the subject was found to have a necrotic gallbladder upon open laparotomy

Ω Metabolic acidosis due to persistent septic shock

Abbreviations: AE, adverse event; Bexa, bexagliflozin; PT, preferred term, RD, risk difference; SOC, system organ class.

7.6.1.3. Serious Adverse Events

The incidence of SAEs was similar between treatment arms in the placebo-controlled pool, occurring in six (1.7%) and five (1.6%) subjects in the bexagliflozin and placebo groups, respectively ([Table 25](#)). No events by PT occurred in more than one subject and there were no apparent trends between treatment groups by SOC (data not shown). Notable SAEs in bexagliflozin-exposed subjects in this pool include single events of urinary tract infection (UTI) and DKA, which are discussed in additional detail in Sections [17.3.6](#) and [17.3.9](#).

Similarly, limited SAE data were 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 (data not shown). Significant SAEs in bexagliflozin-exposed subjects in these trials include single events of pyelonephritis and phimosis with subsequent radial circumcision in C-480 and a single event of gangrene in C-423. The event of gangrene occurred on Day 16 subsequent to a trauma event (subject stepping on a nail), and therefore the event may not be related to bexagliflozin use.

Of note, UTI, including serious events of urosepsis/pyelonephritis, DKA, and genital mycotic infection (GMI) are considered class effects proposed for labeling. SAE data from these trials therefore do not raise new safety concerns.

Most SAEs were observed in C-476. In this trial, there was a lower incidence of SAEs in the bexagliflozin group compared to the placebo group (33% versus 37%, respectively) ([Table 25](#)). SAEs reported in at least two subjects in the bexagliflozin group with risk difference (RD) ≥ 0.1 are shown in [Table 28](#). In line with the enrolled patient population, various cardiac SAEs were observed. Imbalances unfavorable to drug were observed for various PTs including coronary artery disease, cardiac failure, and myocardial ischemia.

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. The 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, osteomyelitis, localized infection, and cellulitis. These are discussed individually below.

Sepsis/Septic Shock

Twelve subjects (1.1%) in the bexagliflozin group and one subject (0.2%) in the placebo group had an SAE of sepsis and/or septic shock in C-476. The imbalance persisted upon evaluation of all events (i.e., SAEs and nonserious AEs), with 14 (1.2%) and 2 (0.4%) subjects experiencing an event of sepsis/septic shock in the bexagliflozin and placebo groups, respectively. Four subjects in the bexagliflozin group with serious events of sepsis died during the trial. Subject 476-(b) (6) died during hospitalization for infective endocarditis with the primary causes of death listed on the death certificate attributed to acute respiratory failure, septic shock, and endocarditis. Subject 476-(b) (6) died after hospitalization for sepsis, gangrene, and severe end-stage peripheral artery disease (PAD). The subject refused below-the-knee (BTK) amputation, and the reported cause of death was gangrene. Subject 476-(b) (6) died of acute respiratory failure in the setting of metabolic acidosis secondary to septic shock that was

presumed to have been caused by a nonhealing sacral ulcer. Subject 476- (b) (6) was hospitalized with an event of sepsis on Day 495 and later died on Day 518 due to acute left ventricular failure. Of the remaining nonfatal SAEs, three events in the bexagliflozin group and the single sepsis event in the placebo group appeared secondary to UTI. Urosepsis will be included as a Warning and Precaution in the labeling.

The potential drug-relatedness of the sepsis events is unclear. While some events appeared to be urosepsis events, which could be drug-related, other sepsis events appeared associated with endocarditis, pneumonia, appendicitis, and cellulitis events. In cases where death occurred, there were multiple contributing factors that lead to the event of death. Laboratory parameter assessments in C-476 did not indicate clinically meaningful changes in relevant hematology parameters (e.g., decreases in WBCs with bexagliflozin treatment) between treatment groups, nor were there significant imbalances in the SOC for “Infections and Infestations” (data not shown). As shown in [Table 29](#), there was no significant imbalance between groups in serious bacterial infections as identified by the “Bacterial Infections” FMQ (4.1% versus 3.9% in the bexagliflozin and placebo groups, respectively). Associations between drug exposure and increased risk of sepsis have not been characterized with approved SGLT2 inhibitors. Despite unclear drug relatedness, labeling is recommended to inform providers on the potential increased risk of sepsis events with bexagliflozin treatment as they are serious and potentially life-threatening. Based on the available information, standard postmarket surveillance appears reasonable to monitor the risk of serious sepsis events. Postmarketing reports related to serious infections should be monitored.

Osteomyelitis

Serious osteomyelitis events occurred in 10 (0.9%) subjects in the bexagliflozin group versus 1 (0.2%) subject in the placebo group. The imbalance persisted when evaluating events of all severity, with 12 (1.1%) and 3 (0.5%) subjects in the bexagliflozin and placebo groups experiencing an event of osteomyelitis, respectively. Seven subjects (six in the bexagliflozin group and one in the placebo group) underwent amputations prompted, at least in part, by osteomyelitis. See [Section 7.7.1](#) for additional discussion regarding increased risk of amputation with bexagliflozin exposure, which is proposed for labeling.

Localized Infection

Serious events of localized infection occurred in five subjects assigned to the bexagliflozin group as compared to none in the placebo group. This imbalance persisted when evaluating events of all severity (12 (1.1%) and 2 (0.4%) subjects with an event in the bexagliflozin and placebo groups, respectively) Narrative review of the serious events revealed that four of the five subjects had toe/foot infections, of which one subject had a subsequent amputation event.

Cellulitis

Serious events of cellulitis occurred in nine (0.8%) and two (0.4%) subject in the bexagliflozin and placebo groups, respectively. However, an imbalance in these events was not observed when assessing cellulitis events of all severity, with 34 (3.0%) and 16 (2.8%) of subjects in the bexagliflozin and placebo groups having an event. Five of the nine subjects with a cellulitis event had concurrent osteomyelitis and/or sepsis events. Eight of the nine serious cellulitis events were located on a lower limb.

Amputation is a serious and clinically meaningful consequence of osteomyelitis and skin infections, including cellulitis. As discussed in Section 7.7.1, the labeling for bexagliflozin should advise prescribers to consider risk factors that may increase a patient's risk of amputation before initiating treatment and monitor for infections or ulcers of the lower limbs and discontinue treatment should these events occur. Labeling that describes predisposing factors (e.g., osteomyelitis, diabetic foot ulcers, etc.) is also recommended.

Table 28. SAEs by PT Reported by at Least Two Subjects in the Bexagliflozin Group With RD ≥ 0.1 , Safety Population, Trial C-476

Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Coronary artery disease	25 (2.2)	8 (1.4)	0.8 (-0.5, 2.1)
Cardiac failure	21 (1.9)	6 (1.1)	0.8 (-0.4, 1.9)
Cardiac arrest	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Osteomyelitis	10 (0.9)	1 (0.2)	0.7 (0.1, 1.4)
Osteoarthritis	15 (1.3)	4 (0.7)	0.6 (-0.3, 1.6)
Sepsis	9 (0.8)	1 (0.2)	0.6 (-0.0, 1.2)
Cellulitis	9 (0.8)	2 (0.4)	0.4 (-0.3, 1.2)
Acute respiratory failure	7 (0.6)	1 (0.2)	0.4 (-0.1, 1.0)
Myocardial ischemia	7 (0.6)	1 (0.2)	0.4 (-0.1, 1.0)
Localized infection	5 (0.4)	0 (0)	0.4 (0.1, 0.8)
Chronic obstructive pulmonary disease	10 (0.9)	3 (0.5)	0.4 (-0.5, 1.2)
Diarrhea	4 (0.4)	0 (0)	0.4 (0.0, 0.7)
Pleural effusion	4 (0.4)	0 (0)	0.4 (0.0, 0.7)
Septic shock	4 (0.4)	0 (0)	0.4 (0.0, 0.7)
Cerebrovascular accident	13 (1.1)	5 (0.9)	0.3 (-0.7, 1.3)
Hypotension	5 (0.4)	1 (0.2)	0.3 (-0.3, 0.8)
Colitis	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Endocarditis	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Femur fracture	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Presyncope	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Spinal stenosis	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Subarachnoid hemorrhage	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Transitional cell carcinoma	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Acute myocardial infarction	30 (2.7)	14 (2.5)	0.2 (-1.4, 1.8)
Respiratory failure	8 (0.7)	3 (0.5)	0.2 (-0.6, 0.9)
Cardiac failure chronic	6 (0.5)	2 (0.4)	0.2 (-0.5, 0.8)
Benign prostatic hyperplasia	4 (0.4)	1 (0.2)	0.2 (-0.3, 0.7)
Abdominal abscess	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Acute pulmonary edema	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Aortic stenosis	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Appendicitis	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Blood loss anemia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Concussion	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Death	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Erysipelas	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Foot fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Gastroenteritis viral	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Hydrocele	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Hypokalemia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Impaired healing	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)

Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Lower limb fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Lung adenocarcinoma	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Lung neoplasm malignant	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Metabolic acidosis	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Edema peripheral	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Patella fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Peripheral artery stenosis	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Rib fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Spinal fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Troponin increased	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Umbilical hernia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Ventricular arrhythmia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Vertigo positional	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Acute kidney injury	9 (0.8)	4 (0.7)	0.1 (-0.8, 1.0)
Carotid artery stenosis	7 (0.6)	3 (0.5)	0.1 (-0.7, 0.8)
Cataract	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Diabetic foot	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Extremity necrosis	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Hyperkalemia	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Orthostatic hypotension	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Peripheral artery occlusion	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Pyelonephritis	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; PT, preferred term, RD, risk difference; SAE, serious adverse event.

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 acute kidney injury (AKI) (0.8% and 0.7% in the bexagliflozin and placebo groups, respectively) in C-476. Various PTs representing fracture events occurred at a RD ≥ 0.1 , which are discussed in additional detail in Section 17.3.1.

To further explore serious events in C-476 for potential safety signals, FMQs were utilized. Table 29 presents SAEs with RD $\geq 0.2\%$ by FMQ. As discussed further in Section 17.3.1, there were more events of serious fracture in the bexagliflozin group compared to placebo. Events in the FMQs for “hypotension” and “dizziness” could indicate volume depletion events, which are known to be associated with the class. Other FMQs had relatively few events per treatment arm and/or did not demonstrate noteworthy differences between bexagliflozin and placebo groups.

Table 29. SAEs With RD ≥ 0.2 by FMQ Sorted by RD, Safety Population, Trial C-476

FMQ (Narrow)	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Fracture	15 (1.3)	2 (0.4)	1.0 (0.1, 1.8)
Arthritis	18 (1.6)	7 (1.2)	0.4 (-0.8, 1.5)
Diarrhea	4 (0.4)	0 (0)	0.4 (0.0, 0.7)
Dizziness	6 (0.5)	1 (0.2)	0.4 (-0.2, 0.9)
Hypotension	8 (0.7)	2 (0.4)	0.4 (-0.3, 1.0)
Purulent material	5 (0.4)	1 (0.2)	0.3 (-0.3, 0.8)
Vertigo	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Abdominal pain	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)

	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
FMQ (Narrow)			
Bacterial infection	46 (4.1)	22 (3.9)	0.2 (-1.8, 2.1)
Dyspnea	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Hepatic injury*	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Peripheral edema	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Self-harm	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Stroke TIA	32 (2.8)	15 (2.6)	0.2 (-1.5, 1.8)
Thrombocytopenia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)

Source: adae.xpt; Software: R; Generated by CDS

* See Section 17.3.5 Hepatic Injury. PTs for hepatic injury were hepatic cirrhosis and Hepatitis B

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference; SAE, serious adverse event; TIA, transient ischemic attack.

7.6.1.4. Dropouts and/or Discontinuations Due to Adverse Events

Data to characterize AEs leading to discontinuation were limited in all trials except C-476. Discontinuations due to AEs in the placebo-controlled pool are shown in Table 30 and include isolated events of frequent urination (polyurea, pollakiuria), DKA, and potential UTI (dysuria). In active-controlled Trials C-480 and C-423, there was a higher incidence of GMI events leading to discontinuation of treatment in the bexagliflozin group as compared to the active comparator groups (data not shown).

Table 30. Subjects With AEs Leading to Treatment Discontinuation by PT Sorted by RD, Safety Population, Placebo-Controlled Pool

	Bexa 20 mg N=372 n (%)	Placebo N=300 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Preferred Term			
AE leading to permanent discontinuation			
of study drug	8 (2.2)	3 (0.9)	1.3 (0, 2.6)
Cardiac failure acute	1 (0.3)	0 (0)	0.3 (-0.2, 0.9)
Coronary artery disease	1 (0.3)	0 (0)	0.3 (0.2, 0.4)
Dysuria	1 (0.3)	0 (0)	0.3 (0.2, 0.4)
Pollakiuria	1 (0.3)	0 (0)	0.3 (-0.2, 0.9)
Polyuria	1 (0.3)	0 (0)	0.3 (0.2, 0.4)
Diabetic ketoacidosis	1 (0.3)	0 (0)	0.3 (-0.2, 0.9)
Gastroesophageal cancer	1 (0.3)	0 (0)	0.3 (0.2, 0.4)
Abdominal pain	1 (0.2)	0 (0)	0.2 (0.1, 0.4)
Liver function test increased*	1 (0.2)	0 (0)	0.2 (0.1, 0.4)
Muscle spasms	1 (0.2)	0 (0)	0.2 (0.1, 0.4)
Gastroenteritis	0 (0)	1 (0.3)	-0.3 (-0.9, 0.2)
Ligament injury	0 (0)	1 (0.3)	-0.3 (-0.9, 0.2)
Hyperhidrosis	0 (0)	1 (0.3)	-0.3 (-0.4, -0.2)

Source: adae.xpt; Software: R; Generated by CDS

Percentages based on study-size adjusted proportions.

* See Section 17.3.5 Hepatic Injury

Abbreviations: AE, adverse event; Bexa, bexagliflozin; PT, preferred term; RD, risk difference.

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, respectively). FMQ analysis was utilized to explore the data. Table 31 presents AEs leading to treatment discontinuation by FMQ with an RD >0.1%. The only FMQ wherein there was a significant difference in events between

treatment groups (e.g., a CI lower bound >0) was the query for “Fungal Infection.” PTs driving this imbalance included “genital fungal infection,” “vulvovaginal candidiasis,” and “vulvovaginal mycotic infection.” While not captured by FMQ, there was also an imbalance unfavorable to bexagliflozin for events of balanoposthitis leading to discontinuation (6 (0.5%) versus 0 (0%) subjects in the bexagliflozin and placebo groups, respectively). In addition, a higher incidence of events leading to treatment discontinuation in the query for “Renal and Urinary Tract Infections” also was observed, including imbalances unfavorable to bexagliflozin for the PTs of UTI and cystitis (please refer to Section 17.3.9, Table 218). All other queries had few events and/or did not show a meaningful difference between treatment groups.

As discussed further in Section 7.6.1.5, GMI, UTI, and frequent urination are AEs commonly occurring with SGLT2 inhibitor products, including bexagliflozin, as demonstrated in this safety review. The data presented herein supports that commonly occurring AEs may lead to treatment discontinuation. Information regarding these important tolerability related events will be included in labeling.

Table 31. Subjects With AEs Leading to Treatment Discontinuation by FMQ With RD ≥0.1 Sorted by RD, Safety Population, Trial C-476

FMQ (Narrow)	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo
			Risk Difference (%) (95% CI)
Fungal Infection	7 (0.6)	0 (0)	0.6 (0.2, 1.1)
Renal and urinary tract infection	9 (0.8)	3 (0.5)	0.3 (-0.5, 1.1)
Bacterial Infection	12 (1.1)	5 (0.9)	0.2 (-0.8, 1.2)
Constipation	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Dyspepsia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Hypoglycemia	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Myocardial ischemia	6 (0.5)	2 (0.4)	0.2 (-0.5, 0.8)
Acute coronary syndrome	5 (0.4)	2 (0.4)	0.1 (-0.5, 0.7)
Alopecia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Anemia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Arthralgia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Back pain	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Depression	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Diarrhea	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Fracture	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Hemorrhage	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Hypotension	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Myocardial infarction	5 (0.4)	2 (0.4)	0.1 (-0.5, 0.7)
Nasopharyngitis	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Peripheral edema	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Purulent material	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Thrombocytopenia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Viral infection	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Volume depletion	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference.

7.6.1.5. Treatment-Emergent Adverse Events

AEs reported in ≥2% of subjects treated with bexagliflozin and greater than placebo in the placebo-controlled pool are shown in Table 32 and include female GMI, increased urination,

vaginal pruritus, UTI, thirst, hypoglycemia, and male GMI. Grouped queries (GQs) were utilized to identify events that represented a similar medical concept (e.g., terms of polyuria, pollakiuria, micturition urgency, and nocturia were grouped for increased urination events). The events resultant from this analysis are considered class effects that are described in the labeling of currently marketed SGLT2 inhibitor products. Aside from the events utilized in the GQ analysis shown in [Table 32](#), there were no other PTs that occurred in $\geq 2\%$ of subjects and more frequently with drug than placebo.

Table 32. AEs Occurring in $\geq 2\%$ of Subjects in the Bexagliflozin Group and Greater and Placebo Sorted by GQ RD, Safety Population, Placebo-Controlled Pool

Group Query Preferred Term	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Genital mycotic infection female ¹	9 (5.6)	0 (0)	5.5 (3.1, 7.9)
Vulvovaginal mycotic infection ¹	5 (3.3)	0 (0)	3.3 (1.4, 5.2)
Vaginal infection ¹	2 (1)	0 (0)	1 (0.2, 1.7)
Genital infection fungal ¹	1 (0.5)	0 (0)	0.5 (-0.1, 1)
Vulvovaginal candidiasis ¹	1 (0.7)	0 (0)	0.8 (-0.4, 2)
Increased urination	25 (6.6)	9 (3.1)	3.4 (1.2, 5.5)
Polyuria	18 (4.6)	8 (2.7)	1.8 (-0.1, 3.7)
Pollakiuria	7 (1.9)	0 (0)	1.9 (1, 2.9)
Micturition urgency	1 (0.2)	0 (0)	0.2 (0.1, 0.4)
Nocturia	0 (0)	1 (0.4)	-0.4 (-0.7, -0.1)
Vaginal pruritus Female ¹	4 (2.7)	0 (0)	2.8 (1.5, 4.2)
Pruritus genital ¹	3 (2)	0 (0)	2 (0.7, 3.4)
Vulvovaginal pruritus ¹	1 (0.8)	0 (0)	0.8 (0.5, 1)
UTI	23 (6.1)	12 (4)	1.9 (-0.3, 4.1)
Dysuria	7 (1.8)	2 (0.7)	1 (0.5, 1.5)
Urinary tract infection	14 (3.7)	9 (3)	0.6 (-1.3, 2.6)
Nitrite urine present	1 (0.2)	0 (0)	0.2 (0.1, 0.4)
Streptococcal urinary tract infection	1 (0.3)	0 (0)	0.3 (0.2, 0.4)
Cystitis	2 (0.6)	1 (0.3)	0.3 (-0.6, 1.3)
Thirst	12 (3.2)	5 (1.6)	1.5 (-0.2, 3.2)
Thirst	4 (1)	0 (0)	1 (0.7, 1.3)
Polydipsia	8 (2.2)	5 (1.6)	0.5 (-1.1, 2.2)
Hypoglycemia	7 (2)	3 (1.2)	0.9 (0, 1.8)
Hypoglycemia	7 (2)	3 (1.2)	0.9 (0, 1.8)
Genital mycotic infection Male ²	5 (2.2)	2 (1.4)	0.8 (-0.3, 1.9)
Balanoposthitis ²	3 (1.4)	0 (0)	1.3 (1, 1.7)
Genital infection fungal ²	1 (0.4)	1 (0.6)	-0.2 (-1.2, 0.8)
Tinea cruris ²	1 (0.4)	1 (0.8)	-0.3 (-0.7, 0)

Source: adae.xpt; Software: R; Generated by CDS, GQs developed by Clinical Reviewer

Percentages based on study-size adjusted proportions

¹The denominator for this data are the number of females in the study arm (bexagliflozin N=156, placebo N=130)

²The denominator for this data are the number of males in the study arm (bexagliflozin N=216, placebo N=170)

Abbreviations: AE, adverse event; Bexa, bexagliflozin; GQ, group query; RD, risk difference; UTI, urinary tract infection.

FMQs were used to investigate potential safety signals in the placebo-controlled pool ([Table 33](#)). Similar to the GQ analysis presented above, FMQs for fungal infection, renal and urinary tract infection, and hypoglycemia demonstrated RDs $>0.5\%$. The FMQ for “Pruritus” contained both events of genital pruritus identified in the above noted grouped queries, as well as additional nonspecific/generalized pruritus events. FMQs for hepatic injury, study abuse potential, and palpitations also demonstrated a risk difference of 0.5; however, the low number of events limits

interpretability. Events of rash and hepatic injury are further discussed in Sections [17.3.4](#) and [17.3.5](#), respectively.

There was a higher incidence in the FMQ for “Tendinopathy” with exposure to drug (1.3% versus 0% of subjects in the bexagliflozin and placebo groups, respectively). PTs included tenosynovitis and trigger finger, and a review of the verbatim terms for the tenosynovitis events indicated events generally involved fingers. Imbalances unfavorable to drug in tenosynovitis events were also observed in FMQ analyses completed with C-448 (3 (1.9%) and 1 (0.6%) subject in the bexagliflozin and placebo groups, respectively), and C-476 (35 (3.1%) and 13 (2.3%) subjects in the bexagliflozin and placebo groups, respectively; [Table 34](#)). These events were generally not serious, nor did they lead to treatment discontinuation. In C-476, the majority of events identified by the FMQ in both treatment groups were events of rotator cuff syndrome (1.0% versus 0.9%, bexagliflozin versus placebo), tendonitis (0.8% v 0.5%, bexagliflozin versus placebo), and trigger finger (0.6% versus 0.2%, bexagliflozin versus placebo) ([Table 34](#)). Events of tendon rupture were balanced between treatment groups (0.2% in each treatment group).

The clinical meaningfulness of the imbalance in events captured by the tendinopathy FMQ is unclear. Drug-induced tendinitis and tendon rupture is associated with quinolones, statins, aromatase inhibitors, and glucocorticoids, but has not been previously characterized with SGLT2 inhibitors (Kirchgesner et al. 2014; Knobloch 2016; Bolon 2017). Drug-induced tendinitis typically affects lower limb tendons, most commonly the Achilles tendon. The pathophysiology of drug-induced tendinopathy is incompletely understood but proposed mechanisms include apoptosis and structural disintegration of tenoblasts and tenocytes in the absence of inflammation. Time to onset varies from days to years and any tendon can be affected. The anatomical location of tendinopathy events in the clinical program is unclear as this information was not systematically collected; however, where information exists, the events appear to occur in the upper extremities (i.e., rotator cuff, trigger finger, etc.). Overall, the clinical meaningfulness of this imbalance is unclear and events were not generally serious or severe. Based on these considerations, specific product labeling is not warranted.

Table 33. Subjects With AEs by FMQ With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Placebo-Controlled Pool

FMQ	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Pruritus	7 (1.9)	0 (0)	1.9 (1.0, 2.9)
Fungal Infection	12 (3.1)	3 (1.2)	1.8 (0.5, 3.2)
Tendinopathy	5 (1.3)	0 (0)	1.3 (0.5, 2.1)
Rash	5 (1.3)	0 (0)	1.2 (0.9, 1.5)
Hypoglycemia	7 (2)	3 (1.2)	0.9 (0, 1.8)
Renal and urinary tract infection	16 (4.3)	10 (3.3)	0.9 (-1.2, 3.1)
Study agent abuse potential	2 (0.6)	0 (0)	0.6 (0, 1.2)
Hepatic injury	2 (0.5)	0 (0)	0.5 (0.3, 0.7)
Palpitations	2 (0.5)	0 (0)	0.5 (0.3, 0.7)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference.

Table 34. Subjects With Tendinopathy (FMQ) Events as Sorted by RD, Safety Population, Trial C-476

FMQ/PT	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Tendinopathy (FMQ)	35 (3.1)	13 (2.3)	0.8 (-0.8, 2.4)
Trigger finger	7 (0.6)	1 (0.2)	0.4 (-0.1, 1.0)
Tendonitis	9 (0.8)	3 (0.5)	0.3 (-0.5, 1.1)
Dupuytren's contracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Rotator cuff repair	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Enthesophyte	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Rotator cuff syndrome	11 (1.0)	5 (0.9)	0.1 (-0.9, 1.0)
Tendon pain	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Tenosynovitis	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Tenosynovitis stenosaurs	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Tendon injury	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Tendon rupture	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference.

To further investigate for important imbalances in AEs, additional analyses were completed with C-476. [Table 35](#) shows the results from an FMQ analysis of FMQs with RD ≥ 0.5 and [Table 36](#) shows AEs by PT with an RD ≥ 0.5 . The results were generally in accordance with the analysis of the placebo-controlled pool utilizing GQs. PTs for hypotension, dizziness and AKI were captured in these analyses, potentially due to the older enrolled population with prior history of cardiovascular disease and heart failure who are more volume sensitive to the diuretic effects of bexagliflozin. There were significantly more events of balanoposthitis in the bexagliflozin group; an imbalance that is more pronounced when the analysis is restricted to males (2.9% versus 0% of male subjects in the bexagliflozin and placebo groups, respectively). Imbalances unfavorable to drug for the FMQ's hemorrhage and thrombocytopenia were observed, which could potentially signal increased bleeds due to decreased platelet count. In addition, there were more subjects with level 3 (<10,000) platelet counts in the bexagliflozin group as compared to the placebo group (2.5% versus 1.3% of subjects in the bexagliflozin and placebo group with at least one level 3 platelet count). However, it is reassuring that there were fewer serious hemorrhage events (as identified by FMQ) in the bexagliflozin group of C-476 (1.2% versus 1.6% of subjects in the bexagliflozin and placebo groups, respectively). In addition, no differences in mean platelet count over time were observed in the placebo-controlled pool (Section [17.4](#), [Figure 76](#)), nor are changes in platelet count labeled for other approved SGLT2 inhibitor products.

Rash, AKI, and hypersensitivity events are further discussed in Section [17.3.4](#).

Table 35. FMQs With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Trial C-476

FMQ	Bexa 20 mg vs. Placebo		
	Bexa 20 mg N=1132	Placebo N=567	Risk Difference (%) (95% CI)
Fungal infection	93 (8.2)	25 (4.4)	3.8 (1.5, 6.1)
Dizziness	83 (7.3)	29 (5.1)	2.2 (-0.1, 4.6)
Rash	61 (5.4)	19 (3.4)	2 (0.1, 4.0)
Hypotension	48 (4.2)	15 (2.6)	1.6 (-0.2, 3.4)
Bacterial infection	258 (22.8)	121 (21.3)	1.5 (-2.7, 5.6)
Arthritis	71 (6.3)	29 (5.1)	1.2 (-1.1, 3.5)
Renal and urinary tract infection	148 (13.1)	68 (12.0)	1.1 (-2.2, 4.4)
Hemorrhage	98 (8.7)	43 (7.6)	1.1 (-1.7, 3.8)
Cough	52 (4.6)	20 (3.5)	1.1 (-0.9, 3.0)
Diarrhea	75 (6.6)	32 (5.6)	1 (-1.4, 3.4)
Myalgia	18 (1.6)	4 (0.7)	0.9 (-0.1, 1.9)
Tendinopathy	35 (3.1)	13 (2.3)	0.8 (-0.8, 2.4)
Thrombocytopenia	15 (1.3)	3 (0.5)	0.8 (-0.1, 1.7)
Acute kidney injury	25 (2.2)	9 (1.6)	0.6 (-0.7, 2.0)
Hypersensitivity	15 (1.3)	4 (0.7)	0.6 (-0.3, 1.6)
Nasopharyngitis	124 (11.0)	59 (10.4)	0.5 (-2.6, 3.7)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference.

Table 36. Subjects With AEs by PT With a RD $\geq 0.5\%$ as Sorted by RD, Safety Population, Trial C-476

Preferred Term	Bexa 20 mg vs. Placebo		
	Bexa 20 mg N=1132	Placebo N=567	Risk Difference (%) (95% CI)
Balanoposthitis	23 (2.0)	0 (0.0)	2 (1.2, 2.9)
Genital infection fungal	30 (2.7)	5 (0.9)	1.8 (0.6, 3.0)
Hypotension	38 (3.4)	9 (1.6)	1.8 (0.3, 3.2)
Polyuria	63 (5.6)	22 (3.9)	1.7 (-0.4, 3.8)
Dizziness	55 (4.9)	18 (3.2)	1.7 (-0.2, 3.6)
Nasopharyngitis	96 (8.5)	39 (6.9)	1.6 (-1.0, 4.2)
Cough	50 (4.4)	17 (3.0)	1.4 (-0.4, 3.3)
Cataract	39 (3.4)	12 (2.1)	1.3 (-0.3, 2.9)
Musculoskeletal pain	37 (3.3)	12 (2.1)	1.2 (-0.4, 2.7)
Diarrhea	74 (6.5)	31 (5.5)	1.1 (-1.3, 3.4)
Pollakiuria	23 (2.0)	5 (0.9)	1.1 (0.0, 2.3)
Chest pain	38 (3.4)	13 (2.3)	1.1 (-0.6, 2.7)
Peripheral arterial occlusive disease	22 (1.9)	5 (0.9)	1.1 (-0.1, 2.2)
Benign prostatic hyperplasia	23 (2.0)	5 (0.9)	1.1 (0.0, 2.3)
Cardiac failure	27 (2.4)	8 (1.4)	1 (-0.3, 2.3)
Urinary tract infection	134 (11.8)	62 (10.9)	0.9 (-2.3, 4.1)
Osteoarthritis	34 (3.0)	12 (2.1)	0.9 (-0.7, 2.4)
Skin ulcer	32 (2.8)	11 (1.9)	0.9 (-0.6, 2.4)
Leukocytosis	10 (0.9)	0 (0.0)	0.9 (0.3, 1.4)
Vulvovaginal mycotic infection	27 (2.4)	9 (1.6)	0.8 (-0.6, 2.2)
Sepsis	11 (1.0)	1 (0.2)	0.8 (0.1, 1.5)
Vulvovaginal candidiasis	9 (0.8)	0 (0.0)	0.8 (0.3, 1.3)
Hematuria	25 (2.2)	8 (1.4)	0.8 (-0.5, 2.1)
Dysuria	21 (1.9)	6 (1.1)	0.8 (-0.4, 1.9)
Localized infection	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Pharyngotonsillitis	8 (0.7)	0 (0.0)	0.7 (0.2, 1.2)

Preferred Term	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo
			Risk Difference (%) (95% CI)
Arthritis	14 (1.2)	3 (0.5)	0.7 (-0.2, 1.6)
Cardiac arrest	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Leukocyturia	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Diabetic foot	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Vulvovaginal pruritus	8 (0.7)	0 (0.0)	0.7 (0.2, 1.2)
Thrombocytopenia	12 (1.1)	2 (0.4)	0.7 (-0.1, 1.5)
Oral candidiasis	7 (0.6)	0 (0.0)	0.6 (0.2, 1.1)
Muscle spasms	23 (2.0)	8 (1.4)	0.6 (-0.7, 1.9)
Myalgia	13 (1.1)	3 (0.5)	0.6 (-0.2, 1.5)
Myocardial ischemia	9 (0.8)	1 (0.2)	0.6 (-0.0, 1.2)
Renal cyst	13 (1.1)	3 (0.5)	0.6 (-0.2, 1.5)
Amnesia	7 (0.6)	0 (0.0)	0.6 (0.2, 1.1)
Contusion	23 (2.0)	8 (1.4)	0.6 (-0.7, 1.9)
Dermatitis contact	7 (0.6)	0 (0.0)	0.6 (0.2, 1.1)
Polycythemia	7 (0.6)	0 (0.0)	0.6 (0.2, 1.1)
Cataract operation	11 (1.0)	2 (0.4)	0.6 (-0.1, 1.4)
Upper respiratory tract infection	112 (9.9)	53 (9.3)	0.5 (-2.4, 3.5)
Osteomyelitis	12 (1.1)	3 (0.5)	0.5 (-0.3, 1.4)
Respiratory tract infection viral	12 (1.1)	3 (0.5)	0.5 (-0.3, 1.4)
Dysphagia	6 (0.5)	0 (0.0)	0.5 (0.1, 1.0)
Angina pectoris	42 (3.7)	18 (3.2)	0.5 (-1.3, 2.4)
Coronary artery disease	28 (2.5)	11 (1.9)	0.5 (-0.9, 2.0)
Acute kidney injury	24 (2.1)	9 (1.6)	0.5 (-0.8, 1.9)
Presyncope	6 (0.5)	0 (0.0)	0.5 (0.1, 1.0)
Chronic obstructive pulmonary disease	24 (2.1)	9 (1.6)	0.5 (-0.8, 1.9)
Rhinorrhea	8 (0.7)	1 (0.2)	0.5 (-0.1, 1.1)
Thirst	12 (1.1)	3 (0.5)	0.5 (-0.3, 1.4)
Wound	16 (1.4)	5 (0.9)	0.5 (-0.5, 1.6)
Dry skin	6 (0.5)	0 (0.0)	0.5 (0.1, 1.0)
Psoriasis	6 (0.5)	0 (0.0)	0.5 (0.1, 1.0)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; PT, preferred term; RD, risk difference.

Lastly, an analysis utilizing Applicant-derived custom MedDRA query (CMQs) for the evaluation of AESIs was performed for C-476 ([Table 37](#)). The results were generally in accordance with results from FMQ analyses, with imbalances unfavorable to drug in GMI, UTI, and diuretic effects. AESIs are discussed in detail in [Section 17.3](#).

FMQ and CMQ analyses differed with regards to their narrowness/broadness, with CMQs being generally more tailored for the detection of class effects. For example, the FMQ for “Fungal Infection” is not specific to genital infections. In addition, the “Fungal Infection” FMQ does not contain all PTs that are typically assessed in SGLT2 inhibitor programs (e.g., PTs for phimosis and balanoposthitis events are not included in the query). To provide another example, the “Volume Depletion” FMQ does not include events that have previously been utilized to identify potential volume depletion events such as events of dizziness and hypotension, which have dedicated FMQs. Therefore, the Applicant’s CMQs are informative as they are more tailored to SGLT2 inhibitor programs. CMQs were reviewed and they appeared appropriate to identify events for each AESI category. Labeling of results from Applicant-derived CMQs appears appropriate when informative.

Table 37. AESIs by Applicant-Derived CMQs, Safety Population, Trial C-476

Applicant AESI CMQ*	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg vs. Placebo
			Risk Difference (%) (95% CI)
Any AESI	690 (61.0)	325 (57.3)	3.6 (-1.3, 8.6)
Genital mycotic infection	102 (9.0)	16 (2.8)	6.2 (4.0, 8.3)
Diuretic effects	100 (8.8)	36 (6.3)	2.5 (-0.1, 5.1)
UTI	164 (14.5)	71 (12.5)	2.0 (-1.4, 5.4)
Hypotension episode	61 (5.4)	27 (4.8)	0.6 (-1.6, 2.8)
Malignancies	42 (3.7)	18 (3.2)	0.5 (-1.3, 2.4)
Renal failure	32 (2.8)	15 (2.6)	0.2 (-1.5, 1.8)
Hypersensitivity reactions	6 (0.5)	3 (0.5)	0.0 (-0.7, 0.7)
Fracture	41 (3.6)	21 (3.7)	-0.1 (-2.0, 1.8)
Pyelonephritis urosepsis	11 (1.0)	6 (1.1)	-0.1 (-1.1, 0.9)
Acidosis	5 (0.4)	4 (0.7)	-0.3 (-1.1, 0.5)
Hepatotoxicity	0 (0)	2 (0.4)	-0.4 (-0.8, 0.1)
Rash	39 (3.4)	26 (4.6)	-1.1 (-3.2, 0.9)
Hypoglycemia	476 (42.0)	248 (43.7)	-1.7 (-6.7, 3.3)

Source: adae.xpt; Software: R; Generated by CDS

*Applicant CMQ utilizing CQ01NAM variable.

Abbreviations: AESI, adverse event of special interest; CMQ, customized Medical Dictionary for Regulatory Activities query; Bexa, bexagliflozin; UTI, urinary tract infection.

7.6.1.6. Laboratory Findings

The following changes in laboratory parameters are proposed for labeling: increases in serum creatinine and decreases in eGFR, increases in hemoglobin/hematocrit, and increase in low-density lipoprotein cholesterol (LDL-C). See Section [17.4](#) for a detailed review of laboratory findings.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Increased Risk of Nontraumatic Amputation With Bexagliflozin Treatment

Issue

An increased incidence of nontraumatic amputation was identified in the bexagliflozin group compared to the placebo group in C-476.

Background

Lower limb amputation is a recognized complication of diabetes mellitus. An excess risk of lower limb amputation beyond background risk has been previously identified with canagliflozin and ertugliflozin, but not dapagliflozin and empagliflozin (Janssen 2020; AstraZeneca 2021; Merck 2021; Ingelheim 2022). The risk of amputation with SGLT2 inhibitor treatment has been assessed in the postmarketing CVOTs for SGLT2 inhibitors, enrolling patients with T2DM and increased CV risk, which were conducted to rule out 30% excess CV risk per the 2008 diabetes CV safety guidance (now withdrawn) (December 2008). In the CANVAS Program, which was

comprised of two nearly identically designed trials (CANVAS and CANVAS-R), an increased risk of lower limb amputations associated with canagliflozin use versus placebo was observed in CANVAS (5.9 versus 2.8 events per 1,000 patient-years) and CANVAS-R (7.5 versus 4.2 events per 1,000 patient-years) (Janssen 2020). Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving canagliflozin in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving canagliflozin in the two trials). Some patients had multiple amputations, some involving both lower limbs. Lower limb infections, gangrene, and diabetic foot ulcers 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. Increased risk of amputation was also observed in a CVOT conducted with ertugliflozin (VERTIS CV), where the occurrence of nontraumatic lower limb amputation was 4.7, 5.7, and 6.0 events per 1,000 patient-years in the placebo, ertugliflozin 5 mg, and ertugliflozin 15 mg treatment arms, respectively (Merck 2021). Similar to the CANVAS Program, amputations of the toe and midfoot were most frequent (81 out of 109 patients) with the most common precipitating events being infection, gangrene, and diabetic foot ulcers.

An underlying mechanism for an increased risk of lower limb amputation has not been clearly identified. It has been hypothesized that volume depletion with SGLT2 inhibitors may lead to hypoperfusion of extremities in patients at risk for an amputation event, which can slow wound healing, make any existing infection become irreparable, and cause tissue damage or necrosis. However, it is unclear how this hypothesis can support a different degree of risk of amputation among SGLT2 inhibitors because volume depletion events can occur with all SGLT2 inhibitors. Overall, given conflicting data from several large, postmarketing clinical programs, it is unclear at this time whether SGLT2 inhibitor treatment increases amputation risk.

Assessment

All nontraumatic amputations that occurred in the bexagliflozin clinical development program were observed in C-476 (one traumatic amputation event occurred in C-448). The potential association with SGLT2 inhibitor treatment and amputation risk became known while the clinical development program, including C-476, was ongoing. Amputation and revascularization procedures were included as AESIs via protocol amendment (protocol Version 8, dated October 28, 2016). In addition, a dedicated case report form (CRF) was introduced in protocol Version 8 to capture additional information regarding amputation and revascularization events including the anatomical location of amputation and the condition leading to the amputation. Eighty-two percent of total study follow-up time occurred under a consent or re-consent to protocol Version 8.

Despite inclusion of a dedicated CRF and specification of amputation as an AESI in protocol Version 8, the Applicant states that failures to record procedures occurred that were not detected until after database lock (integrated summary of safety [ISS], page 165). While the reason for underreporting of these procedures is unclear, the Applicant notes that investigators may have considered amputation events planned treatments/responses to medical conditions as opposed to AEs. To address this, the Applicant performed a review of CRF and SAE narratives for unreported procedures. The information submitted by the Applicant in the ADaM adverse events

analysis (ADAE) and ADaM procedures analysis (ADPR) datasets incorporates their thorough review of the available safety data.

Given that underreporting of amputation events was a concern in this program, exploratory analyses were conducted to identify potentially missed amputation events. A list³ of amputation-related PTs and PTs for events that may precede an amputation event was generated. A search of the terms was conducted in the ADAE and ADPR datasets to identify potential missed amputations. A review of the findings of this search indicated that all additional events identified through this process were not amputation events. Therefore, the Applicant's search of procedures and AEs appears to have adequately captured amputation events in C-476.

Time-to-event data were derived for time-to-first nontraumatic amputation based on the procedure and AE datasets. Post hoc analyses were conducted using the derived data. The results of an on-study analysis are presented in [Table 38](#), while the results of an on-treatment +14-day analysis are presented in [Table 39](#). Both analyses used a Cox proportional hazards model with treatment as the only fixed effect. Estimated 95% confidence intervals for the hazard ratios for both analyses include the null value 1. However, the time-to-event analyses showed a numerical increase in the incidence of amputations associated with bexagliflozin and the point estimates of the hazard ratios (HRs) are both greater than 1.6 (on-study: 1.64; on-treatment: 1.71).

Table 38. On-Study Analysis Results of Nontraumatic Amputations, Safety Population, Trial C-476

Variable	Bexagliflozin N=1132 PY =2772	Placebo N=567 PY =1381
Subjects with an amputation, n (%)	23 (2.0%)	7 (1.2%)
Total amputations	25	13
Incidence rate (per 1000 PYs) *	8.3	5.1
Hazard ratio (95% CI)	1.64 (0.70, 3.82)	

Source: Generated by the statistical reviewer.

*Incidence rate is based on the number of subjects with at least one amputation, and not the total number of amputation events. A subject's follow-up is calculated from Day 1 to the first amputation event date. Some subjects had more than one amputation
Abbreviations: PY, person years.

³ PTs included in search for amputation events included: Amputation, Amputation stump pain, Arm amputation, Arteriosclerotic gangrene, Bone debridement, Calcanectomy, Candida osteomyelitis, Chronic recurrent multifocal osteomyelitis, Debridement, Diabetic foot infection, Diabetic gangrene, Diabetic microangiopathy, Diabetic neuropathic ulcer, Diabetic neuropathy, Diabetic ulcer, Diabetic vascular disorder, Dry gangrene, Epidermal necrosis, Extremity necrosis, Finger amputation, Foot amputation, Foot operation, Fracture debridement, Gangrene, Gas gangrene, Hand amputation, Joint debridement, Leg amputation Limb amputation, Limb operation, Limb reconstructive surgery, Limb traumatic amputation, Metacarpal excision, Metatarsal excision, Nail necrosis, Necrosis, Necrosis ischemic, Necrosis of artery, Necrotising fasciitis, Necrotising fasciitis fungal, Necrotising fasciitis staphylococcal, Necrotising fasciitis streptococcal, Necrotising soft tissue infection, Osteomyelitis, Osteomyelitis acute, Osteomyelitis bacterial, Osteomyelitis Blastomyces, Osteomyelitis chronic, Osteomyelitis drainage, Osteomyelitis fungal, Osteomyelitis salmonella, Osteomyelitis viral, Osteonecrosis, Peripheral embolism, Peripheral revascularization, Peripheral vascular disorder, Phantom limb syndrome, Postoperative wound complication, Postoperative wound infection, Soft tissue necrosis, Spontaneous amputation, Staphylococcal osteomyelitis, Toe amputation, Toe operation, Wound dehiscence, Wound necrosis

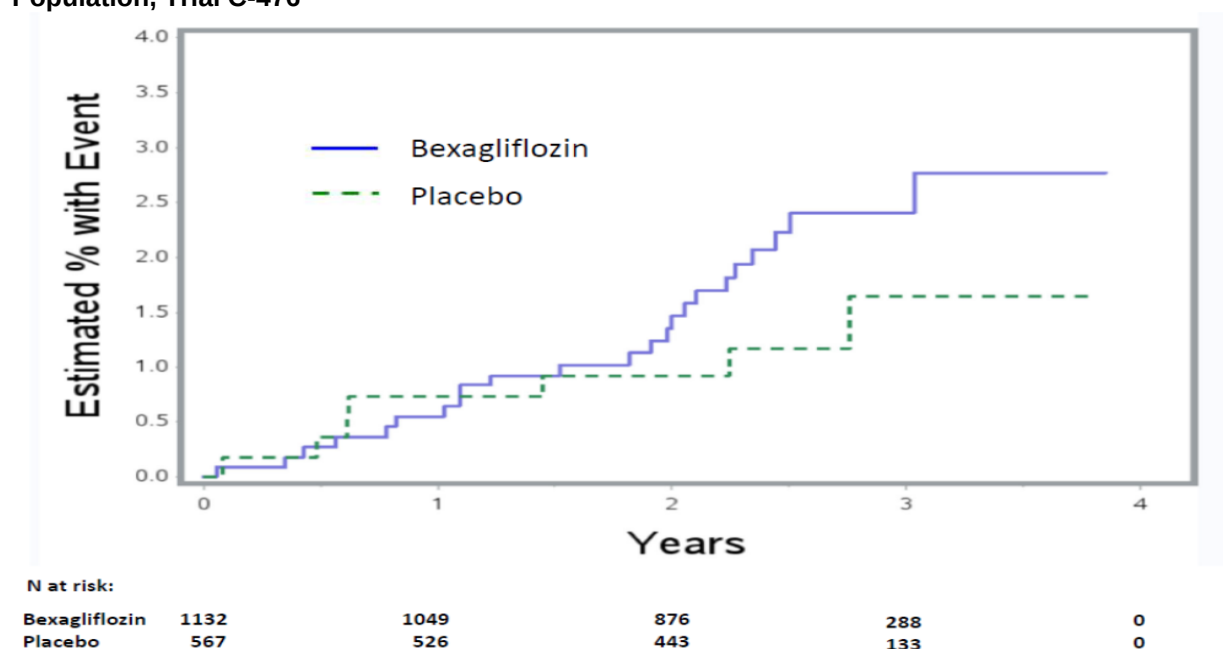
Table 39. On-Treatment +14 Days Analysis Results of Nontraumatic Amputations, Safety Population, Trial C-476

Variable	Bexagliflozin N=1132	Placebo N=567
Subjects with an amputation, n (%)	21 (1.9%)	6 (1.1%)
Hazard ratio (95% CI)	1.71 (0.69, 4.24)	

Source: Generated by the statistical reviewer.

[Figure 15](#) below shows the Kaplan-Meier cumulative probability of experiencing a nontraumatic amputation during on-study follow-up for the two comparison arms in C-476. The Kaplan-Meier curves for the two groups exhibit divergence from about 1.5 years after randomization, while the events steadily accumulated in the bexagliflozin arm until 2.5 years and only two events were observed in the placebo arm through the remainder of the study.

Figure 15. On Study Kaplan-Meier Analysis of Time-to-First Nontraumatic Amputation, Safety Population, Trial C-476



Source: Generated by the statistical reviewer.

As shown in [Table 40](#) below, the risk of amputation was higher in patients with a baseline history of prior amputation, PAD, and neuropathy, compared to patients without such disease history. These risk factors were identified independently of randomized treatment.

Table 40. Incidence of Nontraumatic Amputations in Subjects With Baseline Disease History, Safety Population, Trial C-476

Baseline Disease History	Subjects With Nontraumatic Amputations n (%)
Prior amputation	
Yes (N=26)	5 (19.2%)
No (N=1673)	25 (1.5%)
Peripheral arterial disease	
Yes (N=130)	9 (6.9%)
No (N=1569)	21 (1.3%)
Neuropathy	
Yes (N=515)	19 (3.7%)
No (N=1184)	11 (0.9%)

Source: Generated by the statistical reviewer.

[Table 41](#) provides information on the anatomical location of the amputation events and underlying causes of the event. The majority of amputations in both groups were below-the-knee (BTK), mostly involving toes, but above-the-knee (AKAs) were also observed in both treatment groups. Some subjects also experienced multiple amputation events. The underlying causes leading to the amputation event(s) were multifactorial, but mostly involved infection, gangrene, PAD, and osteomyelitis.

Table 41. Anatomical Location of Amputation Events and Underlying Causes, Safety Population, Trial C-476

Events	Bexagliflozin N=1132	Placebo N=567
All nontraumatic amputations	23 (2.03)	7 (1.23)
Condition(s) leading to amputation [∞]		
Gangrene [%]	13 (1.1)	5 (0.9)
PAD	11 (1.0)	4 (0.7)
Osteomyelitis ^β	6 (0.5)	3 (0.5)
Infection, necrosis, foot ulcer	6 (0.5)	2 (0.3)
Charcot foot	1 (0.1)	0 (0)
Location of amputation*		
Above the knee	1 (0.09)	1 (0.18)
Below the knee	6 (0.53)	1 (0.18)
Foot/ankle	1 (0.09)	0 (0.00)
Metatarsal	4 (0.35)	1 (0.18)
Toe(s)	11 (0.97)	4 (0.71)

Source: Adapted from ISS and Table 77

*Some subjects had multiple amputation events. This Table presents the most serious event reported (e.g., if a subject had a toe(s) amputated and then subsequent amputation to the ankle, only the event involving the ankle is indicated in this table).

[∞]Subjects often had multiple conditions that could have contributed to the amputation event. This Table presents information on various events that could have contributed to the event (e.g., if a subject had an osteomyelitis and gangrene event, they are counted twice in this section of the Table).

[%]Includes events of gangrene, wet gangrene, dry gangrene, and gas gangrene

Abbreviations: PAD, peripheral artery disease.

As noted above, the dedicated CRF was also designed to capture information on revascularization procedures. There was a minor imbalance unfavorable to bexagliflozin in the number of revascularization procedures for PAD (2.5% and 2.1% of subjects having a procedure in the bexagliflozin and placebo groups, respectively). Other revascularization procedures (e.g., coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], etc.) are discussed in additional detail in Section [17.3.14](#).

Conclusion

As detailed above, data from C-476 indicated an increased risk of amputation with bexagliflozin treatment as compared to placebo (HR: 1.64 (0.70, 3.82)). Although the findings above on amputations do not necessarily raise new concerns about the risk of amputation due to treatment with SGLT2 inhibitors, the concern about the potential for excess risk of amputations on the bexagliflozin arm has not been alleviated, especially given the existing concern about increased risk of amputations for this class of drug. Labeling should state that before initiating treatment with bexagliflozin, providers should consider factors that may increase the risk of amputation, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. In addition, labeling will advise providers to monitor patients receiving bexagliflozin for infection, new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue treatment if these complications occur. Labeling is appropriate to inform providers about increased risk of amputation associated with bexagliflozin treatment.

Dissent

Not applicable.

7.7.2. Safety of Bexagliflozin in Subjects With Moderate Renal Impairment

Issue

The safety of bexagliflozin in patients with stage 3 CKD.

Background

The efficacy of bexagliflozin in subjects with moderate renal impairment was a key efficacy review issue. As detailed in Section [6.3.1](#), the efficacy of bexagliflozin in subjects with stage 3 CKD is considered acceptable for approval in the population in the absence of safety findings that could impact the overall benefit-risk assessment in this population.

Assessment

Approach to Review

This key risk review issue was assessed using safety data from the dedicated renal impairment trial (C-448) in addition to supportive information from the subpopulation of subjects with renal impairment in C-476. The subpopulation assessed from C-476 was based on baseline eGFR values (i.e., having a baseline eGFR <60 mL/min/1.73 m²). Protocol synopses for these trials are provided in Section [15](#) and key trial design features, including inclusion/exclusion criteria, are presented in Section [6.2](#). In C-476, treatment was stratified by eGFR category (eGFR <60 or ≥60 mL/min/1.73 m²), and approximately 20% of subjects in each treatment arm had eGFR <60 mL/min/1.73 m². Baseline demographics for C-448 and C-476 are presented in [Table 11](#).

Overview of AEs

The frequency of AEs between treatment arms in C-448 were generally balanced, with 69.4% and 67.7% of subjects experiencing at least one AE in the bexagliflozin and placebo groups, respectively (Table 42). Events by severity were also generally balanced between treatment arms. There were few events of AEs leading to permanent discontinuation or dose interruption of the study drug, limiting interpretability of the data. No deaths occurred in this trial.

Table 42. Overview of AEs, Safety Population, Trial C-448

Event Category	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
SAE	11 (7.0)	9 (5.8)	1.2 (-4.2, 6.6)
AE leading to permanent discontinuation of study drug	4 (2.5)	8 (5.2)	-2.6 (-6.9, 1.7)
AE leading to dose interruption of study drug	9 (5.7)	5 (3.2)	2.5 (-2.1, 7.1)
AE	109 (69.4)	105 (67.7)	1.7 (-8.6, 12.0)
Death	0 (0)	0 (0)	0 (0, 0)
Severe	12 (7.6)	8 (5.2)	2.5 (-2.9, 7.9)
Moderate	31 (19.7)	31 (20.0)	-0.3 (-9.1, 8.6)
Mild	66 (42.0)	66 (42.6)	-0.5 (-11.5, 10.4)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; SAE, severe adverse event.

In C-476, the majority of subjects (92 to 94%) in both treatment groups had at least one AE in the subset of subjects with baseline eGFR <60 mL/min/1.73 m² (Table 43). There was a lower incidence of SAEs and deaths in subjects with baseline eGFR <60 mL/min/1.73 m² in the bexagliflozin group compared to the placebo group (Table 43). AEs by investigator-assigned severity were also generally balanced between treatment groups as well as AEs leading to dose interruption or treatment discontinuation (Table 43).

Table 43. Overview of AEs in Subjects With Baseline eGFR <60 mL/min/1.73 m², Safety Population, Trial C-476

Event Category	Bexa 20 mg N=225 n (%)	Placebo N=109 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
SAE	78 (34.7)	46 (42.2)	-7.5 (-18.7, 3.6)
AE leading to permanent discontinuation of study drug	26 (11.6)	12 (11.0)	0.5 (-6.7, 7.8)
AE leading to dose interruption of study drug	35 (15.6)	16 (14.7)	0.9 (-7.3, 9.0)
Any AE	206 (91.6)	102 (93.6)	-2.0 (-7.9, 3.8)
Death	10 (4.4)	7 (6.4)	-2.0 (-7.3, 3.4)
Severe	57 (25.3)	34 (31.2)	-5.9 (-16.2, 4.5)
Moderate	97 (43.1)	48 (44.0)	-0.9 (-12.3, 10.4)
Mild	52 (23.1)	20 (18.3)	4.8 (-4.4, 13.9)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; SAE, severe adverse event

SAEs and Discontinuations

Few patients experienced SAEs in C-448: 11 (7.0%) subjects in the bexagliflozin group and 9 (5.8%) subjects in the placebo group (Table 44). No serious AKI, DKA, volume depletion, or hypotension events occurred in this trial in the bexagliflozin group (one event of orthostatic hypotension occurred in the placebo group). One insulin-treated subject in the bexagliflozin

group experienced two events of severe hypoglycemia. A Warnings and Precautions statement is proposed for the labeling regarding the risk of hypoglycemia when bexagliflozin is used in combination with insulin or an insulin secretagogue.

Table 44. Subjects With SAEs by PT Sorted by RD, Safety Population, Trial C-448

Preferred Term	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Total SAEs	11 (7.0)	9 (5.8)	1.2 (-4.2, 6.6)
Carotid artery disease	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Cerebral infarction	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Sudden hearing loss	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Hypoglycemia	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Arthralgia	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Lumbar spinal stenosis	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Bundle branch block left	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Myocardial ischemia	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Gastritis erosive	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Esophagitis	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Dyspnea exertional	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Sepsis	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Adenocarcinoma of colon	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Cardiogenic shock	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Coronary artery disease	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Neuropathic arthropathy	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Intestinal ischemia	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Pancreatitis acute	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Respiratory distress	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Cholecystitis acute	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Orthostatic hypotension	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Gastroenteritis	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Lower respiratory tract infection	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Colon cancer	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Gastric cancer	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Rectal adenocarcinoma	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; PT, preferred term, SAE, serious adverse event; RD, risk difference.

There were fewer AEs leading to treatment discontinuation in C-448 in the bexagliflozin group as compared to the placebo group (4 (2.5%) versus 8 (5.2%) subjects, respectively) ([Table 45](#)). There were three subjects who discontinued bexagliflozin treatment due to AKI (one of those subjects also had PTs of fatigue, gait disturbance, and vertigo positional reported as AEs leading to treatment discontinuation) as compared to one subject in the placebo group. All AKI events were classified as stage 1 AKI (defined by the Applicant as serum creatinine 1.5 to 1.9 × or increase ≥0.3 mg/dL from baseline).

Table 45. Subjects With AEs Leading to Treatment Discontinuation by PT Sorted by RD, Safety Population, Trial C-448

Preferred Term	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
AEs leading to treatment discontinuation	4 (2.5)	8 (5.2)	-2.6 (-6.9, 1.7)
Acute kidney injury	3 (1.9)	1 (0.6)	1.3 (-1.2, 3.8)
Vertigo positional	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Fatigue	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Gait disturbance	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Adenocarcinoma of colon	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Malaise	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Lower respiratory tract infection	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Arthralgia	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Respiratory distress	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Gastric cancer	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Rectal adenocarcinoma	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Coronary artery disease	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)
Palpitations	0 (0)	1 (0.6)	-0.6 (-1.9, 0.6)

Source: adae.xpt; Software: R

Abbreviations: AE, adverse event; Bexa, bexagliflozin; PT, preferred term, RD, risk difference

In C-476, 34.7% and 42.2% of subjects with baseline eGFR <60 mL/min/1.73 m² in the bexagliflozin and placebo groups, respectively, had SAEs. An FMQ analysis of SAEs did not show meaningful imbalances, aside from an excess of serious fracture events, in the bexagliflozin group of C-476 (Table 46; discussed further in Section 17.3.1). Of the 15 subjects in the bexagliflozin group with at least one serious fracture event, 5 (33.3%) had baseline eGFR <60 mL/min/1.73 m². There were also no important findings upon evaluations of AEs leading to treatment discontinuation between treatment groups, although data were limited (Table 47).

Table 46. SAEs in Subjects With Baseline eGFR <60 mL/min/1.73 m² by FMQ With RD >0, Safety Population, Trial C-476

FMQ	Bexa 20 mg N=225 n (%)	Placebo N=109 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Fracture	5 (2.2)	0 (0)	2.2 (0.3, 4.1)
Cholecystitis	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Anemia	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Arthralgia	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Confusional state	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Diarrhea	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Dizziness	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Fatigue	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Headache	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Osteoporosis	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Self harm	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Syncope	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Systemic hypertension	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Thrombocytopenia	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Thrombosis venous	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Urinary retention	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Vertigo	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)

	Bexa 20 mg	Placebo	Bexa 20 mg vs. Placebo
	N=225	N=109	Risk Difference
FMQ	n (%)	n (%)	(%) (95% CI)
Hypoglycemia	5 (2.2)	2 (1.8)	0.4 (-2.8, 3.6)
Respiratory failure	5 (2.2)	2 (1.8)	0.4 (-2.8, 3.6)
Stroke TIA	7 (3.1)	3 (2.8)	0.4 (-3.5, 4.2)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference; SAE, severe adverse event; TIA, transient ischemic attack.

Table 47. AEs Leading to Treatment Discontinuation in Subjects With Baseline eGFR <60 mL/min/1.73 m² by PT as Sorted by RD, Safety Population, Trial C-476

	Bexa 20 mg	Placebo	Bexa 20 mg vs. Placebo
	N=225	N=109	Risk Difference
Preferred Term	n (%)	n (%)	(%) (95% CI)
Any AE leading to discontinuation	26 (11.6)	12 (11.0)	0.5 (-6.7, 7.8)
Genital infection fungal	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Cardiac arrest	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Chronic kidney disease	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Adenocarcinoma gastric	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Metastatic renal cell carcinoma	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Squamous cell carcinoma of lung	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Muscle spasms	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Pain in extremity	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Cardio-respiratory arrest	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Myocardial infarction	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Polyuria	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Blood loss anemia	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Vision blurred	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Diabetic complication	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Abdominal pain	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Diarrhea	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Enteritis	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Dyskinesia	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Ischemic stroke	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Nasopharyngitis	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Sepsis	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Hepatic enzyme increased*	1 (0.4)	0 (0)	0.4 (-0.4, 1.3)
Urinary tract infection	3 (1.3)	1 (0.9)	0.4 (-1.9, 2.8)
Acute kidney injury	1 (0.4)	1 (0.9)	-0.5 (-2.5, 1.5)
Headache	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Blood pressure increased	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Diverticulitis	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Gangrene	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Acute respiratory failure	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Arteriosclerosis	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Malaise	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Cardiac failure congestive	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Gastroesophageal reflux disease	0 (0)	1 (0.9)	-0.9 (-2.7, 0.9)
Blood creatinine increased	1 (0.4)	2 (1.8)	-1.4 (-4.1, 1.3)
Asthenia	0 (0)	2 (1.8)	-1.8 (-4.4, 0.7)

Source: adae.xpt; Software: R; Generated by CDS

* See Section 17.3.5 Hepatic Injury for additional analyses

Abbreviations: AE, adverse event; Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; PT, preferred term, RD, risk difference.

Commonly Occurring AEs

AEs reported in $\geq 2\%$ of subjects treated with bexagliflozin and greater than placebo in C-448 are shown in [Table 48](#). GQs were utilized to group PTs of similar medical concept. Commonly occurring AEs were generally similar in C-448 as compared to the placebo-controlled pool, with more subjects experiencing events of female GMI, increased urination, UTI, and thirst in the bexagliflozin group compared to the placebo group. Approximately 25% of subjects in this trial experienced at least one hypoglycemia event, which is likely attributable to over 50% of subjects using insulin at baseline in this trial (as compared to no subjects using baseline insulin in the placebo-controlled pool; [Table 11](#)). Other AEs reported in $\geq 2\%$ of subjects treated with bexagliflozin and greater than placebo in C-448 that were not observed in the placebo-controlled pool include AKI, blood creatinine increased, bronchitis, hypertension, hypotension, sinusitis, back pain, fall, and arthralgia. Higher incidence of these events may be, at least in part, due to differing patient populations between C-448 and the placebo-controlled pool (e.g., an older patient population with more comorbidities, more advanced disease, and poorer renal function in C-448 as compared to the placebo-controlled pool).

Table 48. AEs Occurring in $\geq 2\%$ of Subjects Treated With Bexagliflozin and Greater Than Placebo, Safety Population, Trial C-448

Group Query or Preferred Term	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Genital mycotic infection female (GQ) ¹	6 (9.2)	0 (0)	9.2 (2.2, 16.3)
Increased urination (GQ)	14 (8.9)	5 (3.2)	5.7 (0.4, 10.9)
UTI (GQ)	14 (8.9)	5 (3.2)	5.7 (0.4, 10.9)
Volume Depletion (GQ)	14 (8.9)	6 (3.9)	5.0 (-0.3, 10.4)
Thirst (GQ)	9 (5.7)	2 (1.3)	4.4 (0.4, 8.5)
Hypertension	5 (3.2)	0 (0)	3.2 (0.4, 5.9)
Sinusitis	5 (3.2)	0 (0)	3.2 (0.4, 5.9)
Bronchitis	7 (4.5)	2 (1.3)	3.2 (-0.5, 6.9)
Blood creatinine increased	6 (3.8)	3 (1.9)	1.9 (-1.8, 5.6)
Acute kidney injury	8 (5.1)	6 (3.9)	1.2 (-3.4, 5.8)
Back Pain	5 (3.2)	3 (1.9)	1.2 (-2.3, 4.7)
Fall	5 (3.2)	3 (1.9)	1.2 (-2.3, 4.7)
Hypotension	5 (3.2)	3 (1.9)	1.2 (-2.3, 4.7)
Arthralgia	7 (4.5)	6 (3.9)	0.6 (-3.8, 5.0)
Hypoglycemia	39 (24.8)	38 (24.5)	0.3 (-9.2, 9.9)

Source: adae.xpt; Software: R; Compiled by Clinical Reviewer from CDS analyses

¹ The denominator for this data are the number of females in the study arm (Bexa N=65; Placebo N=51)

GMI GQ: Vulvovaginal mycotic infection, Vulvovaginal candidiasis, Vulvitis, Vulvovaginal discomfort

Increased Urination GQ: Polyuria, Pollakiuria, Micturition urgency

UTI GQ: Urinary tract infection, Dysuria, Cystitis, Escherichia urinary tract infection

Thirst GQ: Polydipsia, Thirst

Volume Depletion GQ: Hypotension, Dehydration, Dizziness postural, Dizziness, Presyncope, Orthostatic hypotension, Vertigo, Vertigo positional

Abbreviations: AE, adverse event; Bexa, bexagliflozin; GQ, group query; UTI, urinary tract infection.

Significant AEs

To investigate potential safety signals in C-448, a FMQ analysis was performed, and queries occurring at an RD $> 0\%$ are shown in [Table 49](#). As anticipated, “Renal and Urinary Tract Infection” and “Fungal Infection” queries had a higher incidence with drug than placebo, reflecting higher rates of UTI and GMI with bexagliflozin treatment. A higher incidence of hypertension (as a reported AE) was observed in the bexagliflozin group (3.2%) compared to the

placebo (0%) group. Analysis of mean changes in SBP demonstrated a mean decrease in SBP over time, with a mean decrease of 8 mm Hg versus 4 mm Hg in the bexagliflozin and placebo groups at Week 24, respectively. There were also more events of hypotension in the bexagliflozin group (3.8%) versus the placebo group (3.2%). The meaningfulness of these findings is unclear, although it is noteworthy that events were not serious and did not lead to treatment discontinuation. Moreover, adverse event reporting for hypotension/hypertension is subjective and investigator dependent, limiting interpretation of reported events. In addition, objective systolic and diastolic blood pressure measurements revealed slight decreases in mean values in the placebo-controlled pool (see Section 17.5, Figure 80).

An imbalance unfavorable to drug occurred for “Dizziness” (4.5% versus 1.3%). While the events of dizziness are nonspecific, these events could potentially indicate mild volume depletion events. There was no imbalance in fracture events as identified by FMQ, with three patients experiencing a nonserious fracture event in each treatment group, although the incidence of falls was slightly higher in the bexagliflozin group (3.2%) compared to the placebo group (1.9%).

Regarding AKI events, the protocol-specified definitions specified changes of serum creatinine from baseline levels as opposed to acute serum creatinine changes as recommended in the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (Khwaja 2012). It is possible that AKI events may be overreported in this trial, as decreases in renal function over time are expected in this patient population; however, this would not be expected to bias the data (i.e., potential AKI overreporting should occur equally in both treatment arms). As shown in Table 49, there was no meaningful imbalance in AKI events in C-448.

Approved SGLT2 inhibitors report volume depletion events in subjects with renal impairment in Section 6 of the labeling, with events reported including events dehydration, dizziness postural, presyncope, syncope, hypotension, and orthostatic hypotension. The FMQ analysis completed in this review differs from previous SGLT2 inhibitor reviews. For example, a single event of “dehydration” was captured by the “Volume Depletion” FMQ, and events considered potential volume depletion events in other SGLT2 inhibitor reviews (e.g., hypotension, dizziness, syncope) were not identified by this query. For the purposes of Section 6 of the labeling, the FMQs for “Volume Depletion,” “Syncope,” “Hypotension,” and “Dizziness” are pooled to characterize potential volume depletion events. There were 14 (8.9%) and 6 (3.9%) subjects having at least one event of volume depletion as assessed by the noted queries in the bexagliflozin and placebo groups, respectively.

Table 49. Subjects With AEs by FMQ Safety Population With RD >0% as Sorted by RD, Trial C-448

FMQ	Bexa 20 mg	Placebo	Bexa 20 mg vs.
	N=157	N=155	Placebo
	n (%)	n (%)	Risk Difference
			(%) (95% CI)
Renal and urinary tract infection	12 (7.6)	5 (3.2)	4.4 (-0.6, 9.4)
Dizziness	7 (4.5)	2 (1.3)	3.2 (-0.5, 6.9)
Fungal infection	6 (3.8)	1 (0.6)	3.2 (-0.1, 6.4)
Systemic hypertension	5 (3.2)	0 (0)	3.2 (0.4, 5.9)
Viral infection	7 (4.5)	2 (1.3)	3.2 (-0.5, 6.9)
Arrhythmia	4 (2.5)	1 (0.6)	1.9 (-0.9, 4.7)
Headache	4 (2.5)	1 (0.6)	1.9 (-0.9, 4.7)
Vertigo	3 (1.9)	0 (0)	1.9 (-0.2, 4.1)
Bacterial infection	16 (10.2)	13 (8.4)	1.8 (-4.6, 8.2)
Arthritis	3 (1.9)	1 (0.6)	1.3 (-1.2, 3.8)

	Bexa 20 mg N=157 n (%)	Placebo N=155 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
FMQ			
Insomnia	2 (1.3)	0 (0)	1.3 (-0.5, 3.0)
Stroke (TIA)	2 (1.3)	0 (0)	1.3 (-0.5, 3.0)
Tendinopathy	3 (1.9)	1 (0.6)	1.3 (-1.2, 3.8)
Back Pain	7 (4.5)	5 (3.2)	1.2 (-3.0, 5.5)
Fall	5 (3.2)	3 (1.9)	1.2 (-2.3, 4.7)
Hypoglycemia	40 (25.5)	38 (24.5)	1.0 (-8.6, 10.6)
Acute kidney injury	8 (5.1)	7 (4.5)	0.6 (-4.2, 5.3)
Arthralgia	7 (4.5)	6 (3.9)	0.6 (-3.8, 5.0)
Bacterial vaginosis	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Dry mouth	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Gynecomastia	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Hemorrhage	6 (3.8)	5 (3.2)	0.6 (-3.5, 4.7)
Hypotension	6 (3.8)	5 (3.2)	0.6 (-3.5, 4.7)
Myocardial ischemia	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Respiratory failure	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Sexual dysfunction	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Somnolence	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Study agent abuse potential	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Thrombosis	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Thrombosis arterial	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Tremor	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Volume depletion	1 (0.6)	0 (0)	0.6 (-0.6, 1.9)
Nasopharyngitis	13 (8.3)	12 (7.7)	0.5 (-5.5, 6.6)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference; TIA, transient ischemic attack.

An FMQ analysis of the subpopulation of subjects with baseline eGFR <60 mL/min/1.73 m² in C-476 was performed, and FMQs with a RD ≥0.5 are shown in [Table 50](#). An imbalance in the “Lipid Disorder” FMQ was observed. PTs that occurred in the bexagliflozin group identified by the FMQ included the following: dyslipidemia, hypertriglyceridemia, hyperlipidemia, blood cholesterol increased, low density lipoprotein increased, blood triglyceride increased, and hypercholesterolemia. As discussed in [Section 17.4](#), SGLT2 inhibitor treatment is associated with modest increases in LDL-C which may, at least in part, support the results observed here. Important clinical consequences of elevated lipid parameters include increased risk of MACE. As presented in [Section 17.1](#), the subgroup analysis by renal function group did not show an increased risk for MACE+ events in subjects with baseline eGFR <60 mL/min/1.73 m² (HR: 0.56 (0.29, 1.1)) as compared to subjects with baseline eGFR >60 mL/min/1.73 m² (HR: 0.88 (0.61, 1.26)). Changes in lipid parameters from laboratory assessments in subjects with renal impairment are further discussed in the next section.

Table 50. AEs in Subjects With Baseline eGFR <60 mL/min/1.73 m² by FMQ With RD ≥0.5 as Sorted by RD, Safety Population, Trial C-476

FMQ	Bexa 20 mg N=225 n (%)	Placebo N=109 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Lipid disorder	14 (6.2)	2 (1.8)	4.4 (0.3, 8.4)
Diarrhea	22 (9.8)	6 (5.5)	4.3 (-1.5, 10.1)
Rash	17 (7.6)	4 (3.7)	3.9 (-1.1, 8.8)
Fracture	14 (6.2)	3 (2.8)	3.5 (-0.9, 7.9)
Hemorrhage	21 (9.3)	8 (7.3)	2.0 (-4.2, 8.2)
Hypersensitivity	4 (1.8)	0 (0)	1.8 (0.1, 3.5)
Paresthesia	6 (2.7)	1 (0.9)	1.7 (-1.0, 4.5)
Alopecia	3 (1.3)	0 (0)	1.3 (-0.2, 2.8)
Erectile dysfunction	3 (1.3)	0 (0)	1.3 (-0.2, 2.8)
Sexual dysfunction	3 (1.3)	0 (0)	1.3 (-0.2, 2.8)
Anxiety	5 (2.2)	1 (0.9)	1.3 (-1.3, 3.9)
Abdominal Pain	13 (5.8)	5 (4.6)	1.2 (-3.8, 6.2)
Cough	17 (7.6)	7 (6.4)	1.1 (-4.6, 6.9)
Cholecystitis	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Decreased appetite	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Urinary retention	2 (0.9)	0 (0)	0.9 (-0.3, 2.1)
Insomnia	4 (1.8)	1 (0.9)	0.9 (-1.6, 3.3)
Dyspnea	12 (5.3)	5 (4.6)	0.7 (-4.2, 5.6)
Pneumonia	12 (5.3)	5 (4.6)	0.7 (-4.2, 5.6)
Headache	14 (6.2)	6 (5.5)	0.7 (-4.6, 6.0)
Viral Infection	20 (8.9)	9 (8.3)	0.6 (-5.7, 7.0)

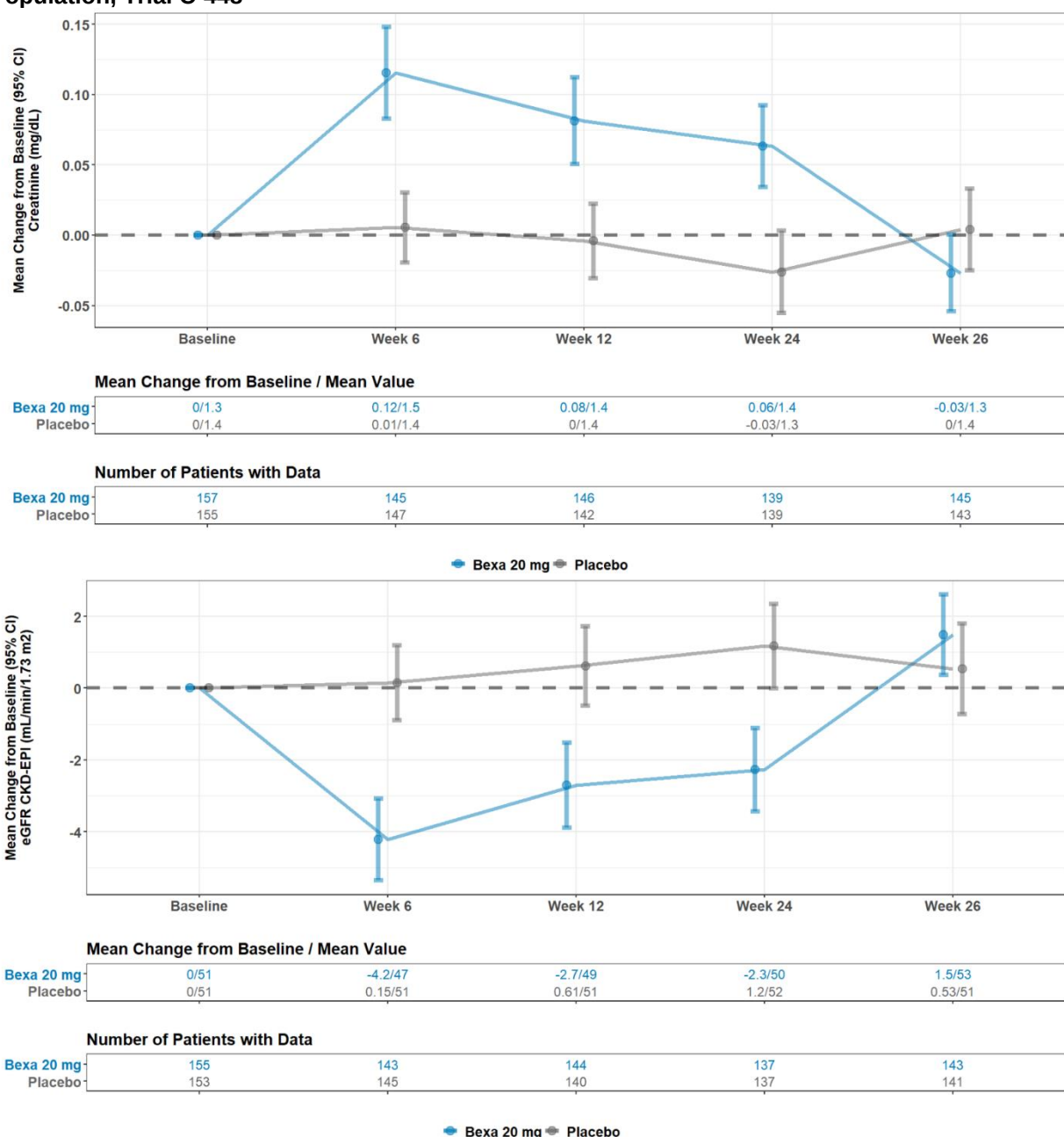
Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AE, adverse event; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; RD, risk difference.

Laboratory Parameters

Changes in laboratory parameters over time in C-448 were generally in line with data observed in other trials, including modest mean increases in serum magnesium, serum phosphate, hemoglobin/hematocrit, and transient decreases in serum bicarbonate (see Section 17.4 for detailed analyses of changes in laboratory parameters over time). Transient increases in serum creatinine and decreases in eGFR are known class effects. The magnitude of change in these parameters was greater in C-448 as compared to the placebo-controlled pool, with a mean increase in serum creatinine of 0.14 mg/dL (10.8%) and a mean decrease in eGFR of -4.6 mL/min/1.73m² (9.0%) from baseline to Week 6 (Figure 16). In contrast, in the placebo-controlled pool, serum creatinine increased 0.03 mg/dL (3.8%) and eGFR decreased -2.3 mL/min/1.73 m² in the bexagliflozin group from baseline to Week 6. These results appear in line with data from other SGLT2 inhibitor programs.

Figure 16. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial C-448



Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Abbreviations: Bexa, bexagliflozin; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

There were no significant mean changes over time in lipid parameters between the bexagliflozin and placebo groups in C-448 (data not shown); however, there were more subjects with level 3 elevations in serum cholesterol (>225 mg/dL), LDL-C (>190 mg/dL), and triglycerides (500 mg/dL) in the bexagliflozin group as compared to the placebo group ([Table 51](#)). Supportive data from the subpopulation of subjects with baseline eGFR <60 mL/min/1.73 m² also indicated a higher incidence of lipid disorders in this population. As discussed above, subgroup analyses

from the MACE+ meta-analyses provide reassurance that the noted changes in lipid parameters do not increase the risk of MACE; however, labeling is proposed in Section 6 to inform providers on potential changes in lipid parameters in this patient population.

Table 51. Patients With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial C-448

Laboratory Parameter	Bexa 20 mg N=157 n/N_w (%)	Placebo N=155 n/N_w (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	55/155 (35.5)	39/152 (25.7)	9.8 (-0.4, 20.1)
Level 2 (>210)	44/155 (28.4)	27/152 (17.8)	10.6 (1.3, 20.0)
Level 3 (>225)	29/155 (18.7)	19/152 (12.5)	6.2 (-1.9, 14.3)
HDL, males, low (mg/dL)			
Level 1 (<40)	37/92 (40.2)	52/101 (51.5)	-11.3 (-25.2, 2.7)
Level 2 (<30)	10/92 (10.9)	13/101 (12.9)	-2.0 (-11.1, 7.1)
Level 3 (<20)	1/92 (1.1)	0/101 (0)	1.1 (-1.0, 3.2)
HDL, females, low (mg/dL)			
Level 1 (<50)	30/63 (47.6)	34/51 (66.7)	-19.0 (-36.9, -1.2)
Level 2 (<40)	12/63 (19.0)	14/51 (27.5)	-8.4 (-24.0, 7.2)
Level 3 (<20)	0/63 (0)	0/51 (0)	0 (0, 0)
LDL, high (mg/dL)			
Level 1 (>130)	31/155 (20.0)	23/152 (15.1)	4.9 (-3.6, 13.4)
Level 2 (>160)	11/155 (7.1)	7/152 (4.6)	2.5 (-2.7, 7.7)
Level 3 (>190)	4/155 (2.6)	1/152 (0.7)	1.9 (-0.9, 4.7)
Triglycerides, high (mg/dL)			
Level 1 (>150)	98/155 (63.2)	102/152 (67.1)	-3.9 (-14.5, 6.8)
Level 2 (>300)	22/155 (14.2)	20/152 (13.2)	1.0 (-6.6, 8.7)
Level 3 (>500)	5/155 (3.2)	3/152 (2.0)	1.3 (-2.3, 4.8)

Source: adlb.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; HDL, high density lipoprotein; LDL, low density lipoprotein.

Conclusion

Overall, considering the safety data from C-448 and C-476, no new safety issues were identified in subjects with stage 3 CKD, although data to characterize certain events (e.g., SAEs, events leading to discontinuation, etc.) were limited. Labeling to inform prescribers regarding changes in certain laboratory parameters (i.e., eGFR/creatinine and lipid parameters) is warranted. The available safety data do not raise new safety concerns and support labeling of bexagliflozin in patients with eGFR >30 mL/min/1.72 m².

Dissent

Not applicable.

7.7.3. Safety Database Quality Concerns

Issue

Safety database quality concerns.

Background

Concerns regarding the quality of the safety database were raised when multiple events of falls and AKI were found in subject narratives that did not have a corresponding PT in the ISS ADAE dataset. For illustrative purposes, the following excerpts have been reproduced from subject narratives where there was no PT of “fall” or “AKI” in the ISS ADAE dataset:

Fall:

- Subject 476- (b) (6): “On 1 (b) (6) (Day 247), the subject had a mechanical fall at home, suffered abrasion of the left shin and subsequently developed cellulitis.”
- Subject 476- (b) (6): “On (b) (6) (Day 577), the subject sustained left hip fracture due to accidental fall at home.”
- Subject: 476- (b) (6): “On (b) (6) (Day 639), the subject sustained a right hip fracture and complained of neuropathic symptoms on the right sole after he had a fall.”

AKI:

- Subject 476- (b) (6): “Hypotension was likely due to over diuresis, which also caused prerenal acute kidney injury.”
- Subject: 476- (b) (6): “The site reported that elevated lipase was due to acute kidney injury secondary to bilateral obstructing ureteral stones.”

In addition, as previously discussed in Section [7.7.1](#), the Applicant acknowledged in their application that amputation events were underreported by investigators, and that additional querying of the safety database was needed to adequately identify all amputation events.

Falls, AKI, and amputation were AESIs in all phase 3 protocols, and robust methods for identifying, reporting, and analyzing these events are expected. As underreporting of AEs, including AESIs, could ultimately impact labeling and the overall benefit-risk assessment, data integrity and quality were examined.

Assessment

Several approaches were taken to investigate the quality of the safety database. First, FDA requested that the Applicant perform additional analyses to investigate whether AESIs may have been underreported in the bexagliflozin clinical program. Second, FDA asked the Applicant to provide detailed information on the processes and procedures used for the collection of clinical safety data, starting from the clinical encounter, and extending to the preparation of the safety database, to provide assurance that the submitted data were of sufficient quality for review. Third, Office of Scientific Investigations (OSI) inspection information was reviewed to inform potential data integrity issues. These approaches are discussed individually below.

Natural Language Processing-Based Data Querying

To investigate whether potential under-coding of safety data occurred in the bexagliflozin clinical program, the Applicant utilized a natural language processing (NLP)-based approach to query available free-text safety data (e.g., subject narratives, verbatim terms, the Argus safety database (the database used to track, review and process individual safety events, including SAEs), etc.). In accordance with the findings observed by the review team, a significant number of additional fall events were identified by the Applicant utilizing the NLP-based approach. For

example, the Applicant states that 69 fall events occurring in 64 subjects were considered to potentially represent distinct fall or fall-like occurrences based on free-text search of narrative sources, 57 of which affected subjects without recorded events of fall in the ADAE database, 6 of which were fall events present in the ADAE database, and 6 of which were additional events in subjects with existing events in the ISS ADAE database (SD0031). In other words, approximately 90% of subjects who experienced a fall event were not included in the ISS ADAE dataset submitted with this application.

The Applicant submitted a modified ISS ADAE dataset that included AEs identified by the NLP-based search for additional events. FMQ analyses were used to assess the original ISS ADAE dataset (adae.xpt) and the NLP-modified ADAE dataset (tadae.xpt). As the majority of additional adverse events found were identified from hospitalization records and/or narrative information for SAEs, C-476 was utilized for this analysis as it contained the majority of SAEs observed in the bexagliflozin clinical development program. In accordance with observations of the review team, there were an additional 40 and 19 subjects who experienced a fall event in the bexagliflozin and placebo groups, respectively, reported in the NLP-modified dataset as compared to the original ISS dataset. A number of additional AKI events were also reported in the NLP-modified dataset. However, the identification of these events appeared primarily based on elevations in creatinine that did not appear to represent events that necessitated coding based on a random review of corresponding subject narratives. There was no significant difference in the FMQs for “Fungal Infection,” “Dizziness,” “Rash,” “Renal and Urinary Tract Infections,” “Hypersensitivity,” “Malignancy,” or “Fracture” between datasets ([Table 52](#)).

For FMQs where additional events were coded in the NLP-modified dataset, there was no evidence of systemic bias towards underreporting in the bexagliflozin treatment group. For example, in the original ISS dataset, there were 2.7% and 3.0% of subjects who had at least one fall (as identified by the FMQ for “Fall”) in the bexagliflozin and placebo group of C-476, respectively. In the NLP-modified dataset, there were 6.3% and 6.3% of events in the bexagliflozin and placebo groups, respectively.

Table 52. Comparison of FMQ Analyses From ISS ADAE Versus NLP-Modified ISS ADAE Datasets, Safety Population, Trial C-476

FMQ	ISS ADAE*			NLP-Modified ISS [‡]		
	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa vs. Placebo RD (%) (95% CI)	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa vs. Placebo RD (%) (95% CI)
Fungal Infection	93 (8.2)	25 (4.4)	3.8 (1.5, 6.1)	96 (8.5)	25 (4.4)	4.1 (1.7, 6.4)
Dizziness	83 (7.3)	29 (5.1)	2.2 (-0.1, 4.6)	83 (7.3)	29 (5.1)	2.2 (-0.1, 4.6)
Rash	61 (5.4)	19 (3.4)	2.0 (0.1, 4.0)	61 (5.4)	19 (3.4)	2.0 (0.1, 4.0)
Renal and urinary tract infection	148 (13.1)	68 (12.0)	1.1 (-2.2, 4.4)	150 (13.3)	70 (12.3)	0.9 (-2.4, 4.3)
Hypersensitivity	15 (1.3)	4 (0.7)	0.6 (-0.3, 1.6)	18 (1.6)	5 (0.9)	0.7 (-0.4, 1.8)
Acute Kidney Injury	25 (2.2)	9 (1.6)	0.6 (-0.7, 2.0)	42 (3.7)	25 (4.4)	-0.7 (-2.7, 1.3)
Volume Depletion	12 (1.1)	4 (0.7)	0.4 (-0.6, 1.3)	20 (1.8)	11 (1.9)	-0.2 (-1.5, 1.2)
Malignancy	39 (3.4)	18 (3.2)	0.3 (-1.5, 2.1)	39 (3.4)	17 (3.0)	0.4 (-1.3, 2.2)
Fracture	45 (4.0)	22 (3.9)	0.1 (-1.9, 2.1)	46 (4.1)	22 (3.9)	0.2 (-1.8, 2.1)
Fall	31 (2.7)	17 (3.0)	-0.3 (-2.0, 1.4)	71 (6.3)	36 (6.3)	-0.1 (-2.5, 2.4)
Hepatic Injury	20 (1.8)	19 (3.4)	-1.6 (-3.3, 0.1)	26 (2.3)	23 (4.1)	-1.8 (-3.6, 0.1)

Source: adae.xpt and tadae.xpt; Software: R; Generated by CDS

*ISS ADAE dataset in original Application

±NLP-derived modified ADAE ISS dataset

Abbreviations: ADAE, ADaM adverse events analysis dataset; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; ISS, integrated summary of safety; NLP, natural language process; RD, risk difference.

A root cause analysis for why fall events were underreported was requested by the Agency. The Applicant states that there was no single explanation for the underreporting of fall events but explained that contributing factors could include lack of guidance to investigators regarding the collection of falls as AEs and the ability for a fall event to be viewed as a symptom of event by investigators as opposed to a stand-alone event requiring independent reporting. In addition, the Applicant also clarified that although “Falls and Fractures” were identified as AESIs in study protocols, beginning with Version 3 of their AESI definitions (March 09, 2018), the PT of fall was no longer included as an AESI. The Applicant provided the following response to FDA’s information request:

There were several reasons for discontinuing fall as a component of the “Falls and Fractures” AESI. Falls in of themselves do not contribute to an understanding of potential adverse effects of bexagliflozin on bone, except as a kind of denominator over which traumatic events leading to fracture could be assessed (e.g., to calculate fractures per fall). Because few falls were expected to lead to fractures, (as was the case), inclusion of falls could reduce the discriminating power of the event category. In addition, fractures could originate from a variety of forms of trauma, not simply falls. Enumerating traumatic events in general is one possible response, but subcategories of trauma have poor support in MedDRA and their inclusion would also likely be dilutive. Fall and related events associated with loss of postural control can have diverse etiologies, such as hypoglycemia, hypotension, seizure, syncope, trauma or vestibular events.

Thus, falls were not considered AESIs for the purposes of the integrated summary of safety. Note, we do not agree with the Applicant’s rationale for removing falls from the AESI category and all AEs related to falls should have been included.

Processes-Based Quality Review

In addition to efforts to uncover evidence of potential under-coding and differential coding (i.e., the same adverse event coded differently) of adverse events, the review team also examined whether the bexagliflozin development program was designed with important data quality and processes in place. We reviewed the Applicant’s data collection, management, and data quality processes and procedures employed during the trial with reference to International Conference on Harmonisation (ICH) E6(R2) Guidance entitled *Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018), as summarized below.

- Confirmed that investigators were qualified by education, training, and experience to assume responsibility for the proper conduct of the trial.
- Confirmed that electronic CRFs (eCRFs) were generated in a structured process following the standard operating procedures by the contracted clinical research organizations (CROs), (b) (4) (C-476) or (b) (4) (C-419, C-423, C-448, C-450, C-480). The eCRF captured relevant clinical, demographic, and safety information on both designated medical events (e.g., hypoglycemia, DKA) and unsuspected adverse events. All CRFs were generated using a Medidata RAVE electronic data capture (EDC) system, which provided a standalone database instance with appropriate middleware to facilitate the secure and auditable entry of clinical data in a manner conforming to FDA Guidance for Industry *Computerized Systems Used in Clinical Investigations* (May 2007) for each study. The design of the eCRF and the incorporated edit checks were a joint

undertaking of the CRO and the Applicant's medical oversight vendor, the (b) (4). Investigators were introduced to each study through investigator meetings where training in the process of data entry into the eCRF was conducted. Each study had an eCRF completion requirements manual that provided guidance for the entry of data and appropriate responses to real-time validation checking initiated by form-control logic incorporated in the system.

- Confirmed that the two primary CROs who conducted all studies in the drug development program have been inspected by FDA's OSI on multiple prior occasions ((b) (4) in (b) (4) and (b) (4) (b) (4) inspected twice in (b) (4)) and had no significant prior citations.
- Clinical sites were routinely audited, wherein CRF entries were verified against source documents (e.g., medical records, medical notes, laboratory results, electrocardiogram traces etc.). Audit certificates were provided by the Applicant.
- Adverse event terminology and reporting standards conformed to the definitions and principles outlined in the ICH E2A Guidance on *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995).
- The standard procedures for coding of AEs in the clinical trials appears to have followed MedDRA principles to ensure complete and accurate coding of events. This included instructions pertaining to term selection to guard against missed concepts.
- The establishment and maintenance of a safety database was undertaken through a contract with the pharmacovigilance provider, (b) (4), doing business as (b) (4). The datastore was an instance of an Oracle Argus Cloud relational database administered by (b) (4) data managers.
- Clinical laboratory data were imported into the RAVE database by direct electronic transfer from the central laboratory sites.
- The Argus safety database was maintained under a safety management plan that was established for all TheracosBio, LLC bexagliflozin clinical studies. The plan was an integral part of an oversight architecture that included a medical responsibility plan, an unblinding plan and a clinical and safety database reconciliation plan, all of which were provided by the Applicant for review.

OSI Review

As detailed in OSI's review (see DARRTS consult dated July 13, 2022), eight domestic clinical investigators were inspected. Investigators/study sites were selected based on the ability of data from their site to potentially impact the overall benefit-risk assessment. Amongst other activities, site inspections reviewed subject source documents including AE and SAE reports, and source records were compared to the Applicant's data line listings in the NDA submission. OSI concludes that no significant regulatory violations were found upon inspection and that, based on the results of inspections and regulatory assessments, Trials C-419, C-423, C-448, C-450, C-476 and C-480 appear to have been conducted adequately.

Conclusion

Results from analyses conducted with the Applicant's NLP-modified dataset (tadae.xpt) were in line with the review teams observations that certain events (i.e., falls, AKI, amputation),

appeared under-coded in the safety database; however, a systematic under-coding of other important events (e.g., fungal infections, fractures, malignancies) does not appear to have occurred. In addition, no evidence of biased underreporting was observed (i.e., under coded events impacted both treatment groups generally equally). The Applicant provided information to support that the trials were designed with appropriate measures to ensure the collection of high-quality data. Lastly, as detailed in OSI's review, pivotal studies appear to have been conducted adequately based on inspectional findings. Overall, the data generated and submitted by the Applicant appear of acceptable quality for review.

Dissent

Not applicable.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

In patients with mild, moderate, and severe renal impairment, bexagliflozin AUC increased by 6.8%, 33.8% and 53.9% compared to patients with normal renal function. The maximum plasma concentration (C_{max}) was not affected. Consistent with the mechanism of action, the 24-hour UGE declined with decreased eGFR, from 100 g without impairment to 83, 40, and 17 g in the setting of mild, moderate, and severe impairment, respectively.

The effects of moderate renal impairment (stage 3 CKD, $30 \leq eGFR < 60$ mL/min/1.73 m²) were evaluated in two phase 3 studies (C-448 and C-476). Based on the efficacy and safety observed in these studies, bexagliflozin can be used in patients with mild and moderate renal impairment without dose adjustment (see Section [6.3](#) for detailed information).

The safety and efficacy of bexagliflozin have not been established in patients with severe renal impairment, with end stage renal disease, or receiving dialysis. However, bexagliflozin is not expected to be effective in these patient populations based on its mechanism of action.

Hepatic Impairment

The use of bexagliflozin has not been studied in patients with severe hepatic impairment. In subjects with moderate hepatic impairment (Child-Pugh class B), bexagliflozin AUC increased by 28.3%, and C_{max} increased by 6.2% compared to subjects with normal hepatic function. The extent of exposure increase is less than that from moderate renal impairment and is not considered clinically relevant and therefore dose adjustment is not needed in patients with mild and moderate hepatic impairment.

UGT1A9 Polymorphism

Bexagliflozin is mainly metabolized by UGT1A9, which is polymorphic. Although the Applicant didn't collect information on UGT1A9 allelic variants in clinical studies, the impact of UGT1A9 genotype on the PK of bexagliflozin may be less than or similar to that observed in the clinical

study with UGT1A9 inhibition. Based on a <40% increase in bexagliflozin AUC in the presence of UGT1A9 inhibitor probenecid, UGT1A9 polymorphism is unlikely to contribute a sufficiently substantial effect to warrant a change in the dosing regimen.

Other Intrinsic Factors

The impact of intrinsic factors on bexagliflozin PK exposure was evaluated. Intrinsic factors included in the population PK analysis (i.e., creatinine clearance, body weight, Asian race, healthy status) were not considered to have a clinically meaningful effect on bexagliflozin PK. Refer to the covariate effect assessment in the Pharmacometrics Review Appendix (Section [14.3.4](#)).

8.2. Food Effect

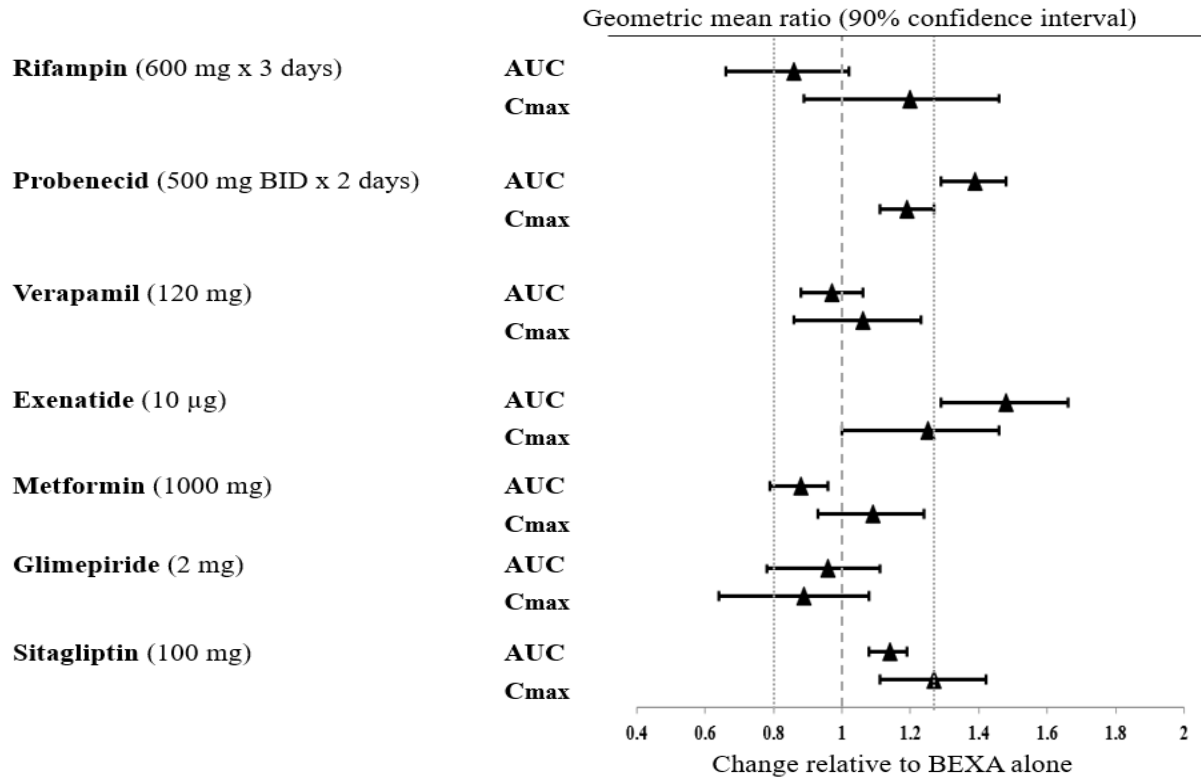
Administration of bexagliflozin after consumption of a high-fat, high-caloric meal delayed bexagliflozin time to maximum concentration (T_{max}) by about 1.5 hours and increased its C_{max} and AUC values by 31% (90% CI: 17%, 48%) and 10% (90% CI: 3.9%, 17%), respectively, compared to the values observed following dosing in the fasted state (Trial C-481). The observed exposure increases are not considered clinically meaningful and bexagliflozin can be administered with or without food.

8.3. Drug Interactions

In vitro studies indicated that bexagliflozin is mainly metabolized by UGT1A9 with minor contribution from the cytochrome (CYP)3A enzyme. In addition, bexagliflozin is a substrate and inhibitor of P-gp at clinically relevant concentrations. Based on the in vitro findings, the Applicant conducted several clinical drug-drug interaction (DDI) studies to further evaluate the effect of UGT1A9 inhibition (probenecid), CYP3A/uridine diphosphate-glucuronosyltransferase (UGT) induction (rifampin), and p-gp inhibition (verapamil) on the PK of bexagliflozin, as well as the effect of bexagliflozin on the PK of a sensitive P-gp substrate (digoxin). The Applicant also evaluated the potential interactions between bexagliflozin and commonly prescribed antidiabetic agents including exenatide, glimepiride, sitagliptin, and metformin.

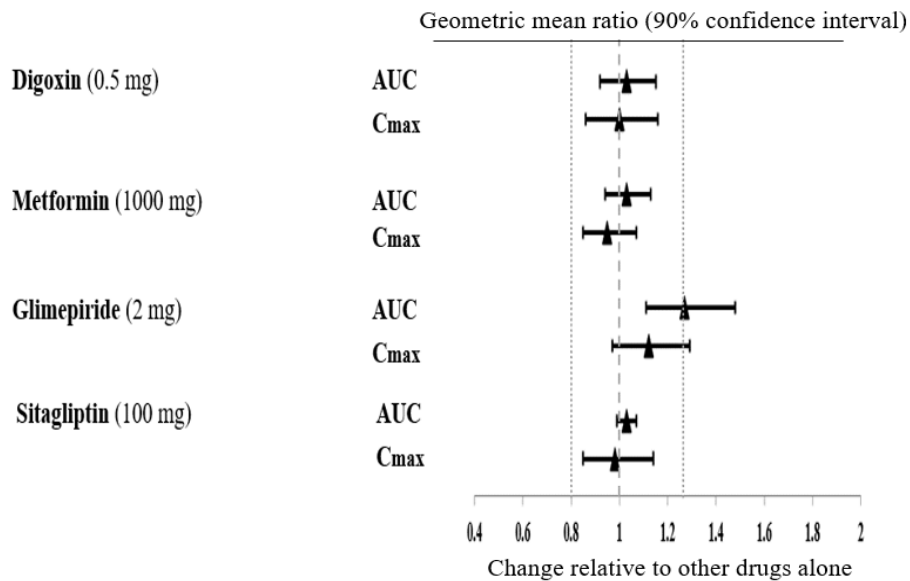
Based on the results of these studies ([Figure 17](#) and [Figure 18](#)), clinically meaningful DDI is not expected when bexagliflozin is taken with 1) antihyperglycemic agents including exenatide, glimepiride, sitagliptin, metformin, 2) drugs that are substrates of P-gp, and 3) drugs that inhibit P-gp or UGT1A9, (see Section [8.3.3](#) for further details). UGT enzyme inducers may significantly reduce bexagliflozin exposure and decrease its efficacy. Therefore, adding another antihyperglycemic agent may be considered in patients who require additional glycemic control.

Figure 17. Effect of Other Drugs on Bexagliflozin PK



Source: Plot generated by clinical pharmacology reviewers based on PK dataset from Trial C-454, C-458 and C-453;
Note: Rifampin dosing regimen may not represent maximal impact on bexagliflozin exposure (see Section 8.3.1 for more details)
Abbreviations: AUC, area under the concentration-time curve; Bexa, bexagliflozin; BID, twice daily; C_{max}, maximum plasma concentration; PK, pharmacokinetics.

Figure 18. Effect of Bexagliflozin on the PK of Other Drugs



Source: Plot generated by clinical pharmacology reviewers based on PK dataset from trial C-453 and C-443;
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; PK, pharmacokinetics.

8.3.1. DDI Potential as a Victim

Effect of UGT Inhibition on the PK/PD of Bexagliflozin

Effect of UGT inhibition on bexagliflozin PK/PD was assessed in 16 healthy subjects using a nonspecific UGT inhibitor probenecid. During the study, subjects took a single dose of bexagliflozin 20 mg on Day 1 and Day 5. Probenecid 500 mg twice a day was administered from Day 3 to Day 6. Coadministration with probenecid increased bexagliflozin AUC_{0-t} and C_{max} by 38.8% [29.5%, 48.8%] and 18.7% [11.1%, 26.7%], respectively, compared to bexagliflozin alone. Bexagliflozin T_{max} and $t_{1/2}$ were similar between treatments. Postdose UGE for each 12-hour collection interval was similar for both treatments, indicating no impact on UGE. Based on the safety profile of bexagliflozin, the magnitude of exposure increase observed in this study was not considered clinically significant. Therefore, bexagliflozin can be taken with drugs that inhibit UGT.

Effect of CYP3A/UGT Induction on the PK/PD of Bexagliflozin

Effect of CYP3A/UGT induction on bexagliflozin PK/PD was assessed in 16 healthy subjects using a strong CYP3A/UGT inducer (rifampin). During the study, subjects took a single dose of bexagliflozin 20 mg on Day 1 and Day 6. Rifampin 600 mg once daily was administered from Day 3 to Day 7. The point estimate of geometric mean ratio (GMR) (90% CI) for treatments bexagliflozin + rifampin vs. bexagliflozin alone was 86.1% (70.2%, 105.6%) for AUC_{0-t} and 119.6% (94.4%, 151.6%) for C_{max} . The half-life of bexagliflozin was decreased from 12.9 hours to 5.9 hours when co-administered with rifampin. Postdose UGE for each 12-hour collection interval was similar for both treatments.

The review team is concerned that a 3-day pretreatment with rifampin is too short to achieve the full potential of CYP3A/UGT induction. The induction effect-time profile of rifampin on CYP3A has been demonstrated by several publications. In general, at least 5 days of treatment with rifampin (600 mg per day) is needed to approach the plateau of CYP3A induction. Based on the shared activation pathway of Pregnane X Receptor between CYP3A and UGT, it's anticipated that a 3-day pretreatment duration may not fully reach the peak of UGT1A9 induction as well.

Overall, the current study may not capture the worst-case scenario on the impact of CYP3A/UGT induction on bexagliflozin PK. This speculation is further supported by the smaller extent of exposure decrease with bexagliflozin compared to other SGLT2 inhibitors, all of which are also mainly metabolized by UGT1A9. Specifically, DDI studies with rifampin showed AUC reductions of 51%, 22%, and 39%, respectively, for canagliflozin, dapagliflozin, and ertugliflozin.

Overall, the current study result may not reflect the maximum effect of CYP3A/UGT induction on the PK of bexagliflozin. It is expected that strong CYP/UGT inducers may lead to significantly decreased bexagliflozin exposures and may potentially result in compromised efficacy in glycemic control. Therefore, adding another antihyperglycemic agent may be considered in patients who require additional glycemic control. The impact of UGT enzyme inducers on bexagliflozin and the potential requirement for additional antihyperglycemic agents will be included in the prescribing information.

Effect of P-gp Inhibition the PK of Bexagliflozin

When bexagliflozin (20 mg) was administered one hour after the intake of a P-gp inhibitor verapamil (120 mg), the mean GMR (90% CI) was 96.6% (88.1%, 105.9%) and 106.0% (88.1%, 126.7%) for bexagliflozin AUC_{0-t} and C_{max} , respectively. Therefore, concomitant drugs that are P-gp inhibitors are unlikely to affect bexagliflozin PK.

8.3.2. DDI Potential as a Perpetrator

In vitro studies indicate that bexagliflozin may be a P-gp inhibitor at the clinically relevant dose. Therefore, a clinical DDI study with a sensitive P-gp substrate digoxin was conducted. The results show no significant changes in the systemic exposures of digoxin when coadministered with bexagliflozin (20 mg one daily for 8 days). Therefore, bexagliflozin administered as 20 mg daily is unlikely to affect the PK of concomitant drugs that are substrates of P-gp.

8.3.3. DDI Potential With Commonly Prescribed Antidiabetic Agents

DDIs With Exenatide

Following injection of 10 µg of exenatide, the GMR (90% CI) for AUC_{0-t} , and C_{max} of bexagliflozin with exenatide compared to bexagliflozin alone were 1.47 (1.30, 1.67), and 1.25 (1.04, 1.50), respectively, and the median T_{max} increased from 2 hours to 5 hours. Per the Applicant, the effects of exenatide, a glucagon-like peptide (GLP)-1 receptor agonist, were consistent with the known delay of gastric emptying by GLP-1 receptor agonists and mimicked the effects of prior consumption of food (Trial C-481). However, it should be noted that the impact on the PK of bexagliflozin was much larger with exenatide compared to the food effect (47% versus 10% increase in AUC). The exact mechanism of interaction is not clear. The PD response of 24-hour UGE was lower in the bexagliflozin plus exenatide group (~55 g) compared to the bexagliflozin alone group (~65 g). Nonetheless, the decreased UGE is unlikely to translate to diminished efficacy, given the 24-hour UGE value of 55 g is still on the plateau of the bexagliflozin dose-UGE response curve ([Figure 5](#)). In addition, the observed 47% exposure increase in bexagliflozin is not considered clinically relevant as no major safety concerns were identified when bexagliflozin was given to patients with T2DM for 28 days at the dose of 50 mg. Therefore, no dose adjustment is needed when bexagliflozin is taken with a GLP-1 receptor agonist.

DDIs With Metformin, Glimepiride and Sitagliptin

DDI potential of bexagliflozin with commonly prescribed antidiabetic agents including metformin, glimepiride, and sitagliptin was assessed in 54 healthy subjects (N=18 per group). For each group, subjects received a single dose of bexagliflozin 20 mg alone, a single dose of an oral hypoglycemic agent (1000 mg metformin, 2 mg glimepiride, or 100 mg sitagliptin) alone, and the combination of both (bexagliflozin and antidiabetic agents) alternately in a crossover fashion, with three treatment periods separated by a washout period of at least 7 days.

The results show that bexagliflozin had no significant effect on the PK of metformin, glimepiride, and sitagliptin. Similarly, there was no clinically relevant impact on the PK of bexagliflozin. UGE values of bexagliflozin were slightly lower when administered with other antidiabetic agents but the differences were not statistically significant. Overall, no dose adjustment is needed for bexagliflozin when administered with metformin, glimepiride, and sitagliptin.

Other Drug Interactions

A few drug interaction warnings have been added to the product labeling, but they were not reviewed in the current submission. These drug interactions are related to the class effects of SGLT2 inhibitors including increased risk of hypoglycemia when used combination with insulin and/or insulin secretagogues, interference with the 1,5-anhydroglucitol (1,5-AG) assay, a positive urine glucose test and potential reduction in serum lithium levels during the treatment with SGLT2 inhibitors.

8.4. Plans for Pediatric Drug Development

The initial approval of bexagliflozin will be limited to adults as the trials included in this application did not enroll pediatric subjects. The Division agrees to waive the pediatric study requirement for ages 0 through 9 years (inclusive) because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with T2DM to study. Furthermore, the Division agrees to defer submission of the Applicant's pediatric study for ages 10 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

The Applicant's deferred pediatric study is required under section 505B(a) of the FDCA as a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the FDCA. The required pediatric study is listed below:

- 1) A 24-week, randomized, double-blind, placebo-controlled, parallel group study of the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of bexagliflozin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 28-week double-blind, controlled extension. The bexagliflozin dose will be determined based on the initial PK/PD lead-in portion of the study.

Draft Protocol Submission: January 2023
Final Protocol Submission: July 2023
Study Completion: May 2031
Final Report Submission: October 2031

8.5. Pregnancy and Lactation

There are no available data on bexagliflozin use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes, or information regarding the presence of bexagliflozin in human milk. A standard battery of reproductive

toxicology studies and a juvenile toxicology study with relevance to pregnancy were conducted with bexagliflozin. No treatment-related adverse effects on fertility, embryo-fetal development, or pre- and postnatal development were observed at clinically relevant exposures. Based on adverse renal effects (adverse renal pelvic and tubular dilatation) in juvenile rats administered bexagliflozin during periods of renal development corresponding to the late second and third trimester of human renal development, bexagliflozin is not recommended during pregnancy. Detailed summaries of the results of these studies are contained in Section [13](#) of this review.

Table 53. Nonclinical Data Supporting Labeling

Labeling Section	Nonclinical Data
8.1 Pregnancy	Bexagliflozin dosed directly to juvenile rats at 0.3, 3, 30 mg/kg by oral gavage from postnatal day (PND) 21 to 90 caused a dose dependent increase in the incidence and severity of renal pelvic and tubular dilatation at ≥ 3 mg/kg (11 times the MRHD). These effects occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. In embryofetal development studies, bexagliflozin was administered by oral gavage to rats at 0, 7, 40 or 200 mg/kg/day and to rabbits at 0, 5, 25 or 150 mg/kg/day during the period of organogenesis. No adverse developmental effects were observed in rats at doses up to 200 mg/kg/day (550 times the clinical dose of 20 mg based on AUC). Reduced maternal body weight, embryo lethality, and fetal malformations were observed in rabbits at 150 mg/kg/day (370 times the clinical dose of 20 mg based on AUC). In a pre- and postnatal development study, bexagliflozin was administered to maternal rats by oral gavage from gestation Day 6 throughout lactation Day 20 at doses of 7, 40 or 200 mg/kg/day. Maternal mortality occurred at ≥ 40 mg/kg (79 times the clinical dose of 20 mg based on AUC), primarily following parturition. Reduced gestational body weight, increased postimplantation loss, and smaller litter size were noted at 200 mg/kg (361 times the clinical dose of 20 mg based on AUC). In the offspring, lower body weight gain and decreased survival were noted at 200 mg/kg, which occurred in the presence of significant maternal toxicity.
8.2 Lactation	Bexagliflozin was present in rat milk at a milk: plasma ratio of approximately 2. If a drug is present in animal milk, it is likely the drug will be present in human milk. Juvenile rats directly administered dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during the period of renal development in rats corresponding to the late second and third trimester of human renal development.

Labeling Section	Nonclinical Data
13.1 Carcinogenesis, mutagenesis, impairment of fertility	Carcinogenesis: The carcinogenic potential of bexagliflozin was evaluated in 2-year studies in Sprague-Dawley (SD) rats and CD-1 mice. There were no neoplastic findings in mice and rats up to the highest doses tested (150 mg/kg/day for mice and 30 mg/kg/day for rats, representing approximately 135 and 54 times the clinical dose of 20 mg based on AUC, respectively). The male rat study was terminated prematurely at Weeks 82-88, due to excessive mortality. Mutagenesis: Bexagliflozin was not mutagenic or clastogenic in the in vitro Ames bacterial mutagenicity assay, the in vitro mammalian chromosomal aberration assay, an in vivo micronucleus test in rats, and in vivo unscheduled hepatic DNA synthesis in rats. Impairment of fertility: Bexagliflozin had no effects on mating, fertility, or early embryonic development in male or female rats at any dose up to the highest dose of 200 mg/kg/day, which resulted in exposures 280 times (males) and 439 times (females) the clinical dose 20 mg based on AUC.

Source: Nonclinical reviewer

Abbreviations: AUC, area under the concentration-time curve; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

9. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team has assessed NDA 214373 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

Bexagliflozin is a new chemical entity. The chemical name for bexagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol. Bexagliflozin tablets are blue film-coated tablet debossed with “2” and inverted “2” on one side and no markings on the other side. Tablets contain 20 mg of bexagliflozin along with colloidal silicon dioxide, glyceryl dibehenate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene oxide, and poloxamer 188. The film coat contains FD&C Blue #1/Brilliant Blue FCF aluminum lake, FD&C Blue #2/Indigo carmine aluminum lake, macrogol 3350, polyvinyl alcohol, talc, and titanium dioxide. Bexagliflozin tablets are packaged in a 30 or 90 count HDPE bottle.

Tablets are manufactured by (b) (4).

The original manufacturing process control strategy did not include (b) (4).

(b) (4). Per FDA recommendation, the Applicant agreed to implement (b) (4).

(b) (4) testing as well as comprehensive stratified (b) (4).

(b) (4) at appropriate intervals for at least 25 commercial batches to demonstrate drug product (b) (4). To this end, we are requesting the following Postmarketing Commitments (PMCs):

- Perform additional (b) (4) testing on the next 25 (at a minimum) commercial scale batches of bexagliflozin tablets, 20 mg, and

provide the data to FDA in the annual reports after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024.

- Perform comprehensive stratified (b) (4) at appropriate intervals for at least 25 commercial batches to demonstrate (b) (4)

(b) (4)

(b) (4) Provide the data to FDA in the annual reports, after the completion of each production campaign that is tentatively scheduled from 3Q 2022 through 2Q 2024

The Applicant commits to providing a final report for the first PMC by June 30, 2024 and the second PMC by June 30, 2024.

See OPQ reviews dated June 22, 2022 and January 9, 2023 in DARRTS for additional information on FDA's product quality review.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Applicant states that all clinical trials were conducted in compliance with Good Clinical Practice, applicable laws, and regulations, and in accordance with the Declaration of Helsinki (1996). Eight domestic clinical investigators were selected for inspection based on their participation in pivotal efficacy studies conducted to support this application. No significant regulatory violations were reported by OSI. Based on the results of the inspections and regulatory assessments, the studies appear to have been conducted adequately, and the data generated by the Applicant appear acceptable. Review of the financial disclosures did not raise any concerns about the validity or reliability of the data. Please see Section [20](#) for a summary of inspection findings and Section [23](#) for financial disclosures.

11. Advisory Committee Summary

There was no advisory committee meeting conducted for this application. Although bexagliflozin is an NME, the efficacy endpoint (HbA1c) was straightforward and well accepted, and there were no controversial efficacy or safety issues with this fifth-in-class product that would have benefitted from an advisory committee meeting.

III. Appendices

12. Summary of Regulatory History

The following two sections provide a summary of the regulatory history. The first section provides a general summary of the regulatory history, while the subsequent section is focused on regulatory history related to statistical aspects of this application.

12.1. General Regulatory History

Opening IND 103822

The Division received the opening IND 103822 for bexagliflozin on January 7, 2009. Non-hold issues were identified during the IND safety review regarding aspects of the proposed nonclinical program, and feedback was provided to the Sponsor on February 13, 2009. Additional nonclinical and clinical pharmacology feedback was provided on April 8, 2009, June 16, 2009, and September 11, 2009, to which the Sponsor provided responses on June 26, 2009, and October 19, 2009.

Carcinogenicity SPAs

A request for a carcinogenicity special protocol assessment (SPA) for the protocol “104-Week Oral Carcinogenicity Study of bexagliflozin in CD-1 Mice,” was received on March 17, 2010, and denied. It was resubmitted with the requested full report of the mouse toxicity study and received by the Agency on April 14, 2010. Another carcinogenicity SPA request for the protocol, “26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with bexagliflozin in Rats with a 4-Week Recovery Phase,” was received on June 17, 2010. FDA recommended doses of 0 (distilled water), 0 (vehicle: 1% medium viscosity carboxymethylcellulose), 15, 50, and 150 mg/kg/day in male and female CD1 mice, 0 (distilled water), 0 (vehicle: 30% PEG400 vehicle), 2, 7, and 20 mg/kg/day in male rats, and concurred with the Sponsor’s proposed doses of 0 (distilled water), 0 (30% PEG400 vehicle), 3, 10, and 30 mg/kg/day in female rats.

On February 1, 2012, the Agency received a carcinogenicity SPA amendment containing dosing and vehicle changes with which the Executive Carcinogenicity Assessment Committee (ECAC) did not concur. The Agency responded with advice on February 3, 2012. Further carcinogenicity protocol amendments and advice requests were received on February 17, 2012, and April 6, 2012. The Agency responded on February 29, and April 5, 2012, respectively. An additional amendment was received on August 14, 2012, with the Agency again responding on September 5, 2012, with ECAC reiterating their lack of concurrence with dosing and vehicle changes.

On May 10, 2013, the Agency received nonclinical study reports for 104-Week Oral Carcinogenicity Studies THR-1442-T-405 and THR-1442-T-406, along with a request for comments on the carcinogenicity studies. The Agency’s reply on July 18, 2013, again reiterated ECAC’s lack of concurrence with doses and vehicle change, along with a need for a complete study review. A response from the Sponsor containing the requested study data was received on November 12, 2013.

On May 20, 2017, the Agency issued feedback stating that the Division agrees that no additional assessments of the carcinogenic potential of bexagliflozin are required. However, the Division reiterated that the assessment of the carcinogenic potential of bexagliflozin in male rats was not adequate given the limited duration of exposure, due to excessive early mortality. Based on the absence of preneoplastic findings and tumors in males exposed for up to 88 weeks at 3 times the MRHD and in females exposed for 100 weeks at doses up to 68 times the MRHD, repeating the carcinogenicity study in male rats was not considered warranted.

Thorough QT Study

Protocol C-428 for a thorough QT (TQT) study was received on May 19, 2011. The Interdisciplinary Review Team for Cardiac Safety Studies (IRT-CS) reviewed the protocol (see memo in DARRTS dated July 12, 2011) and feedback was provided to the Sponsor on July 26, 2011. The Sponsor adequately incorporated feedback from the IRT-CS (see IRT-CS memo in DARRTS dated March 19, 2013). The clinical study report (CSR) was reviewed by the IRT-CS on November 4, 2013. The memo concludes that no significant QTc prolongation effect was detected in C-428.

(b) (4)

End-of-Phase 2 and Follow-Up Meetings

An End-of-Phase 2 (EOP2) Meeting was held with the Sponsor on January 15, 2015, with final meeting minutes issued on February 12, 2015. The following topics were discussed:

- **Clinical Dose Selection:** The Agency did not agree with the Sponsor's proposal to select phase 3 doses based on data from phase 1/2 studies conducted with the capsule formulation of bexagliflozin and recommended that the Sponsor perform a dose-finding study with the modified formulation prior to initiating their phase 3 program. The Agency noted that, given the lack of established bioequivalence between the capsule and tablet formulations, it is unlikely that the findings from phase 2 trials C-402 and C-418 will be relevant to the formulation they intend to evaluate in their phase 3 program.
- **Phase 3 Program:** The Sponsor stated that the efficacy and safety of bexagliflozin in the context of combination therapy will be evaluated in: Trials C-419, C-423, and C-480, in which metformin will be coadministered; Trial C-420, in which sulfonylureas will be coadministered; Trial C-470, in which insulin will be coadministered; and Trials C-448 and C-476, in which all approved antidiabetic therapies will be candidates for coadministration. In addition, Trials C-423 and C-480 will be designed to demonstrate that bexagliflozin will be as effective as sitagliptin or glimepiride. FDA indicated concurrence on the proposed phase 3 development program.
- **Adverse events of special interest (AESIs):** In addition to the AESIs proposed by the Sponsor (hypoglycemia, hypovolemia, falls, fractures, urosepsis, pyelonephritis, urinary tract infections, genital infections, hepatic adverse events, and malignancies), the Agency

recommended that the Sponsor also prospectively collect and evaluate hypersensitivity reactions, hypotension episodes, acid-base disorders, and renal failure events as AESIs.

- **Studies in Older Adults:** The Sponsor proposed not to perform dedicated studies in older adults. The Agency agreed with this proposal.
- **Cardiovascular (CV) Risk Assessment:** FDA confirmed that the Sponsor's proposed major adverse cardiac event (MACE+) primary composite endpoint is acceptable for the premarketing assessment of CV safety to exclude an excess risk of over 80%. Additional feedback on the proposed inclusion criteria for C-476 and the statistical analysis plan for the proposed MACE meta-analysis was also provided.

On July 8, 2016, the Agency received a request for a Type C guidance meeting to follow-up on the clinical discussions that occurred during the End-of-Phase 2 meeting. Agency feedback was provided on September 21, 2016. Feedback included the following:

- **Dose Selection:** The Sponsor requesting feedback regarding dose selection for their phase 3 program. The Agency encouraged the Sponsor to evaluate two bexagliflozin dosage strengths.
- **Insulin Trial:** The Sponsor requested FDA feedback on their proposal not to conduct a dedicated trial evaluating the effectiveness of bexagliflozin as an add-on to insulin therapy. The Sponsor stated that approximately 50% of the population enrolled in C-476 to date used background insulin and proposed that a substudy of C-476 could be used to inform the safety and efficacy of bexagliflozin in this population. The Agency noted that this approach is reasonable provided that the design and conduct of the glycemic efficacy portion of the trial is consistent with what would be expected if the study were conducted as a separate study.
- **Diabetic ketoacidosis (DKA):** The Sponsor provided their DKA monitoring and analysis plan for the bexagliflozin clinical program and requested FDA feedback on the DKA case definitions. FDA stated that the proposed case definitions and DKA monitoring and analysis plan appear acceptable.
- **C-476:** Several aspects of C-476 were discussed. See section below (C-476 Protocol Review) for additional information
- **Amputations:** FDA recommended that amputations be included as an AESI. (Additional FDA recommendations on how amputation events should be monitored, evaluated, and analyzed was provided on October 25, 2016).

***FDA Reviewer Comment:** Overall, the Sponsor incorporated key FDA recommendations from this EOP2 meeting and written response only feedback dated September 21, 2016 into their clinical development program. The Sponsor did not take the Agency's recommendation to evaluate two doses of bexagliflozin in the phase 3 program.*

Initial Pediatric Study Plan

On March 12, 2015, the Sponsor submitted an initial Pediatric Study Plan (iPSP), which received a written response from the Agency on June 5, 2015. Additional communications between the Sponsor and Agency resulted in the submission of an Agreed iPSP dated September 28, 2015, to which the Agency responded with an initial agreement letter on October 27, 2015. The iPSP states the Sponsor's intention to request a waiver for pediatric assessments for bexagliflozin for

patients aged 0 to 9 years because studies would be impossible or highly impracticable, and to defer studies in patients aged 10 to 17 years.

C-476 Protocol Review

The Sponsor submitted protocol C-476, entitled “A double blind placebo-controlled study to evaluate the effects of bexagliflozin on hemoglobin A1c (HbA1c) in patients with type 2 diabetes and increased risk of cardiovascular adverse events” on May 15, 2015. A letter containing statistical and clinical comments and requests was issued by the Agency on July 30, 2015. A copy of the clinical endpoint committee (CEC) Charter was also requested for review. The Sponsor provided responses to FDA’s comments/requests on October 7, 2015. In addition, the CEC Manual of Operations (i.e., adjudication charter for MACE events), DSMB Charter, and meta-analysis plan was provided for FDA review and comment. Additional feedback from the Divisions of Biometrics II and VII was provided January 8, 2016, to which the Sponsor provided responses on February 23, 2016.

On July 8, 2016, the Agency received a request for a Type C guidance meeting to follow-up on the clinical discussions that occurred during the EOP2 meeting. The Sponsor requested FDA agreement regarding updated inclusion/exclusion criteria for C-476 (e.g., change HbA1c criteria from >7.5%-<11% to >7%-<11%; allowance of enrollment of subjects with a diagnosis of heart failure (HF) with preserved left ventricular ejection fraction [LVEF]). FDA stated that these changes to the protocol are generally acceptable given that heart failure is an exploratory endpoint in C-476.

(b) (4)

PreNDA Meeting

On October 1, 2019, FDA received a request for a preNDA meeting. Final meeting minutes were issued December 17, 2019. The meeting focused on the proposed NDA package and its sufficiency to support a marking application for bexagliflozin for the treatment of T2DM.

12.2. Statistical Regulatory History

The Division of Metabolism and Endocrinology Products (DMEP)⁴ received Theracos’ IND 103822 for bexagliflozin for treatment of T2DM on January 7, 2009. Since then, the FDA statistical team has been providing review comments/statistical advice to the Sponsor regarding study design and analysis methodologies.

⁴ After Center for Drug Evaluation and Research (CDER)’s 2019 reorganization, Division of Diabetes, Lipid Disorders, and Obesity (DDLO).

The statistical advice has been focused on aspects of missing data related to trial design and analysis methods: missing data prevention, estimand, and missing data handling strategies. Among them, advice common to all pivotal trials are summarized below.

- FDA considers the treatment policy estimand critical to support effectiveness.
- Provided advice on strategies for missing data prevention
- Reiterated the importance of “off treatment” data collection
- Analysis population should include all randomized subjects regardless of treatment adherence or availability of follow-up data.
- For the primary analysis model, at different stages, the following advice has been given:
 - Advice against the last observation carried forward (LOCF) approach in missing data handling;
 - Advice against the mixed model repeated measures (MMRM) approach in missing data handling;
 - Recommended addressing missing data by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement;
 - Recommended retrieved drop-out based pattern mixture modeling approach; in case the retrieved drop-out is not enough to support this analysis, recommended a return-to-baseline approach in missing data handling.
- Recommended to use sensitivity analyses to study the limitation of the missing data assumptions made in the primary analysis.
 - Recommended the tipping point sensitivity analysis

Theracos’ IND phase responses to the above FDA advice is summarized below:

- Implemented actions in all phase 2/3 controlled studies to minimize missing data
- The Sponsor still proposed MMRM as primary analysis for all studies, even though the Sponsor agrees that MMRM cannot be used to account for missing data entirely.
- The primary analysis will include the post-rescue data.
- Proposed a list of sensitivity analysis including the tipping point analysis method.

A comprehensive chronological listing of the key FDA statistical advice/comments and the Sponsor’s responses can be found in [Table 54](#).

Table 54. Summary of Regulatory History – Statistical Advice – Efficacy

Date Received/ Submission SDN	Review DARRTS Date	FDA Advice/Sponsor Responses
May 6, 2015/64	July 08, 2015	- Analysis population should include all randomized subjects regardless of treatment adherence or availability of follow-up data - FDA deems the treatment policy estimand critical to support effectiveness - Use sensitivity analyses to study the limitation of the primary analysis
November 09, 2016 /79	May 12, 2017	- Advised against the MMRM approach in missing data handling; - Recommended addressing missing data by having the missing data from subjects who do not adhere to therapy represented by the data from those subjects on the same arm that also did not adhere to therapy but had the measurement; - Recommended post treatment discontinuation data collection - Unequal randomization design with heterogeneous variability may result in type I error inflation. Proposed analysis should take into account this consideration.
January 10, 2017 /82	May 12, 2017	- Review comments common to Study 450, 480 and 448 (Protocol V4): - Recommendations on trial conduct for missing data prevention. - Advice against MMRM approach - Noted inadequacy in sensitivity analysis planning - Study 450 Protocol V3 review comments: - Potential Type I error inflation in an unequal randomization design setting (as described above for study 476). - Study 480 Protocol V3 review comments: - Request justifications for the choice of the noninferiority margins of 0.35% in protocol THR-1442-480, regardless of if the noninferiority margin was used in previous studies. A justification should be based on the effect of glimepiride (the active control) on HbA1c from previous clinical trials in the same or similar clinical trial setting as the proposed clinical trial. - Disagreement on hypoglycemia event rate as a key secondary endpoint in a noninferiority study setting, as it would be difficult to interpret the hypoglycemia results especially in a scenario when noninferiority is declared but do not achieve superiority/equivalence for the primary endpoint on hyperglycemic control. Noninferiority does not imply equivalence of the test drug and the control.
April 26, 2017 /87		- Study 450 Protocol V4 Submission - FDA didn't review the submission
August 29, 2017 /95		Sponsor Responses to FDA Comments

Date Received/ Submission SDN	Review DARRTS Date	FDA Advice/Sponsor Responses
September 25, 2017 /98	• December 18, 2017	• Study 419 Protocol V1 review comments: • Maintain 0.025 one sided type I error in conducting testing for endpoints of interest. • Study 423 Protocol V2 review comments: • Request justifications for the choice of the noninferiority margin of 0.35% in protocol THR-1442-480, regardless of if the noninferiority margin was used in previous studies. A justification should be based on the effect of sitagliptin (the active control) on HbA1c from previous clinical trials in the same or similar clinical trial setting as the proposed clinical trial. The noninferiority margin should be informed by the considerations described in the draft Guidance for Industry - Noninferiority Clinical Trials (November 2016) and should be adequately justified. • Review comments common to Study 419 & Study 423 • Clarification on secondary and exploratory endpoints specifics, such as timing of endpoints and analysis methods • Recommendations on trial conduct for missing data prevention. • Advice against the MMRM approach in missing data handling; • Inadequacy in sensitivity analysis planning • Recommendation of Tipping Point sensitivity analysis
December 20, 2017 /100	February 01, 2018	• Study 476 SAP V1 review comments: • Reiteration of disagreement with the proposed MMRM for primary analysis • Advice against LOCF methodology • Strongly recommend on continually collecting off-treatment data. • For the proposed control based multiple imputation sensitivity analysis, recommended the use of a “washout” approach multiple imputation. • Recommendation on a consistent analysis window definition across timepoints. • Study 476 is powered for safety endpoint MACE+ assessment, it is overpowered for HbA1c assessment. In this case, both statistical significance and clinical meaningfulness are requirements for treatment benefit determination. • Note: Study 476 - substudies • Study 476 SAP V2 (November 21, 2019) was not submitted to FDA for a review. Study 476 database was locked on November 22, 2019. The Sponsor newly added a key secondary endpoint, “Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes “ in protocol V7 (October 12, 2016) and described as a substudy in SAP V2. • For a subset who have been prescribed sulfonylurea, the Sponsor newly added HbA1c changes from baseline to Week 24 for this subset as an exploratory endpoint and described as substudy in SAP V2 (November 21, 2019). • These two subsets were not used as randomization stratification factors. • PreNDA meeting package was received (November 4, 2019) and C-476 substudies were not discussed during the preNDA meeting (December 5, 2019) based on meeting minutes issued on December 15, 2019.

Date	Received/ Submission SDN	Review DARRTS Date	FDA Advice/Sponsor Responses
March 09, 2018 /102			• Study 423 Responses: • For Trial C-423, the Sponsor proposed a hierarchical testing procedure for primary and key secondary endpoints to control the overall type I error rate at one-sided 0.025. • Study 419 Responses: • For Trial C-419, the Sponsor stated that only the primary endpoint will be formally tested. • For study 423, the Sponsor proposed multiple imputation for missing data under an assumption that nonadherent subjects with missing data will follow the same trajectory of nonadherent subjects with values observed to explore the impact of missing data. Tipping point analysis will also be conducted but excluding the post-rescue data. Missing data in the Bexagliflozin group will be imputed with penalized delta from 0.1 to 0.5. Missing data in the comparator group will be imputed with rewarded delta from 0.1 to 0.5. • General Responses common to both trials • Implemented actions in all phase 2/3 controlled studies to minimize missing data • The Sponsor still proposed MMRM as the primary analysis for both studies, even though the Sponsor agrees that MMRM cannot be used to account for missing data entirely. The primary analysis will include the post-rescue data.
March 09, 2018 /102		May 21, 2018	• Review Comments for Study 419 and Study 423 (Protocol Amendments in addressing December 22, 2017 FDA comments) • Recommend a “retrieved dropout” analysis for handling missing data as the primary analysis. • Reiteration of disagreement with the proposed MMRM for primary analysis • Recommend including all observed data (including post-rescue data) in the sensitivity analyses to explore the impact of missing data.

Source: FDA statistical reviewer

Abbreviations: DARRTS: The Document Archiving, Reporting and Regulatory Tracking System; SDN, supporting document number; V, Version; LOCF, last observation carried forward; MACE+, 4-points major adverse cardiovascular events; MMRM, mixed model repeated measures; SAP, statistical analysis plan.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the Investigational New Drug Application

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

See section [5.1](#).

13.1.1.2. Secondary Pharmacology

Bexagliflozin showed no notable off-target effects when screened against a panel of 70 enzymes, receptors, transporters, and ion channels.

13.1.1.3. Safety Pharmacology

Table 55. Safety Pharmacology Studies

Study	Key Findings
THR-1474-N-322: Neuropharmacological Profile (NPP) of EGT0001474 in Rats Sprague-Dawley rats 10 males/group 0 (30% PEG400), 20, 67, 200 mg/kg Single dose, oral gavage	Bexagliflozin did not cause adverse effects in a functional observational battery (FOB) evaluation at doses up to 300 mg/kg (AUC _{0-24h} : 474,385 ng.h/mL, 377-fold exposure at the MRHD)
THR-1474-N-323: Evaluation of Respiratory Function Following Oral Administration of EGT0001474 in Rats Sprague-Dawley rats 6 males/group 0 (30% PEG400), 20, 67, 200 mg/kg Single dose, oral gavage	Decreased respiratory rate and minute volume (17% and 16% vs. control, respectively) for up to 6 hours postdose, the last time point evaluated, were observed at all doses ($\geq 13,697$ ng.h/mL, 11-fold MRHD). The magnitude of these changes was similar across all bexagliflozin treatment groups. Although no NOAEL was identified, similar findings were absent in repeat-dose rat and monkey toxicology studies.
THR-1474-N-325: Effects of EGT0001474 on Cloned hERG Potassium Channels expressed in Human Embryonic Kidney Cells Concentrations: 0, 10, 25 μ M (reached solubility limit of EGT0001474 in DMSO)	Bexagliflozin did not affect hERG channel-mediated potassium current in HEK293 cells up to the maximum tested concentration of 25 mM (17,380 ng/mL, 99-fold MRHD based on clinical C _{max} of 176 ng/ml)

Study	Key Findings
THR-1474-N-324: EGT0001474: Evaluation of Cardiovascular Function in Conscious Male Cynomolgus Monkeys Given Single Oral Doses Cynomolgus monkeys 4/group (using 3 days of washout period between doses) 0 (30% PEG400), 2, 20, and 200 mg/kg Single dose, oral gavage	Single oral doses of bexagliflozin did not adversely affect blood pressure, heart rate, cardiac rhythm, or ECG morphology in conscious telemetered cynomolgus monkeys at doses up to 200 mg/kg (337-fold MRHD).
THR-1442-N-383: Effects on Gastrointestinal Transit in Male Rats Following Oral Administration Sprague-Dawley rats 6 males/group 0 (30% PEG400), 7, 70, and 200 mg/kg or morphine 75 mg/kg Single dose, oral gavage	Bexagliflozin inhibited stomach emptying (increased stomach and content weight) by 36% at 200 mg/kg. Positive control, 75 mg/kg morphine, induced 145% increase in stomach plus content weight. NOAEL was 70 mg/kg (AUC_{0-24h}: 152,811 ng.h/mL, 121-fold MRHD).
THR-1442-384: Effects on Renal function in Male Rats Following Oral Administration Sprague-Dawley rats 6 males/group 0 (30% PEG400), 7, 70 and 200 mg/kg or furosemide 30 mg/kg Single dose, oral gavage	Increased urine volume and urine glucose, decreased urine electrolytes (Na⁺, K⁺, Cl⁻, Ca⁺, creatinine and protein) within 24 hours postdose, and increased urine specific gravity, plasma sodium, and plasma osmolality were observed within 6 hours postdose. Additionally, increased blood and/or myoglobin in urine and increased plasma phosphorus and creatinine at 24 hours postdose were noted at 200 mg/kg (532,157 ng.h/mL, 423-fold MRHD). Furosemide, a Na⁺-K⁺-2Cl⁻ cotransporter inhibitor, showed similar effects on urine output and urine electrolytes within 6 hours postdose, but no dehydration-related findings.

Source: Nonclinical reviewer

Exposure multiples were based on AUC derived from a rat 5-day study (THR-1442-T-385), a monkey 31-day study (THR-1474-T-337) in comparison with human AUC of 1259 ng.h/mL and C_{max} of 176 ng/mL at the MRHD of 20 mg (from food effect study THR-1442-C-481).

EGT0001474: Bexagliflozin

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; ECG, electrocardiogram; MRHD, maximum recommended human dosage; NOAEL, no observed adverse effect level

Absorption Distribution, Metabolism, Excretion (ADME)/Pharmacokinetics

Absorption

Following oral administration, bexagliflozin was rapidly absorbed with a time to maximum concentration (T_{max}) ranging between 0.4 to 2.5 hours in rats, dogs, and monkeys. Exposure (maximum plasma concentration [C_{max}] and area under the concentration-time curve [AUC_{0-t}]) generally increased in a dose-proportional manner. Oral bioavailability in rats, dogs, and monkeys ranged from 46% to 82%.

Table 56. Pharmacokinetic Parameters of Bexagliflozin Following Single Oral Doses

Dosage	Sex	T _{max} , h	C _{max} , ng/mL	AUC _{0-∞} , ng.h/mL	T _{1/2} , h	MRT, h	F, %
Rats, 3 mg/kg	M	2.56	813	5876	3.61	6.13	80.5
	F	2.50	914	8298	3.74	6.3	82.1
Dogs, 1 mg/kg	M	0.58	784	2579	3.78	4.48	64.9
	F	0.33	813	2790	3.87	4.74	77.3
Monkeys, 1 mg/kg	F	1.67	112	493	5.31	6.77	45.7

Source: Nonclinical reviewer

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity; C_{max}, maximum plasma concentration; F, bioavailability; MRT, mean residence time; T_{1/2}, half life; T_{max}, time to maximum plasma concentration.

Distribution

Bexagliflozin was 93 to 97% bound to plasma proteins across all species tested (human, rhesus monkeys, beagle dog, SD rat, and CD-1 mouse).

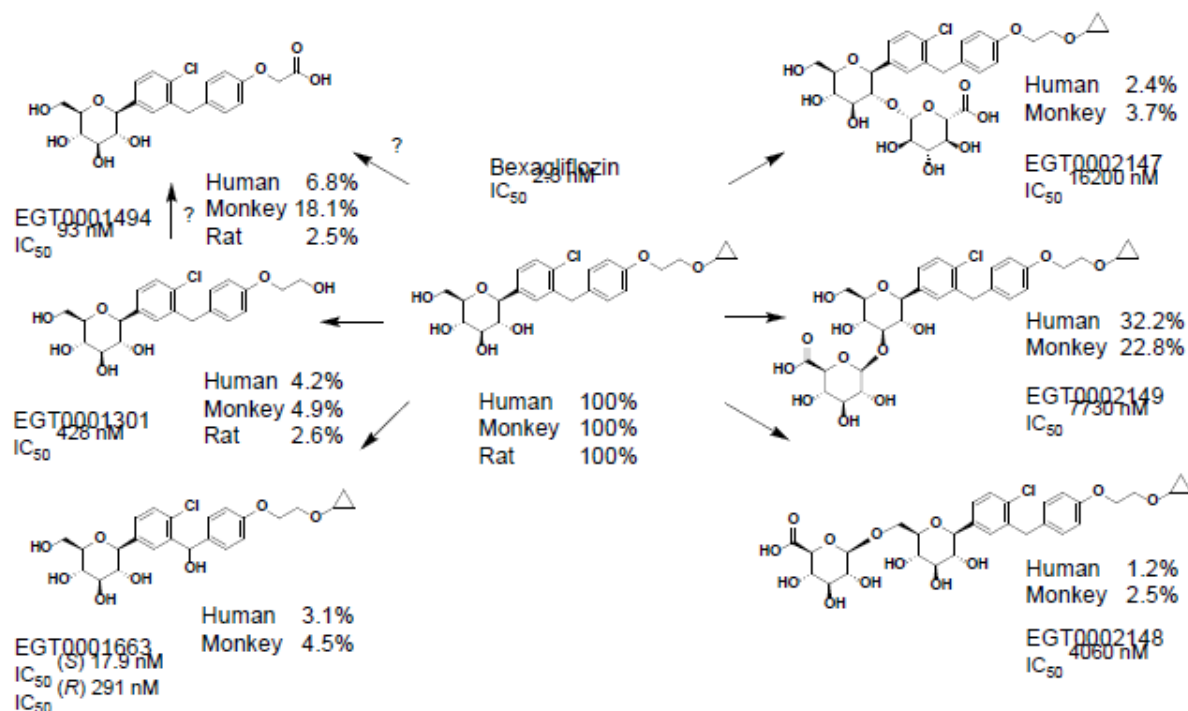
In a distribution study in rats, the kidney medulla and cortex, liver, adrenal cortex and medulla, pancreas, harderian gland, and preputial gland showed the highest bexagliflozin concentration between 4 to 12 hours postdose.

In lactating female rats, bexagliflozin distributed into maternal milk with a concentration higher than maternal plasma (1.4 to 1.8 times), which resulted in detectable plasma levels of bexagliflozin in nursing pups at levels 20 to 50 times lower than in milk. Levels in rat milk and nursing pups are not predictive of drug levels in human milk or nursing infants.

Metabolism

Metabolism studies were conducted in vitro using liver microsomes or recombinant cytochrome (CYP) P450 enzymes, and in vivo using radiolabeled test article. The metabolic profile was similar across the species tested and there were no unique or disproportionate human metabolites. Parent drug was the predominant drug-related component in the circulation in rats, monkeys, and humans. In humans, the majority of biotransformation appears to be by phase II metabolism and the most abundant circulating metabolite was glucose 3'-O-gluconide (32.8% in humans versus 22.8% in monkeys), which was considered qualified given the high clinical exposure multiples achieved in monkeys. An additional oxidative metabolite, EGT0001494, was also observed in monkeys. Oxidative metabolites (EGT0001301, EGT0001663, EGT0001494) were identified in incubations with animal and human liver microsomes, as well as in animal studies, with EGT0001301 (O-dealkylated metabolite) being the predominant metabolite. The metabolic enzymes CYP3A4 and UGT1A9 were responsible for the metabolism. After oral or intravenous dosing, the terminal plasma half-life of bexagliflozin in rats, dogs, and monkeys ranged between 3 to 5 hours.

Figure 19. Composite Metabolic Pathway for Rats, Monkeys, and Humans



The percentages shown for the species represents the plasma AUC proportionality relative to bexagliflozin. Rat data are from males, monkey data are averaged for sexes (no significant sex-dependent metabolism was observed) at a dose level of 60 mg kg⁻¹ day⁻¹, and human data are from 1 Black and 5 White male subjects administered a single oral dose of 50 mg [¹⁴C]-bexagliflozin (100 µCi) uniformly labeled in the glucose moiety. Data from studies THR-1474-N-368, -369 (rat), -403 (monkey) and THR-1442-C-410 (human). EGT0001663 is the racemic mixture of EGT0001684 and '1685, which co-elute under the chromatographic conditions used. IC₅₀ values are from THR-1474-N-364 and THR-1442-N-488.

source: Fig. 2.6.4-15 in the submission

Abbreviations: AUC, area under the concentration-time curve; IC₅₀, half maximal inhibitory concentration

No induction/inhibition of drug metabolizing enzymes and/or drug-drug interactions were observed (Section 5).

Excretion

Following an oral dose of radio-labeled bexagliflozin, fecal excretion was the primary route of elimination, accounting for 86.6% and 54.1% in rats and monkeys, respectively. Urinary excretion was the secondary route, accounting for 14.4% and 29.2% in rats and monkeys, respectively. The radiolabel in excreta consisted mainly of parent drug.

Table 57. Composition of Radiolabel in Excreta (% of Input Label)

Composition	Feces		Urine	
	Rat	Monkey	Rat	Monkey
Bexagliflozin	61.5%	15.3%	3.5%	5.4%
EGT0001494 + EGT0001301	16.5%		8.7%	

Source: Nonclinical reviewer

Toxicokinetic Data

Systemic exposures in rats and monkeys were generally dose proportional. No accumulation occurred with repeated dosing. Safety margins were calculated based on average AUC for males and females unless otherwise specified, using a clinical exposure of 1259 ng.h/mL at the maximum recommended human dosage (MRHD) of 20 mg/day.

Table 58. Toxicokinetic Studies

Study/Styd No.	Major Findings					
26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study with Bexagliflozin in Rats with a 4-Week Recovery Phase Sample collection times: 1, 2, 4, 12 and 24 hrs postdose on Day 1, Weeks 4 and 24 NOAEL: 10 mg/kg/day Safety Margin: 20-fold	Bexagliflozin Toxicokinetics in Rats, Day 1					
	Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng•hr/mL)
	7	1	M	311	1.00	2173
			F	401	1.00	2459
	8	3	M	1157	1.00	6913
			F	1330	2.00	8041
	9	10	M	3003	2.00	20770
			F	4050	2.00	25257
	10	30	M	7520	2.00	71995
			F	11003	2.00	89414
Bexagliflozin Toxicokinetics in Rats, Week 24						
Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng•hr/mL)	
7	1	M	338	1.00	2089	
		F	509	2.00	2874	
8	3	M	916	1.00	5804	
		F	1467	1.00	8900	
9	10	M	2893	1.00	20288	
		F	5117	2.00	29273	
10	30	M	8960	2.00	54031	
		F	16567	2.00	112292	

Study/Styd No.	Major Findings								
39-Week Nasogastric Intubation Toxicity and Toxicokinetic Study with Bexagliflozin in Cynomolgus Monkeys with a 4-Week Recovery Period Sample collection times: 1, 2, 4, 12 and 24 hrs postdose on Day 1, Weeks 4, 13 and 39 NOAEL: 60 mg/kg/day Safety Margin: 78-fold	Bexagliflozin Toxicokinetics in Monkeys, Day 1								
	Dose Group	Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} (ng/mL) (mg/kg/day)	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)
	2	2	M	Mean	298	149	2.75	2707	2707
			F	Mean	382	191	2.75	2980	2980
	3	6	M	Mean	874	146	3.50	8412	8412
			F	Mean	801	134	3.25	8098	8098
	4	20	M	Mean	2510	126	4.67	26201	26201
			F	Mean	3177	159	3.17	27788	27788
	5	60	M	Mean	13723	229	3.17	107050	107050
			F	Mean	10898	182	2.50	93492	93492
Developmental Toxicity and Toxicokinetic Oral Gavage Study with Bexagliflozin in Rats Sample collection times: 1, 2, 4, 12 and 24 hours postdose on GD6 and GD17. NOAEL: 200 mg/kg Safety margin: 551-fold	Bexagliflozin Toxicokinetics in Monkeys, Week 39								
	Dose Group	Dose Level (mg/kg/day)	Sex		C _{max} (ng/mL)	DN C _{max} (ng/mL) (mg/kg/day)	T _{max} (hr)	AUC ₀₋₄ (ng·hr/mL)	AUC ₀₋₂₄ (ng·hr/mL)
	2	2	M	Mean	245	123	3.33	3058	3058
			F	Mean	522	261	1.50	3370	3370
	3	6	M	Mean	738	123	2.25	8943	8943
			F	Mean	962	160	1.75	9146	9146
	4	20	M	Mean	2715	136	2.17	31529	31529
			F	Mean	3355	168	2.33	33260	33260
	5	60	M	Mean	9783	163	2.50	97462	97462
			F	Mean	9002	150	1.83	99135	99135
Developmental Toxicity and Toxicokinetic Oral Gavage Study with Bexagliflozin in Rabbits Sample collection times: 1, 2, 4, 12 and 24 hours postdose on GD6 and GD17. NOAEL: 25 mg/kg Safety margin: 34-fold	Bexagliflozin Toxicokinetics in Pregnant Rats								
	Dose, mg/kg	Time point		C _{max} , ng/mL		AUC _{0-24h} , ng.h/mL		T _{1/2} , hrs	
	7	GD6		2627		24972		3.07	
		GD17		2533		23622		3.45	
	40	GD6		15233		149668		NA	
		GD17		13300		136848		NA	
	200	GD6		77767		763803		NA	
		GD17		69900		694193		4.93	
	Source: Nonclinical reviewer								
	Developmental Toxicity and Toxicokinetic Oral Gavage Study with Bexagliflozin in Rabbits Sample collection times: 1, 2, 4, 12 and 24 hours postdose on GD6 and GD17. NOAEL: 25 mg/kg Safety margin: 34-fold	Bexagliflozin Toxicokinetics in Pregnant Rabbits							
Dose, mg/kg		Time point		C _{max} , ng/mL		AUC _{0-24h} , ng.h/mL		T _{1/2} , hrs	
5		GD7		1013		4044		NA	
		GD20		1124		4859		7.06	
25		GD7		4993		33524		NA	
		GD20		6030		42905		8.92	
150		GD7		63000		354525		4.93	
		GD20		54333		463447		4.90	
Source: Nonclinical reviewer									

Study/Study No.	Major Findings					
Oral gavage study for effects on pre- and postnatal development, including maternal function, with Bexagliflozin in rats Sample collecting times: 2, 4, 12 and 24 hours postdose on lactating Day 20 F1 NOAEL: 40 mg/kg Safety margin: 79-fold	Bexagliflozin Toxicokinetics in F0 Female Rats at LD20					
	Group	Dose Level (mg/kg/day)		C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)
	2	7.0	Mean	1840	2.67	15700
			SD	480	1.15	2530
			N	3	3	3
	3	40.0	Mean	7970	6.00	100000
			SD	2400	5.29	20300
			N	3	3	3
	4	200.0	Mean	34600	2.67	455000
			SD	8320	1.15	61300
			N	3	3	3

Source: Nonclinical reviewer

Summary of Bexagliflozin Toxicokinetic Parameters on PNDs 21 and 90									
Dose Group	Dose Level (mg/kg/day)	Sex	T _{max} (h)	C _{max} (ng/mL)	AUC ₍₀₋₂₄₎ (h·ng/mL)	T _{1/2} (h)	AR		
							C _{max}	AUC ₀₋₂₄	
PND 21	2	Male	2.00	142	1580	4.33	NC	NC	
		Female	2.00	154	1380	4.47	NC	NC	
		Male/Female	2.00	148	1480	4.39	NC	NC	
	3	Male	2.00	1550	14800	3.72	NC	NC	
		Female	2.00	1620	16000	3.15	NC	NC	
		Male/Female	2.00	1580	15400	3.45	NC	NC	
	4	Male	2.00	10800	80500	5.24	NC	NC	
		Female	2.00	10500	126000	4.72	NC	NC	
		Male/Female	2.00	10700	103000	4.92	NC	NC	
	PND 90 2	Male	4.00	147	1370	NR	1.04	0.865	
		Female	4.00	193	1980	NR	1.26	1.43	
		Male/Female	4.00	170	1670	NR	1.15	1.13	
PND 90	3	Male	4.00	1510	14100	NR	0.972	0.955	
		Female	1.00	1990	14400	3.58	1.23	0.905	
		Male/Female	1.00	1470	14300	3.43	0.929	0.929	
	4	Male	4.00	13000	160000	NR	1.21	1.99	
		Female	2.00	16200	175000	2.91	1.53	1.39	
		Male/Female	4.00	12400	167000	NR	1.16	1.62	

PND = Postnatal day; NC = Not calculated.
NR: Not reported due to an inability to characterize the elimination phase per Test Site SOP criteria.
Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

Bexagliflozin Toxicokinetics in 2-Year Rat Study						
Interval	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)	
Day 1	3	M	587	2.00	4047	
		F	805	2.00	5896	
	10	M	2010	4.00	16331	
		F	3270	2.00	23472	
	30	M	8913	2.00	50122	
		F	10847	2.00	78885	
Week 26	3	M	645	2.00	4334	
		F	1079	2.00	7446	
	10	M	1873	2.00	14702	
		F	3587	2.00	24555	
	30	M	8183	2.00	50248	
		F	14300	2.00	85423	

Study/Std No.	Major Findings												
104-Week Oral Carcinogenicity Study of Bexagliflozin in CD-1 Mice NOAEL 150 mg/kg, Safety margins: 135-fold	Bexagliflozin Toxicokinetics in 2-Year Mouse Study												
	Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]	T _{max} (hr)	AUC ₀₋₂₄ (ng hr/mL)	DN AUC ₀₋₂₄ [(ng hr/mL)/(mg/kg/day)]	AUC _{0-∞} (ng hr/mL)	t _{1/2} (hr)	CL/F (mL/hr/kg)	V _d /F (mL/kg)
	Day 1	6	15	M	3113	208	1.00	12677	845	12696	2.71	1181	4618
				F	2830	189	1.00	11794	786	11799	2.12	1271	3885
		7	50	M	16433	329	1.00	66698	1334	66734	2.17	749	2348
				F	11083	222	1.00	42696	854	42852	2.77	1167	4664
		8	150	M	44900	299	1.00	232049	1547	232206	2.21	646	2063
				F	41033	274	1.00	188811	1259	188888	2.07	794	2370
	Week 26	6	15	M	2697	180	1.00	10700	713	NA	3.05	1402	6174
				F	2107	140	1.00	10703	714	NA	2.51	1401	5081
		7	50	M	12273	245	1.00	51324	1026	NA	2.40	974	3378
				F	8333	167	2.00	41636	833	NA	2.61	1201	4517
		8	150	M	42200	281	1.00	144972	966	NA	2.67	1035	3983
				F	46433	310	1.00	196131	1308	NA	2.20	765	2424
NA: Not applicable.													

NA: Not applicable.

Source: Reviewer generated table

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; CL/F, apparent clearance; C_{max}, maximum plasma concentration; NOAEL, no observed adverse effect level; PND, postnatal day; T_{1/2}, half life; T_{max}, time to maximum plasma concentration

13.1.1.4. Toxicology

13.1.1.4.1. General Toxicology

26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study With Bexagliflozin in Rats With a 4-Week Recovery Phase

Key Study Findings

- Rats were administered bexagliflozin by oral gavage at doses of 1, 3, 10, or 30 mg/kg/day for 26 weeks
- Consistent with the intended pharmacology, marked glucosuria and slightly decreased plasma glucose levels were observed in all bexagliflozin treatment groups.
- Chronic progressive nephropathy (CPN), particularly in the male treatment groups, was observed at ≥ 3 mg/kg. The severity of this finding remained increased in the high dose recovery males (slight/moderate). CPN is a common background finding in aging male Sprague Dawley rats and is generally not considered to be relevant to human risk.
- A low incidence and severity (minimal to slight) of glandular stomach erosion/ulcer was observed in all male treatment groups, not dose-related, at Week 26 or after 4 weeks of recovery, and in high dose females at Week 26. Similar stomach findings have been observed with other sodium-glucose cotransporter 2 (SGLT2) inhibitors. The clinical relevance of stomach erosion is likely limited considering the low incidence and severity and due to the absence of similar findings in other species (monkeys with bexagliflozin and dogs with other drugs in this class), as well as in humans with other drugs in this class.
- The no observed adverse effect level (NOAEL) was considered 30 mg/kg (54031 and 112292 ng·h/mL, 43- and 89-fold MRHD, respectively).

Table 59. Study Information for 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study in Rats

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 1, 3, 10, 30 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	30% PEG400 in water
Species/strain:	Rats, Sprague Dawley
Number/sex/group:	Main study: 10/sex/group Recovery phase: 5/sex/group for control, mid, high, and high dose groups
Age:	6 weeks old
Satellite groups/unique design:	TK animals: 6/sex/dose groups, 3/sex/control
Deviation from study protocol affecting interpretation of results:	None affecting the interpretation of the data

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice; TK toxicokinetic.

Table 60. Observations and Results for 26-Week Oral Gavage Chronic Toxicity and Toxicokinetic Study in Rats

Parameters	Major Findings
Mortality	None
Clinical signs	Rough hair coat was observed for individual males in the 10 and 30 mg/kg/day male groups and for most groups including the control in the female treated animals.
Body weights	No statistically significant body weight changes
Ophthalmoscopy	No remarkable findings
ECG	Not performed
Hematology	No remarkable findings
Clinical chemistry	Relative to control, decreased serum glucose (up to -25%), increased urea nitrogen (up to 2-fold) and ALT (up to 1.6-fold) were observed in bexagliflozin treated groups. All these findings resolved after 4 weeks of recovery period.
Urinalysis	Consistent with the test article pharmacology, dose-related increases in urinary glucose concentration (up to 445-fold), glucose excretion (>1000-fold), urine volume (up to 2-fold) and specific gravity (up to 1.5-fold) were observed. All findings resolved after 4 weeks of recovery period.
Gross pathology	Bexagliflozin treatment groups showed discolored (black, ran, red or dark red) foci in the mucosa of the glandular stomach (males at ≥ 3 mg/kg/day; females at 30 mg/kg/day) which correlated with microscopic findings of minimal to slight erosion/ulcer.
Organ weights	Increased organ weights in the kidney (up to 30.5%), adrenal gland (up to 20%), and liver (up to 14%), and decreased prostate gland weight (up to -28%) were observed in bexagliflozin treatment groups, in a dose-related manner. Organ weight changes in the liver, adrenal and prostate did not correlate with microscopic changes.

Parameters	Major Findings																																												
Histopathology	Bexagliflozin treatment exacerbated chronic progressive nephropathy in males and caused glandular stomach erosion/ulcer in both males and females. These findings were not resolved or only partially resolved after 4 weeks of recovery period.																																												
Adequate battery:	Chronic progressive nephropathy (CPN) represents a common rodent-specific finding that typically increases in incidence and severity with age in rats, with males more greatly affected than females. The CPN was characterized by dilated tubules filled with proteinaceous fluid in the inner cortical region and basophilic regenerating tubules in the cortex with aggregates of pigment-laden macrophages within the interstitium around regenerating tubules.																																												
Yes	Minimal to slight glandular stomach erosion/ulcer, characterized by minimal to moderate degeneration of gastric epithelium associated with submucosal edema and/or submucosal inflammation in more extensive lesions, was observed in all treated male groups, not dose related, and in high dose females. This finding was still present in high dose males after the recovery period.																																												
	Incidence (Average Severity) ^a of EGT0001442-related Findings -Dosing Phase																																												
	<table><tr><th>Sex:</th><th colspan="5">Males</th><th colspan="5">Females</th></tr><tr><th>Dose Level (mg/kg/day):</th><td>0</td><td>1</td><td>3</td><td>10</td><td>30</td><td>0</td><td>1</td><td>3</td><td>10</td><td>30</td></tr><tr><th>Group:</th><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr><tr><th>Number Examined:</th><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td><td>10</td></tr></table>	Sex:	Males					Females					Dose Level (mg/kg/day):	0	1	3	10	30	0	1	3	10	30	Group:	1	2	3	4	5	1	2	3	4	5	Number Examined:	10	10	10	10	10	10	10	10	10	10
Sex:	Males					Females																																							
Dose Level (mg/kg/day):	0	1	3	10	30	0	1	3	10	30																																			
Group:	1	2	3	4	5	1	2	3	4	5																																			
Number Examined:	10	10	10	10	10	10	10	10	10	10																																			
Kidney																																													
Nephropathy, Chronic Progressive	10 (1.3) 9 (1.3) 9 (1.6) 9 (1.6) 10 (1.7) 4 (1.3) 2 (1.0) 5 (1.2) 5 (1.2) 4 (1.3)																																												
Stomach, Glandular Erosion/Ulcer	0 (0.0) 1 (1.0) 3 (1.7) 1 (2.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 3 (2.0)																																												
	a Average severity of animals with finding.																																												

Text Table 6
Incidence (Average Severity)^a of EGT0001442-related Findings -Recovery Phase

Sex:	Males					Females				
Dose Level (mg/kg/day):	0	1	3	10	30	0	1	3	10	30
Group:	1	2	3	4	5	1	2	3	4	5
Number Examined:	5	0	0	5	5	5	0	0	5	5
Kidney										
Nephropathy, Chronic Progressive	4 (1.3)	0	0	5 (1.4)	5 (2.2)	2 (1.0)	0	0	3 (1.0)	4 (1.0)
Stomach, Glandular Erosion/Ulcer	0 (0.0)	0	0	0 (0.0)	2 (2.0)	0 (0.0)	0	0	0 (0.0)	0 (0.0)

a Average severity of animals with finding.

Source: Applicant's submission

Source: Nonclinical reviewer
Abbreviations: ALT, alanine transferase; ECG, electrocardiogram.

39-Week Nasogastric Intubation Toxicity and Toxicokinetics Study With Bexagliflozin in Cynomolgus Monkeys With a 4-Week Recovery Period

Key Study Findings

- Monkeys were administered bexagliflozin orally at doses of 2, 6, 20, or 60 mg/kg/day for 39 weeks.
- Consistent with the intended pharmacology, marked glucosuria and slightly decrease in blood glucose concentration were observed in all bexagliflozin treatment groups.
- Kidney tubular vacuolation (minimal to slight in severity) was observed in all bexagliflozin treatment groups at Week 39 and in one recovery male at 20 mg/kg after 4 weeks of recovery period. This kidney finding is likely glucosuria-related and not toxicologically significant.

- A focal stomach erosion/ulcer of slight severity was observed in two females, one each at 2 mg/kg and 60 mg/kg. The finding is likely incidental due to the low incidence and absence of dose-relationship.
- NOAEL is 60 mg/kg (sex combined AUC_{0-24h} of 98299 ng.h/mL, 78-fold MRHD_{AUC} of 20 mg) based on lack of toxicologically significant findings in the study.

Table 61. Study Information for 39-Week Nasogastric Intubation Toxicity and Toxicokinetics Study in Cynomolgus Monkeys

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 2, 6, 20 and 60 mg/kg/day
Route of administration:	Nasogastric intubation
Formulation/vehicle:	30% PEG400 in water
Species/strain:	Monkey/Cynomolgus (<i>Macaca fascicularis</i>)
Number/sex/group:	Main study: 4/sex/group Recovery: 2/sex for vehicle, mid, high, (20 mg/kg) and high dose (60 mg/kg)
Age:	2-5 years
Satellite groups/unique design:	No
Deviation from study protocol affecting interpretation of results:	None affecting interpretation of the data

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice

Table 62. Observations and Results: for 39-Week Nasogastric Intubation Toxicity and Toxicokinetics Study in Cynomolgus Monkeys

Parameters	Major Findings
Mortality	No treatment related mortality
Clinical signs	No remarkable findings
Body weights	No statistically significant changes.
Ophthalmoscopy	No remarkable findings
ECG	No test article-related changes at study days 91 or 274, or in recovery animals
Hematology	No remarkable findings
Clinical chemistry	Compared to baseline, blood glucose concentration was decreased in bexagliflozin treatment groups without a dose relationship. This finding was resolved by Day 27 of the recovery phase.
Blood Glucose Changes From Baseline at Treatment Day 273	
Dose, mg/kg	0 2 6 20 60
Males	-8% -32% -22% -19% -38%
Females	-31% -41% -19% -43% -29%
Source: Nonclinical reviewer	
Urinalysis	Consistent with the expected pharmacology, marked increases in urine glucose concentration (up to 683-fold) and urinal glucose excretion (up to 955-fold) was noted in both males and females at Days 86 and 273. No clear pattern of urine volume change was noted. Recovery animals showed no glucosuria after 4 weeks of recovery period.
Gross pathology	No remarkable findings

Parameters	Major Findings
Organ weights	The liver weight was increased in all bexagliflozin treated groups (up to 1.2-fold in males and 1.1-fold in females) generally in a dose-related manner. This finding was not considered adverse given the absence of clinical chemistry or histopathology correlates.
Histopathology Adequate battery: Yes	Histopathology findings include kidney tubular cell vacuolation and stomach erosion/ulceration. The kidney finding was characterized by cytoplasmic microvacuolation in the cortical tubular cells, primarily in the basal region adjacent to basement membrane. This finding is likely glucosuria-related. Toxicological significance is unclear.

The stomach erosion/ulceration, presented as a slight degree of single focal lesion in the gastric mucosa, was observed in two females at 2 mg/kg and 60 mg/kg each. There was no evidence of any widespread degenerative (ulcerative) changes in the gastric mucosa from these animals. Given the low incidence and absence of dose-response, this finding is considered incidental.

All findings were reversible except for minimal kidney tubular vacuolation in one recovery male at 20 mg/kg.

Microscopic Findings in Monkeys at Week 39

Dose, mg/kg		0	2	6	20	60
Kidney tubule cell vacuolation	M				3 (1.0)	4 (1.0)
	F		4 (1.5)	2 (1.0)	3 (2.3)	3 (1.8)
Stomach focal erosion/ulcer	M					
	F		1 (2.0)			1 (2.0)

Source: Nonclinical reviewer

n=4/sex/dose, except n=3 for males at 2 mg/kg; blanks indicate zero incidence

In parenthesis: grade of severity in a scale of 5 (1 = minimal, 2 = slight, 3 = moderate, 4 = marked, 5 = severe).

Histopathologic Finding Incidence in Monkeys After Four Weeks of Recovery

Variable	Males			Females		
Dose, mg/kg	0	20	60	0	20	60
Kidney tubule cell vacuolation		1 (1)				

Source: Nonclinical reviewer

n=2/sex/dose

[Other evaluations]	Serum concentrations of bone turnover biomarkers PINP and CTx1 were evaluated at weeks 13 and 39, and after 4 weeks of recovery. There were no significant and/or a clear pattern of treatment-related changes. Based on these bone biomarker data, bone turnover/metabolism was not affected by bexagliflozin treatment.

Source: Reviewer generated table

Abbreviations: ECG, electrocardiogram; PINP, procollagen Type I N-terminal propeptide.

13.1.1.4.2. Genetic Toxicology

Bexagliflozin was not mutagenic or clastogenic in the Ames mutagenicity assay, in vitro mammalian chromosomal aberration assay, in vivo micronucleus test in rats, and in vivo unscheduled hepatic DNA synthesis in rats.

Table 63. Genetic Toxicology Studies

Study No/Study Title	Key Study Findings
THR-1474-n-374 Evaluation of EGT0001442 in the <i>Salmonella typhimurium</i> - <i>Escherichia coli</i> Reverse Mutation (Ames) Assay GLP compliant Study is valid	• Test strain: TA98, TA100, TA1535, TA1537 and WP2uvrA • Bexagliflozin concentration: 313 - 5000 mcg/plate, with or without metabolic activation ($\pm$S9) • Treatment duration: 48-72 hours • Cytotoxicity was observed at 5000 mcg/plate in most strains except TA100 • Neither a concentration-related increase nor a 2-fold increase in revertants in any of the tester strain at any test concentration or conditions were observed • Bexagliflozin was negative in this Ames assay
THR-1474-n-375 In Vitro Mammalian Chromosome Aberration Assay in Chinese Hamster Ovary Cells Challenged With EGT0001442 GLP compliant Study is valid	• Bexagliflozin concentration: 9 to 288 mcg/mL were selected based on cytotoxicity: 4h +S9, 18-144 mcg/mL; 4h-S9, 36-144 mcg/mL; 19h-S9, 9-36 mcg/mL) • Treatment duration: 4 hours $\pm$ S9; 19 hour -S9 • In the absence of S9, either 4-hour or 9-hour treatment, bexagliflozin did not produce a trend of increasing incidence of chromosomal aberrations. • In the presence of S9, bexagliflozin did cause a trend towards increasing chromosome aberrations. However, the vehicle control had an unusually low incidence of aberrant cells, bexagliflozin 36 μg/mL had very few evaluable metaphases due to a drug-related issues on cell attachment, and bexagliflozin 144 μg/mL had a cytotoxicity of 68%, which was outside the target range. Therefore, the positive trend observed was considered not biologically meaningful. • Bexagliflozin was negative for clastogenic potential in this study.
THR-1474-N-376 Rat Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of EGT0001474 GLP compliant Study is valid	• Sprague-Dawley rats (5/sex/group) were administered single oral doses of vehicle (30% PEG400), positive control (cyclophosphamide 40 mg/kg) or bexagliflozin 500, 1000 or 2000 mg/kg and were euthanized at 24-hour postdose for bone marrow collection. An additional group was administered vehicle or bexagliflozin 2000 mg/kg and were euthanized at 48-hour postdose. • Systemic exposure was confirmed at 2 hours postdose in all animals given bexagliflozin. • No mortality or bone marrow toxicities were observed. Bexagliflozin did not increase the incidence of micronucleated polychromatic erythrocytes (MPCE) at any dose levels at 24-hour or 48-hour sampling time. • Bexagliflozin was negative in the micronucleus test in rats

Study No/Study Title	Key Study Findings
THR-1442-N-398 Unscheduled DNA Synthesis (UDS) Study in Hepatocytes from Male Rats Given Single Oral Doses of EGT0001442 GLP complaint Study is valid	- Sprague Dawley rats (3/group per harvest timepoint) were administered single oral doses of vehicle (30% PEG400), positive control (DMN 35 mg/kg), or bexagliflozin at 1000 and 2000 mg/kg and were euthanized 2-4 hours or 12-16 hours postdose to harvest liver tissue. - Mean net nuclear grain count (MNNGC) was quantified by the tritiated thymidine incorporated into hepatocytes after 4 hours of incubation. - Bexagliflozin did not increase average MNNGC and is considered negative for genotoxic potential in this study.

Source: Nonclinical reviewer

Abbreviations: EGT0001474, EGT0001442: bexagliflozin; GLP, good laboratory practice.

13.1.1.4.3. Carcinogenicity

104-Week Oral Carcinogenicity Study of Bexagliflozin in Sprague-Dawley Rats

Male rats were administered bexagliflozin by oral gavage in 1% medium viscosity carboxymethylcellulose at 3, 10, and 30 mg/kg for 507 days (72.4 weeks) and then at 1, 3, and 10 mg/kg for additional 12, 5, and 2 weeks for the low dose, mid dose, and high dose group, respectively. In the male study, dosing was stopped at Week 75, 78, and 85 and the groups were terminated at Week 82, 85, and 88 at the high, mid, and low dose, respectively. Female rats were administered bexagliflozin at 3, 10 and 30 mg/kg for 100 weeks. Treatment-related findings included higher mortality in males, lower body weight (up to -14%) and higher food consumption (up to 26%) in both males and females. Treatment-related exacerbation of CPN and associated secondary findings (widespread vascular mineralization and diffuse hyperplasia of parathyroid gland), observed primarily in males, were considered to be the cause of death. There was no increase in the incidence of preneoplastic findings or tumors in any treatment group at doses up to 30 mg/kg/day.

The study in males was conducted at doses that exceeded those recommended by the Executive Carcinogenicity Assessment Committee (ECAC: 2, 7, and 20 mg/kg/day), which were selected based on adverse kidney findings (increased kidney weight and chronic progressive nephropathy) in a 6-month dose ranging study. ECAC and the Division considered the study in males inadequate to assess the risk of carcinogenicity because the duration of exposure was limited. However, based on the absence of preneoplastic findings and tumors in males exposed for up to 88 weeks at 3 times the MRHD and in females exposed for 100 weeks at doses up to 68 times the MRHD, repeating the carcinogenicity study in male rats was not considered warranted.

104-Week Oral Carcinogenicity Study of Bexagliflozin in CD-1 Mice

Mice were administered bexagliflozin by oral gavage at 0 (1% medium viscosity carboxymethylcellulose in water), 15, 50, or 150 mg/kg/day for approximately 2 years (males, 104 weeks; females, 97 weeks). The high dose of 150 mg/kg was selected based on AUC ratio and maximum tolerated dose (MTD) in males based on mortality at 120 to 160 times the clinical AUC. ECAC concurred with the Applicant's dose selection. No treatment-related non-neoplastic

or neoplastic findings were observed at doses up to 150 mg/kg, corresponding to an AUC of 170550 ng.h/mL (135 times the MRHD of 20 mg/day).

13.1.1.4.4. Reproductive and Developmental Toxicity

Oral Gavage Study of Fertility and Early Embryonic Development to Implantation With Bexagliflozin in Rats

Key Findings

There were no bexagliflozin-related adverse effects on male and female fertility or early embryonic development up to the highest dose of 200 mg/kg (237-fold MRHD_{AUC}, based on an AUC of 299,000 ng.h/mL derived from a 28-day rat study).

Table 64. Study Information for Oral Gavage Study of Fertility and Early Embryonic Development to Implantation With Bexagliflozin in Rats

Study Features and	
Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 2, 20, 200 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	30% PEG400 in water
Species/strain:	Rats, Sprague Dawley
Number/sex/group:	22/sex/dose
Age:	9 weeks old at initiation of the study
Study design:	Males were dosed for 10 weeks beginning from 28 days prior to mating, throughout the mating period until the day prior to termination. Females were dosed for 14 days prior to mating, throughout the mating phase (maximum 3 weeks) and gestation day (GD) 7.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice

Table 65. Observations and Results for Oral Gavage Study of Fertility and Early Embryonic Development to Implantation With Bexagliflozin in Rats

Parameters	Major Findings
Mortality	None
Clinical signs	During the premating phase, yellow and rough haircoat, and soft/liquid feces during early dosing days were observed in some animals at 200 mg/kg.

Body weights Lower body weight gain was observed in high dose males (-33%). No changes were observed in females during mating or gestation.

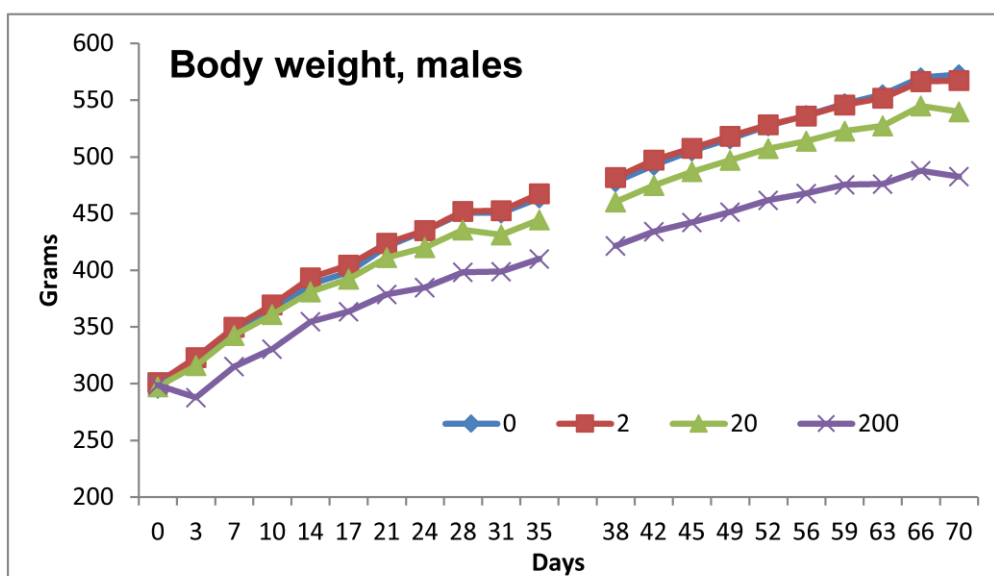
Body Weight (g) and Percentage Changes During Mating and Gestation

Variable		Dose, mg/kg				
		0	2	20	200	
Males	D0	296	301	297	298	
	D14	388	393	381	355	
	Δ% D14-D0	+31.0	+30.6	+28.3	+19.1	
	D71	579	571	547	490	
	Δ% D71-D0	+95.6	+89.7	+84.2	+64.4	
Female	Prior to mating	D0	213	212	213	214
		D14	251	250	247	256
		Δ% D14-D0	+17.8	+17.9	+16.0	+19.6
	Gestation	GD0	262	257	252	260
		GD7	306	299	291	292
		Δ% GD7-GD0	+16.8	+16.3	+15.5	+12.3
		GD13	342	336	329	327
		Δ% GD13-GD0	+30.5	+30.7	+30.5	+25.8

Source: Nonclinical reviewer

Abbreviations: GD, gestation day.

Body Weight During Mating and Gestation



Parameters	Major Findings																																																																											
	Body weight, mating, females <table><thead><tr><th>Days</th><th>0</th><th>2</th><th>20</th><th>200</th></tr></thead><tbody><tr><td>0</td><td>215</td><td>215</td><td>215</td><td>215</td></tr><tr><td>3</td><td>225</td><td>225</td><td>225</td><td>225</td></tr><tr><td>7</td><td>235</td><td>235</td><td>235</td><td>235</td></tr><tr><td>10</td><td>240</td><td>240</td><td>240</td><td>240</td></tr><tr><td>14</td><td>250</td><td>250</td><td>250</td><td>250</td></tr><tr><td>17</td><td>265</td><td>265</td><td>265</td><td>265</td></tr><tr><td>21</td><td>275</td><td>305</td><td>290</td><td>290</td></tr><tr><td>24</td><td>290</td><td>310</td><td>305</td><td>305</td></tr></tbody></table> Body weight, gestation <table><thead><tr><th>Days</th><th>0</th><th>2</th><th>20</th><th>200</th></tr></thead><tbody><tr><td>GD0</td><td>265</td><td>260</td><td>255</td><td>260</td></tr><tr><td>GD3</td><td>285</td><td>280</td><td>275</td><td>275</td></tr><tr><td>GD7</td><td>305</td><td>300</td><td>295</td><td>295</td></tr><tr><td>GD10</td><td>320</td><td>315</td><td>310</td><td>310</td></tr><tr><td>GD13</td><td>340</td><td>335</td><td>325</td><td>325</td></tr></tbody></table> Source: Nonclinical reviewer Abbreviations: GD, gestation day.	Days	0	2	20	200	0	215	215	215	215	3	225	225	225	225	7	235	235	235	235	10	240	240	240	240	14	250	250	250	250	17	265	265	265	265	21	275	305	290	290	24	290	310	305	305	Days	0	2	20	200	GD0	265	260	255	260	GD3	285	280	275	275	GD7	305	300	295	295	GD10	320	315	310	310	GD13	340	335	325	325
Days	0	2	20	200																																																																								
0	215	215	215	215																																																																								
3	225	225	225	225																																																																								
7	235	235	235	235																																																																								
10	240	240	240	240																																																																								
14	250	250	250	250																																																																								
17	265	265	265	265																																																																								
21	275	305	290	290																																																																								
24	290	310	305	305																																																																								
Days	0	2	20	200																																																																								
GD0	265	260	255	260																																																																								
GD3	285	280	275	275																																																																								
GD7	305	300	295	295																																																																								
GD10	320	315	310	310																																																																								
GD13	340	335	325	325																																																																								
Reproductive indices, necropsy findings Cesarean section data	No treatment-related effects were observed on copulation index for males, pregnancy index for females, sperm counts and motility, female estrus cycle, macroscopic examination on placenta, amniotic sac, number of live fetuses, number of early or late resorption, and the number of ovarian corpora lutea.																																																																											

Source: Reviewer generated table

Source: Reviewer generated table

Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rats

Key Findings

Maternal:

- Decreased gravid weight at 200 mg/kg/day (22%)
- Maternal NOAEL was 40 mg/kg/day (AUC_{0-24h} , 136848 ng.h/mL), which is 108-fold MRHD of 20 mg, based on AUC

Fetal:

- No remarkable findings in fetal viability, growth, or development
- Fetal NOAEL was 200 mg/kg (AUC_{0-24h} , 694193 ng.h/mL), 551-fold MRHD of 20 mg, based on AUC

Table 66. Study Information for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rats

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 7, 40, 200 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	30% PEG400 in water
Species/strain:	Rats, Sprague Dawley
Number/sex/group:	25 pregnant females/dose
Satellite groups	9 pregnant females/dose (3 for control group)
Age:	12 weeks old at initiation of treatment
Study design:	Pregnant rats were given test drug daily by oral gavage from GD6 to GD17 and were sacrificed on GD21. TK blood samples were collected on GD6 and GD17.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table

Abbreviations: GD, gestation day; GLP, good laboratory practice; TK, toxicokinetic.

Table 67. Observations and Results for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rats

Parameters	Major Findings
Mortality	No bexagliflozin-related deaths occurred
Clinical signs	Yellow haircoat or rough haircoat, and soft feces were observed at 200 mg/kg/day, predominantly between dosing days 2 and 8.

Body weights

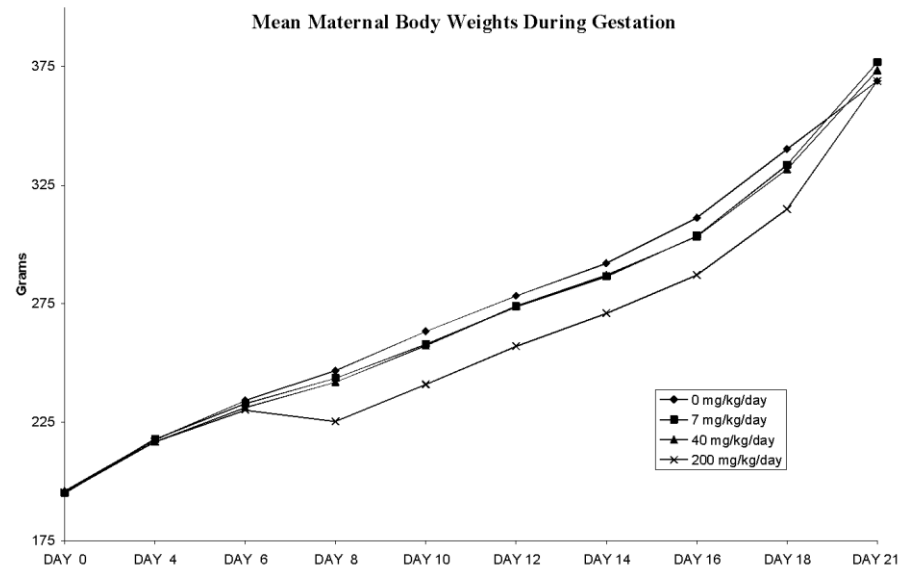
Dose-related lower body weight gain throughout the treatment period (up to -22% relative to control) was observed in Bexagliflozin treatment groups.

Mean Body Weight (g) and Relative Changes

Variable	Dose, mg/kg			
	0	7	40	200
GD6, g	231.4	232.8	231.2	230.2
GD18, g	340.2	333.5	331.6	314.8
GD18-GD6	108.8	100.7	100.4	84.6
Δ% over GD6	+47.0	+43.3	+43.4	+36.8
Δ% of control	100	92.0	92.4	78.2

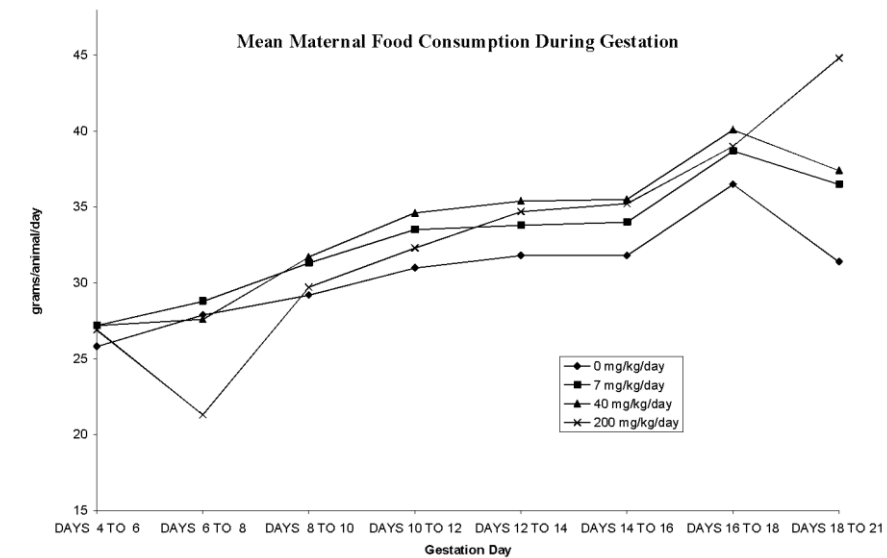
Abbreviations: GD, gestation day (GD6 = first day of dosing)

Maternal Body Weight



Source: Applicant's submission

Maternal Food Consumption



Source: Applicant's submission

Parameters	Major Findings
Necropsy findings Cesarean section data	Cesarean section data: Implantation sites, pre-implantation loss, and postimplantation loss were not affected by bexagliflozin treatment. Relative to control, postimplantation loss appears slightly increased in bexagliflozin treated groups (control, 0.7%; LD, 4.6%; MD, 1.7%; HD, 3.2%). However, there was no dose-relationship, and the percent increases were mostly within the historical range (0.8-4.2%). Therefore, the postimplantation findings were considered incidental. Offspring: Fetal weight and sex ratio were not affected by treatment and there were no malformations.

Source: Reviewer generated table
Abbreviations: LD, low dose; MD, medium dose; HD, high dose.

THR-1442-T-394: Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rabbits

Key Findings

Maternal:

- Abortions or moribund sacrifice with no viable fetuses at 150 mg/kg

Fetal:

- Significantly decreased gestational weight gain (-65%) at 150 mg/kg
- Malformations in two fetuses from two dams administered bexagliflozin 150 mg/kg: pulmonary trunk stenosis in one fetus and adipose tissue abnormal distribution, protruding tongue and abnormal position of the digits in the second fetus were noted. Although occurred at low incidence (litter incidence: 6.2% for each malformation, 12.4% for total malformations), these malformations are rare and possibly treatment-related, but they are not considered clinically relevant as they occurred at high exposure multiples (282-fold the MRHD based on AUC).
- NOAEL was 25 mg/kg (AUC_{0-24h}, 42,905 ng.h/mL, 34 times the MRHD based on AUC)) for both maternal and fetal toxicity.

Table 68. Study Information for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rabbits

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0 (sham control, reverse osmosis/distilled water), 0 (vehicle control), 5, 25, 150 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	30% PEG400 in water
Species/strain:	Rabbits, Hra: (NZW)SPF
Number/sex/group:	20 mated rabbit/dose group, with additional 10 sham control (reverse osmosis deionized water)
Satellite groups	3 mated females/dose group for TK analysis
Age:	5.5 months old at initiation of treatment
Study design:	Pregnant rabbits were administered bexagliflozin daily by oral gavage from GD7 through GD20 and were sacrificed on GD29. Blood samples for TK analysis were collected on GD7 and GD20.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table

Abbreviations: GD, gestation day; GLP, good laboratory practice; TK, toxicokinetic.

Table 69. Observations and Results for Developmental Toxicity and Toxicokinetic Oral Gavage Study With Bexagliflozin in Rabbits

Parameters	Major Findings
Mortality	Four animals at 150 mg/kg were removed from study either as moribund (two on GD16) or as a consequence of abortion (two on GD20). Clinical signs in these animals included few or no feces, red fluid in the cage pan, decreased body weight and food consumption. Necropsy findings were limited to a distended urinary bladder with yellow fluid in one moribund animal. There were no viable fetuses in the two moribund animals and four resorptions were noted in one animal that aborted
Clinical signs	Higher incidence of few or no feces were noted in the low dose (8/20) and high dose (6/20) groups relative to control (3/20)
Body weights	Dose-related lower gravid body weight gain was observed during treatment period. Compared to sham control, vehicle group also had significant lower body weight gain. Thus, it appears that both vehicle and bexagliflozin contributed to the finding. By GD29 (8 days after dosing cessation), the gravid body weights were still lower than sham control although less significantly.

Maternal Body Weight (g) and Percent Changes in Rabbits

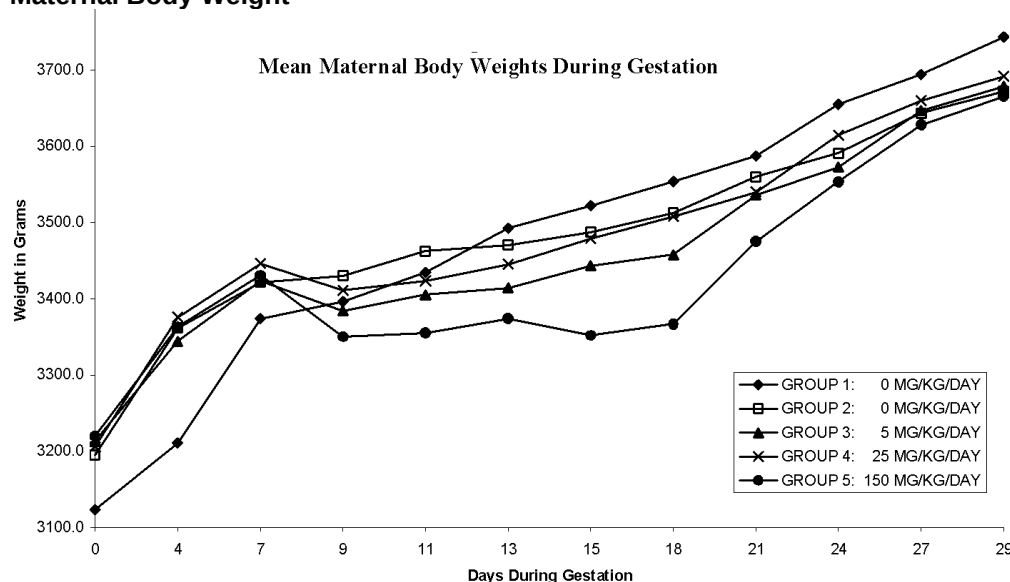
Variable	Group				
	Sham	Vehicle	LD	MD	HD
GD7, g	3374.1	3421.6	3423.8	3446.1	3430.9
GD21, g	3587.1	3559.9	3536.2	3540.2	3475.4
GD21-GD7, g	213.0	138.3	112.4	94.1	44.5
Δ% of GD7	+6.3	+4.0	+3.3	+2.7	+1.3
GD29, g	3743.5	3672.0	3678.8	3691.9	3666.0
GD29-GD21, g	156.4	112.1	142.6	151.7	190.6

Source: Nonclinical reviewer

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, medium dose.

Parameters Major Findings

Maternal Body Weight



Source: Applicant's submission

Necropsy findings Cesarean section data:
There were no viable fetuses in the two 150 mg/kg animals sacrificed moribund.
Cesarean section data Decreased food consumption (50%-100% reduction for 10 days prior to moribund sacrifice) and low body weight gain were observed in these animals, therefore the absence of viable fetuses is considered maternal toxicity related.
Gravid uterine weight was not affected. Excluding gravid uterine weight, maternal net weight gain during the pregnancy (GD4 to GD29) was decreased in a dose-related manner (sham, +19.98 g; vehicle, -154 g; LD, -183 g; MD, -178 g; HD, -197 g).
Postimplantation loss, fetal weight and sex ratio were not affected by treatment.

Offspring:

Malformations occurred in two fetuses from two high dose dams (150 mg/kg). One fetus showed adipose tissue abnormal distribution, protruding tongue and abnormal position of the digits; another fetus showed stenosis of the pulmonary trunk. The external malformations and pulmonary trunk stenosis are rare and not reported in (b) (4) historic control data (819 litters and 6839 fetuses from 44 studies during year 2005-2009). Considering that both fetuses with these malformations were from high dose group, treatment relationship cannot be completely excluded.

Malformations in Rabbits (Fetal Incidence% / Litter Incidence%)

Variable	Group			
	Sham	Vehicle	LD	MD
Adipose tissue abnormal distribution				0.7/6.2*
Protruding tongue				0.7/6.2*
Abnormal position of digits				0.7/6.2*
Pulmonary trunk stenosis				0.7/6.2

Source: Nonclinical reviewer

*findings from the same fetus; blanks indicate zero incidence

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, medium dose

Source: Reviewer generated table

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, medium dose

THR-1442-T-459: Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats

Key Findings

Maternal (F0 generation):

- Mortalities at 40 mg/kg/day and 200 mg/kg/day (mostly occurred shortly after parturition)
- Reduced gestational weight gain at 200 mg/kg/day (-34%)
- Higher postimplantation loss at 200 mg/kg/day (+9%) and related smaller litter size (-15%)
- Maternal NOAEL was 7 mg/kg/day (AUC_{0-24h} , 15700 ng.h/mL), corresponding to 12.5 times MRHD, based on AUC.

Offspring (F1 generation):

- Reduced pup weight gain at 200 mg/kg during lactation phase (18%) which was no longer noticeable by postweaning Week 4 for males and Week 2 for females.
- Slightly reduced lactation index at 200 mg/kg (5.5%)
- Dose-related decrease in postweaning food consumption
- No remarkable findings in physical development, neurologic function, or reproduction ability
- NOAEL for F1 was 40 mg/kg/day (100,000 ng.h/mL) based on reduced litter size and reduced pup weight during lactation and growth phase. This NOAEL represent 79 times the human exposure at the MRHD of 20 mg.

Toxicokinetics:

- Plasma AUC in F0 was dose proportional
- Drug concentration in F0 milk on lactation day (LD) 14 was 1.4 to 1.8 times F0 plasma C_{max}
- F1 plasma concentrations were 25 to 50 times lower than that of F0 milk

Table 70. Study Information for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 7, 40, 200 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	1% carboxymethylcellulose (CMC), medium viscosity, in reverse osmosis (RO) water
Species/strain:	Crl:CD(SD) rats
Number/sex/group:	25/dose
Satellite groups	None
Age:	11-13 weeks age at initiation of treatment
Study design:	F0 females were dosed from Gestation Day (GD) 6 through parturition and Lactation Day (LD) 20. For the F1 offspring, the attainment of developmental landmarks and growth were assessed at preweaning. At weaning, one male and one female per litter were selected to continue on study during the Maturation phase. In this phase, the F1 males and females were assessed for growth, sexual development, locomotor activity, reflex development, learning and memory, and reproductive capability (through GD 13 cesarean sections). Systemic exposures in F0 females and F1 animals were evaluated on LD20 and LD14, respectively. Additionally, on LD 14, drug concentrations in milk from F0 dam were analyzed.

STUDY DESIGN, GROUP DESIGNATION AND DOSE LEVELS

Group ^a	Number of Mated Females (F ₀)	Dose Level (mg/kg/day)	Dose Concentration (mg/mL)	Dosing Schedule
1 (Control)	25	0	0	GD 6 thru LD 20
2 (Low)	25	7.0	1.4	GD 6 thru LD 20
3 (Mid)	25	40.0	8.0	GD 6 thru LD 20
4 (High)	25	200.0	40.0	GD 6 thru LD 20

^a Group 1 will receive control article only.

Source: Applicant's submission

Deviation from study protocol affecting interpretation of results: None

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice.

Table 71. Observations and Results for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats, F0-Generation Dams

Parameters	Major findings
Mortality	Moribund sacrifices occurred in three mid dose animals (one at LD2 and two at LD0) and two high dose animals (one at GD9 and one another at LD1). Clinical signs of poor physical conditions were observed at mid gestation phase (HD), late gestation phase (all doses) and lactation phase (MD and HD). It seems that bexagliflozin treatment weakened animal's tolerance to the stress related to late gestation and delivery process. An additional high dose female was sacrificed on lactation Day 0 due to stillbirths of most pups.
Clinical signs	Dose- and duration-related clinical signs, including rough hair coat, nonformed/liquid feces, red or cloudy genital discharge, thin appearance, hunched appearance, squinting, irregular respiration and cold to touch, were observed at 40 mg/kg throughout lactation, and at 200 mg/kg in mid to late gestation. Similar findings except irregular respiration and cold to touch were also seen in animals at 7 and 40 mg/kg in the late gestation phase

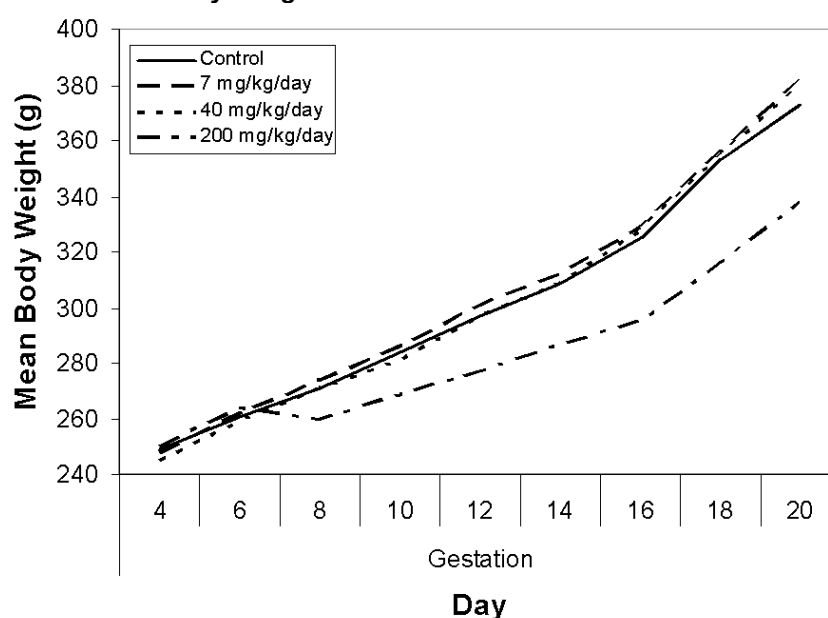
Parameters	Major findings
Body weights	<u>Gestation</u> Lower gestation body weight gain was observed at 200 mg/kg (34% lower than control at GD20).

Maternal Body Weight During Gestation (g)

Variable	Dose, mg/kg			
	0	7	40	200
GD6	261	262	259	264
GD20	373	382	380	338
GD20-GD6	112	120	121	74
% gain relative to control	100	107	108	66

Source: Nonclinical reviewer

Gestational Body Weight



Source: Applicant's submission

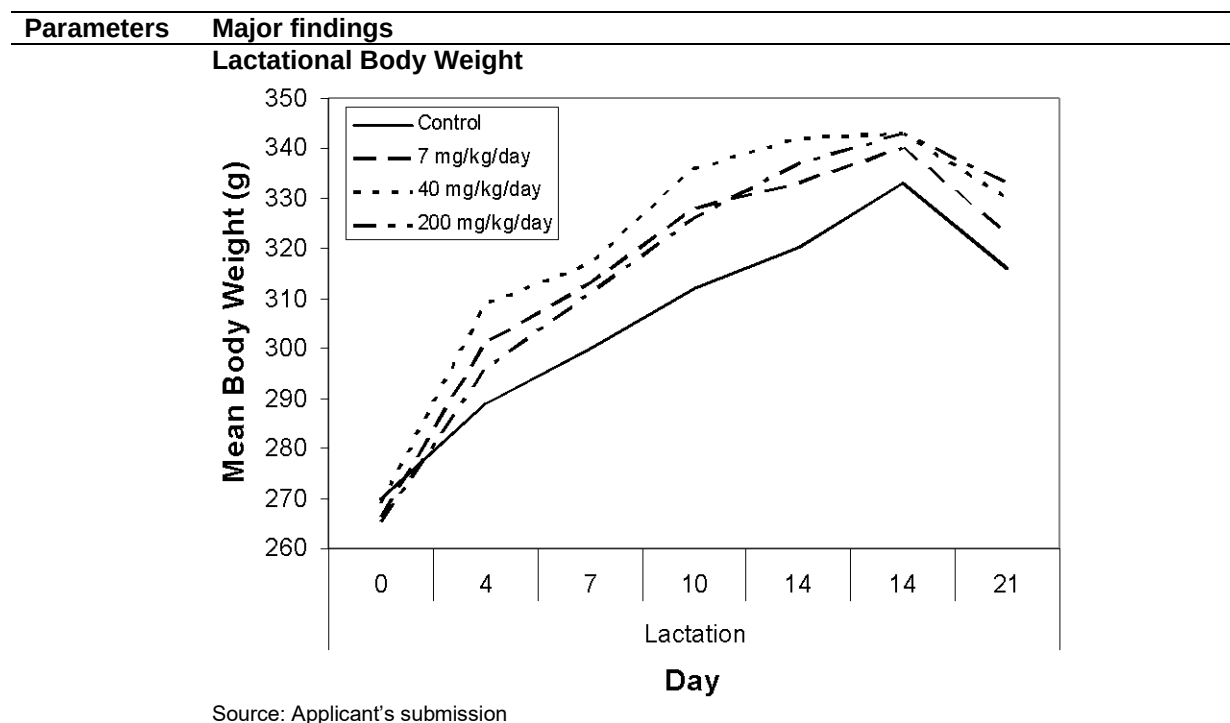
Lactation

During lactation phase, maternal body weight gain increased in a dose-related manner (51% more than control).

Maternal Body Weight During Lactation

Variable	Dose, mg/kg			
	0	7	40	200
LD0	270	266	269	265
LD21	316	323	330	333
LD21-LD0	46	57	61	68
% gain relative to control	100	124	133	148

Source: Nonclinical reviewer



Gestation, parturition, and lactation	Slightly lower gestation index (96%), due to one moribund sacrifice on GD9 and smaller litter size (10.7 versus 12.5 in controls), were noted at 200 mg/kg. The smaller litter size is attributable to higher postimplantation loss (14.1% versus 5.1% in control; historical range of 0.8%-4.2%). Postimplantation loss was not increased in the rat embryofetal development study at doses up to 200 mg/kg from GD6 to GD 17. The reason for the discrepancy might be related to adverse clinical signs/stress during late gestation.

Natural Delivery Data and Litter Data

Variable	Dose, mg/kg			
	0	7	40	200
Pregnant females	24	24	22	25
Duration of gestation, days	23.0	23.3	23.1	23.4
Females with liveborn pups	24	24	22	24
Gestation index	24/24=100%	24/24=100%	22/22=100%	24/25=96%
Litter size	12.50	12.63	12.73	10.67
Liveborn/litter	12.50	12.50	12.32	10.42
Implantation sites/dam	13.17	13.13	13.36	11.96
Postimplantation loss, %	5.09	4.42	8.19	14.11

Source: Nonclinical reviewer

Source: Reviewer generated table

Abbreviations: GD, gestation day; HD, high dose; LD, lactation day; MD, mid dose.

Table 72. Observations and Results for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats, F1-Generation

Parameters	Major findings
Mortality	Pup survival index (percentage of pups survived to LD4) was similar in all groups. Lactation index (percentage of pups survived from LD4 to LD21) was slightly lower in the high dose group (70.6% vs. 74.5% in control)
Clinical signs	Unremarkable
Body weights	Pup weights at birth were similar in all groups. However, lower body weight was noted for the pups from 200 mg/kg dams during lactation (18% and 17% less for males and females, respectively). During the maturation phase (postweaning), the pup weights were comparable to control levels by postweaning Week 4 in males and Week 2 for females.

Pup Weight (g) and Percent Gain Relative to Control During Lactation

Variable		Maternal Dose, mg/kg/day			
		0	7	40	200
LD 0 (g)	M	6.51	6.53	6.48	6.75
	F	6.17	6.09	6.02	6.54
LD 21 (g)	M	52.07	55.05	51.96	43.91
	F	50.85	52.68	50.45	43.64
% gain relative to control	M	100	106	100	82
	F	100	104	99	83

Source: Nonclinical reviewer

Physical development	No treatment-related findings on eye opening, hair growth, incision eruption, pinna unfolding, balanopreputial cleavage, vaginal opening, and estrous cycling.
Neurological assessment	Surface righting, pupillary reflex, and locomotor activity were not affected by treatment. On PND 28, auditory startle response was increased at variable degrees in one or two intervals in the 7 and 40 mg/kg groups. The 200 mg/kg group, however, showed similar response as controls. By PND 62, all groups displayed evidence of habituation. The auditory startle findings at earlier times are considered not toxicologically significant.
Motor activity and learning and memory	Not affected by bexagliflozin treatment
Reproductive performance (mating, fertility, and fecundity indices, etc)	No treatment-related findings in mating index or fertility index
Macroscopic examinations	Necropsy evaluation on a standard battery of organs/tissues, and Cesarean section (corpora lutea, implantation sites, pre-implantation loss and postimplantation loss) revealed no remarkable findings.
F2 generation	Upon C-section on GD13, number of live F2 fetuses was similar in all groups.

Source: Reviewer generated table

Abbreviations: LD, lactation day; PND, postnatal day.

Table 73. Toxicokinetics for Oral Gavage Study for Effects on Pre- and Postnatal Development, Including Maternal Function, With Bexagliflozin in Rats

F0 Dam Blood plasma
Drug exposures in nursing dams were measured on LD20. The C_{max} was less than dose proportional, but AUC was approximately dose proportional.

TK Parameters of Bexagliflozin in F0 Female Rats on LD20

Group	Dose Level (mg/kg/day)		C_{max} (ng/mL)	T_{max} (hr)	AUC ₀₋₂₄ (ng·hr/mL)
2	7.0	Mean	1840	2.67	15700
		SD	480	1.15	2530
		N	3	3	3
3	40.0	Mean	7970	6.00	100000
		SD	2400	5.29	20300
		N	3	3	3
4	200.0	Mean	34600	2.67	455000
		SD	8320	1.15	61300
		N	3	3	3

Milk

Drug concentrations in milk samples on LD 14 (sampling time was not provided) were 1.4-1.8 times the plasma C_{max} on LD 20 (assuming comparable C_{max} on LD 14 and LD 20).

F0 Milk to F0 Plasma Concentration Ratio

Variable	Dose, mg/kg		
	7	40	200
Plasma C_{max} at LD20, ng/mL	1840	7970	34600
F ₀ milk concentration at LD14, ng/mL	2640	14500	60600
Milk conc:Plasma C_{max}	1.44	1.82	1.75

Source: Nonclinical reviewer

F1 offspring Bexagliflozin concentration in F1 plasma was significantly lower than that in F0 milk (25-50-fold differences).

F0 Milk to F1 Plasma Concentration Ratio

Group	Dose Level (mg/kg/day)		F ₁ Male Milk:Plasma	F ₁ Female Milk:Plasma
2	7.0	Mean	50.6	46.9
		SD	23.2	19.1
		N	22	20
3	40.0	Mean	37.3	39.8
		SD	17.6	22.7
		N	19	19
4	200.0	Mean	25.7	28.1
		SD	7.90	9.70
		N	19	21

Source: Applicant's submission

Source: Reviewer generated table

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum plasma concentration; LD, lactation day; T_{max} , time to maximum plasma concentration

THR-1442-T-482: A 10-Week Toxicity Study of Bexagliflozin by Oral Administration (Gavage) in Juvenile Rats With a 4-Week Recovery Period

Key Findings

- Bexagliflozin doses: 0, 0.3, 3, 30 mg/kg/day.
- Increased kidney weight in all treated female groups (up to 45%) and in males at ≥ 3 mg/kg/day (up to 35%) correlated with increased incidence of minimal to mild renal dilatation in males at ≥ 3 mg/kg/day (11 times the MRHD) and in females at 30 mg/kg/day (139 times the MRHD). There were no toxicologically significant changes in kidney injury molecule-1 (KIM-1), a biomarker of tubular injury. A longer treatment duration (~26 weeks) in adult rats (e.g., 6 weeks old) did not alter renal structures, suggesting a particularly susceptible window for renal toxicity if exposed to bexagliflozin during postnatal weeks 3 to 6. This susceptible window in the young rats is characterized by active morphological and functional development of the kidneys and is equivalent to the events in the second and third trimester of human gestation and continuing until approximately 2 years of age.
- Increased trabecular bone (femur) in the high dose groups (127 times the MRHD), associated with increased trabecular bone mineral content (BMC) and bone mineral density (BMD) at the distal metaphysis in males. No changes were observed in recovery animals. Similar findings have been observed with other approved SGLT2 inhibitors and are likely related to calorie-wasting and/or off-target inhibition of SGLT1, which is not expected at the clinical exposure.
- NOAEL was 0.3 mg/kg/day in males (1,370 ng.h/mL, at the MRHD) and 3 mg/kg/day in females (14,400 ng.h/mL, 11 times the MRHD) based on renal dilatation.

Table 74. Study Information for 10-Week Toxicity Study of Bexagliflozin by Oral Administration (Gavage) in Juvenile Rats With a 4-Week Recovery Period

Study Features and Methods	Details
GLP compliance:	Yes
Dose and frequency of dosing:	0, 0.3, 3, 30 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	1% carboxymethylcellulose
Species/strain:	Crl:CD(SD) Sprague Dawley rats
Number/sex/group:	15/sex/group for both main study and recovery study
Satellite groups	TK analysis: 24/sex/dose group and 6/sex for control
Age:	Postnatal Day 21 at initiation of treatment
Study design:	Juvenile rats were administered bexagliflozin daily by oral gavage starting at PND21 for 10 weeks. In addition to the standard set of observation/examinations, sexual maturation, neuromuscular system function and development were evaluated. Histopathology examinations were performed on all tissues from control and high dose groups for both main study and recovery study.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table

Abbreviations: GLP, good laboratory practice; PND, postnatal day; TK, toxicokinetic.

Table 75. Observations and Results for 10-Week Toxicity Study of Bexagliflozin by Oral Administration (Gavage) in Juvenile Rats With a 4-Week Recovery Period

Parameters	Major findings
Mortality	No treatment-related mortalities
Clinical signs	No remarkable findings
Body weights	Dose-related lower body weight gain was observed in male treated groups (up to -8.3%), which was reversible when dosing stopped. Female body weights were not affected.

Summary: Body Weight (g) and Body Weight Gain (g) in Juvenile Rats

Dose Level (mg/kg/day)	0 (Control)		0.3		3		30	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
Dose Period								
BW PND 21	48.1	45.9	-3.6	-2.3	-2.4	-3.3	-3.3	-4.8
BW PND 90	514.8	278.4	-6.6**	-1.8	-7.7**	+0.3	-7.8**	-2.1
BW Gain PND 21-90	466.7	232.5	-7.0**	-1.7	-8.2**	+1.0	-8.3**	-1.5
Recovery Period								
BW PND 118	577.5	294.2	-1.6	+0.0	-6.0	+1.8	-3.0	-1.0
BW Gain PND 91-118	75.1	27.4	+23.8**	+22.8	+10.9	+11.4	+26.2**	+26.8
BW Gain PND 21-118	529.6	249.5	-1.2	+0.2	-6.0	+2.8	-3.0	-0.6

BW = Mean body weight; BW Gain = Mean body weight gain

PND = Postnatal day; NA = Not applicable

^a For controls, group means are shown. For treated groups, percent differences from controls are shown.

Statistical significance was based on actual data (not on the percent differences).

* = Statistically significant (p ≤ 0.05)

** = Statistically significant (p ≤ 0.01)

Source: Applicant's submission

Food consumption	Dose-related increased food consumption was noted in both male and female treatment groups.

Food Consumption (g/animal/day) in Juvenile Rats

Dose Level (mg/kg/day)	0 (Control)		0.3		3		30	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
Dose Period								
Food Consumption (g/day) PND 21-90	13.5	11.9	-1.9	+6.8	+9.2	+12.1	+13.1**	+1
Overall Study Period								
Food Consumption (g/day) PND 21-118	13.5	12.1	+0.0	+5.9	+10.8	+8.8	+17.2*	+1

PND = Postnatal day; NA = Not applicable.

^a For controls, group means are shown. For treated groups, percent differences from controls are shown.

Statistical significance was based on actual data (not on the percent differences).

* = Statistically significant (p ≤ 0.05).

** = Statistically significant (p ≤ 0.01).

Source: Applicant's submission

Sexual maturation	No remarkable findings
Ophthalmology	No remarkable findings
Functional Observation	No statistically significant or toxicologically relevant findings
Battery, motor activity, acoustic startle habituation, and Morris water maze	
Hematology	No remarkable findings

Parameters	Major findings
Clinical Chemistry	No toxicological significant findings. On PND 91, there were mild increases (up to 1.8-fold) in urea nitrogen in high dose males and in females at ≥ 3 mg/kg/day. No changes in creatinine were observed. Additionally, slight decreases in total protein and albumin in high dose females (6% and 7%, respectively) and slight increase in potassium levels in high dose males and females (7% and 8%, respectively) were noted. All these findings were reversible after 4 weeks of recovery period.
Urine Chemistry	Consistent with the intended pharmacology, moderate to marked increases in urine glucose excretion in all treatment groups and mild increases in renal calcium (up to 5.9 times the control group) and/or phosphorus excretion (up to 1.9 times the control group) in all treatment groups, except 0.3 mg/kg/day males, were observed. There were no toxicologically relevant bexagliflozin-related effects in urinary kidney injury molecule-1 (KIM-1), a marker of renal tubule injury.
Necropsy findings	Increased incidence of renal pelvic dilatation in males at ≥ 3 mg/kg/day.

Summary of Gross Pathology Findings – Renal Pelvic Dilatation

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	0.3	3	30	0	0.3	3	30
End of dosing (PND 91)	1/15	0/14	4/15	7/15	0/15	0/15	0/15	0/15
End of recovery (PND 119-122)	0/15	1/15	2/15	2/14	0/15	0/15	0/15	0/15

Source: Applicant's submission

Organ weight	Dose-related increases in the kidney weights and liver weights were observed. These findings were reversible.

Summary of Organ Weight Data – Terminal Euthanasia (PND 91)

	Males			Females		
Group	2	3	4	2	3	4
Dose (mg/kg/day)	0.3	3	30	0.3	3	30
No. Animals per Group	14	15	15	15	15	15
Kidney (No. Weighed)^a	(14)	(15)	(15)	(15)	(15)	(15 ^b)
Absolute value	4.06	12.0	17.6	11.2	24.0	37.5
% of body weight	17.2	23.4	35.2	17.7	25.9	45.3
% of brain weight	4.11	14.3	22.1	12.0	27.1	40.6
Liver (No. Weighed)	(14)	(15)	(15)	(15)	(15)	(15 ^b)
Absolute value	-10.5	-10.6	-4.06	1.46	8.17	20.4
% of body weight	0.17	-1.28	10.6	6.94	9.91	27.0
% of brain weight	-10.6	-8.83	-0.29	2.08	10.7	21.9

^a All values expressed as percent difference of control group means.

Based upon statistical analysis of group means, values highlighted in bold are significantly different from control group – $p \leq 0.05$; refer to data tables for actual significance levels and tests used.

^b For Group 4 females, only 14 animals were included for % of brain weight values.

Source: Applicant's submission

Parameters	Major findings
Histopathology	Renal pelvic dilatation and renal tubular dilatation were noted in males at ≥ 3 mg/kg/day and in females at 30 mg/kg/day.

Increased trabecular femoral bone (42% in both mineral content and mineral density) was also observed microscopically at 30 mg/kg/day or 81 times the MRHD_{AUC}.

The kidney findings were not fully reversible but trabecular bone findings were fully reversible after 4 weeks of recovery period.

Summary of Microscopic Findings – Renal Pelvic and Tubular Dilatation and Increased Trabecular Bone

	Males				Females			
Group	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	0.3	3	30	0	0.3	3	30
No. Animals Examined	15	14	15	15	15	15	15	15
Renal Pelvic Dilatation	15	14	15	15	15	15	15	15
End of dosing (PND 91)								
Minimal	1/15	1/14	4/15	8/15	0/15	0/15	0/15	3/15
Mild	0/15	0/14	0/15	2/15	0/15	0/15	0/15	0/15
Total	1/15	1/14	4/15	10/15	0/15	0/15	0/15	3/15
End of recovery (PND 119-122)								
Minimal	0/15	1/15	3/15	5/14	0/15	0/15	0/15	2/15
Renal Tubular Dilatation								
End of dosing (PND 91)								
Minimal	0/15	0/14	7/15	9/15	0/15	0/15	0/15	2/15
Mild	0/15	0/14	0/15	3/15	0/15	0/15	0/15	0/15
Total	0/15	0/14	7/15	12/15	0/15	0/15	0/15	2/15
End of recovery (PND 119-122)								
Minimal	1/15	1/15	2/15	3/14	0/15	0/15	0/15	0/15
Increased Trabecular Bone in Femur								
End of dosing (PND 91)								
Minimal	0/15	0/11	0/15	4/15	0/13	0/15	0/14	3/13
End of recovery (PND 119-122)								
Minimal	0/15	0/14	0/14	0/14	0/15	0/14	0/14	0/15

Source: Applicant's submission

Biomarkers of bone turnover	Procollagen Type I N-terminal propeptide (PINP) was slightly reduced (up to -44%) in males at ≥ 3 mg/kg, without changes in C-telopeptides of Type I collagen (CTxI). This effect on bone metabolism was associated with a minimal decrease in femur length (-2%) and increase in trabecular bone mineral content (BMC) and bone mineral density (BMD; +42% for both) in high dose males (127 times the MRHD). None of these changes persisted into the recovery period. There were no significant findings on bone measurements or pQCT parameters at the midfemur diaphysis in males or females.

Source: Reviewer generated table

Abbreviations: MRHD, maximum recommended human dosage; PND, postnatal day.

Table 76. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	Nonclinical Exposure (ng.hr/mL)	Exposure Margins¹ (Multiples)
Fertility rat	200	M, 352,259; F, 552,950 ²	M, 280x; F, 439x
EFD rat	200	694,193	551x
EFD rabbit	25	42,905	34x
PPND rat (maternal)	7	15,700	12x
PPND rat (offspring)	40	100,000	79x
Juvenile rat	M, 0.3; F, 3	M, 1,370; F, 14,400	M, 1.1x; F, 11.4x

Source: Nonclinical reviewer.

¹ Exposure multiples were based on population pharmacokinetics analysis where a 20 mg clinical dose resulted in systemic exposures of $AUC_{0-24hr} = 1259 \text{ ng}\cdot\text{hr/mL}$

² data obtained from the 5-day toxicology study in rats

Abbreviations: AUC, area under the concentration time curve; EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Impurity Evaluation

Drug substance and drug product-related impurities are within International Conference on Harmonisation (ICH) Q3A and ICH Q3B limits. Potentially genotoxic impurities were qualified by Q(SAR) analysis using DEREK and SARAH software.

13.2. Individual Reviews of Studies Submitted to the New Drug Application

Not applicable.

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

14.1.1. Protein Binding (Study THR-1474-N-371)

Method: An ultrafiltration technique was used for assessing drug binding to plasma protein. The samples were analyzed for bexagliflozin and (b) (4) (as a positive control) by liquid chromatography mass spectrometry (LC-MS/MS).

Results:

- At concentrations of 200, 1000, and 5000 ng/mL, protein-bindings of bexagliflozin were $96.6 \pm 0.7\%$, $97.0 \pm 0.3\%$, and $93.3 \pm 0.7\%$, respectively, in pooled plasma samples from healthy human subjects.
- The human plasma protein binding of the positive control of (b) (4) was determined to be $96.7 \pm 0.7\%$, a value consistent with literature reports.

14.1.2. Protein Binding (Study THR-1442-C-424)

Method: The effect of concentration on the plasma protein binding of bexagliflozin was assessed by equilibrium dialysis at 37°C for 7 hours, the experimentally determined equilibration time, in pooled plasma from subjects with T2DM and normal renal function at concentrations of 25, 50, 100, 250, and 500 ng/mL. Subsequently, in vitro experiments to assess whether or not bexagliflozin and its major metabolite EGT0002149 would interact with each other with respect to their binding to plasma proteins were performed by equilibrium dialysis at 37°C for 7 hours. Finally, the plasma protein binding of bexagliflozin was determined by equilibrium dialysis at 37°C for 7 hours in predose and 3-hour postdose plasma samples obtained from subjects enrolled in Trial C-424.

Results:

- The mean percentages of bexagliflozin bound to plasma proteins of donors with type 2 diabetes and normal renal function ranged from 90.9 to 93.0%, with no dependence on concentration over the range of 25 to 500 ng/mL.
- The mean percentages of bexagliflozin bound to plasma proteins when incubated with 0, 75, or 150 ng/mL EGT0002149 were 90.4, 90.3, and 89.3%, respectively, indicating that EGT0002149 did not affect the extent of bexagliflozin bound to plasma proteins.
- The mean or average percentages of bexagliflozin bound to plasma proteins when incubated with 0, 75, or 150 ng/mL bexagliflozin were 90.6, 88.7, and 86.3%, respectively, suggesting that bexagliflozin had a minor effect on the extent of EGT0002149 bound to plasma proteins.
- The mean or individual percentages of bexagliflozin bound to plasma proteins of 3-hour postdose plasma samples from subjects enrolled in Trial C-424 analyzed ex vitro ranged from 73.7 to 92.7%. However, with the exception of a single replicate sample at 73.7% (Subject 424- (b) (6)), all other postdose samples ranged from 83.7 to 92.7%.

14.1.3. Protein Binding (Study THR-1442-C-455)

Method: In the hepatic impairment study, subjects with normal hepatic function and moderate hepatic impairment received a single dose of bexagliflozin 20 mg. Fraction of unbound drug substance was determined by an equilibrium dialysis method using a single sample from each study subject at 3 hours postdose (around T_{max}) and 24 hours postdose.

Results:

Table 77. Free Fraction (Mean $\pm$ SD) of Bexagliflozin in Plasma at 20-mg Dose

	Normal Hepatic Function (N=8)	Moderate Hepatic Impairment (N=8)
Fu %		
At T_{max}	6.7 $\pm$ 1.15	7.0 $\pm$ 1.10
At 24 hours postdose	9.8 $\pm$ 1.93	8.5 $\pm$ 1.79

Source: Table 9 of Study Report THR-1442-C-455

Abbreviations: Fu, free fraction.

14.1.4. In Vitro Metabolism in Human Liver Microsomes (Study THR-1474-N-341)

Methods: [^{14}C] bexagliflozin (100 μM) was incubated in the presence of human liver microsomes for 0, 15, 30, and 60 min at 37°C and a protein concentration of 1 mg/mL. Blank incubations were conducted (60 min) in the absence of microsomes and presence of an NADPH regenerating system and in the presence of microsomes and absence of an NADPH regenerating system to assess chemical degradation. Samples were analyzed with high-performance liquid chromatography (HPLC) using on-line ultraviolet (UV) and radiochemical detection.

Results:

- At the end of the 60 min incubation, turnover was approximately 9%.
- The predominant CYP450 mediated metabolite (based on retention time) in human liver microsomes was EGT0001301. EGT0001663 and M6 were also detected as minor metabolites.

Table 78. Distribution of Metabolites as a % of Total Metabolite Formation Following Incubations in the Presence and Absence of Human Liver Microsomes (1 mg/mL; 37°C) at 100 μM [^{14}C] Bexagliflozin

Peak identification	M1	M2 EGT0001301	M3 EGT0001663	M4	M5 [^{14}C] EGT0001442	M6
60 min blank (no cofactor)	nd	nd	nd	nd	98.1	1.89
0 min	nd	nd	nd	nd	98.3	3.45 – 1.53**
15 min	nd	2.61	nd	nd	97.4	nd
30 min	0.980*	3.39 – 3.52**	nd	nd	95.8	1.99 – 2.80**
60 min	nd	5.19	1.73	nd	91.2	1.92

Mean data reported (n = 3 replicates) except for blank where n = 1.

* = peak detected in 1 out of 3 replicates.

** = peak detected in 2 out of 3 replicate.

nd = not detected.

Source: Table 10 of Study Report THR-1442-N-341

14.1.5. In Vitro Metabolism by Recombinant CYP3A (Study THR-1474-N-367)

Methods: Bexagliflozin (50 μM or 20 μM) was mixed with cell membrane preparations containing human recombinant CYP3A4 (20 pmol/mL or 10 pmol/mL) in potassium phosphate buffer (pH 7.4). An equal volume of NADPH regeneration system was added and incubated at 37°C for either 30 or 90 minutes. The reaction was terminated by the addition of acetonitrile to a final concentration of 33.33% and centrifugation at 10,000 g for 3 minutes. High performance liquid chromatography-photodiode-array mass spectrometry (HPLC-PDA/MS) was used to identify the metabolites.

Results:

- The incubation of bexagliflozin with human recombinant CYP3A4 resulted in the identification of two metabolites, EGT0001301 and EGT0001663.

- The metabolic rates for odealkylation (EGT0001301) and hydroxylation (EGT0001663) increased as the amount of CYP3A4 increased ([Table 79](#)).

Table 79. The SIM Chromatogram Peak Response of Bexagliflozin and Its Metabolites After Incubation With CYP3A4 Isoenzyme

Vial	bexagliflozin (18.13 min)	EGT0001301 (13.5 min)	EGT0001663 (15.38 min)	MX ^a (16.4 min)	bexagliflozin (μM)	CYP3A4 (pmol)	Incubation time (min)
1	269	13.6	25.1	NA	25	10	30
2	219	34.2	60.4	NA	25	10	90
3	73.2	4.8	16.3	NA	10	10	30
4	88.1	15.6	20.7	193	10	10	90
5	317	7.2	9.6	NA	25	5	30
6	253	13.3	14.9	NA	25	5	90
7	124	NA	NA	NA	10	5	30
8	83.5	6.2	13.0	NA	10	5	90
9	15.1	NA	NA	NA	0	10	90
10	204 ^b	23.6 ^b	45.4 ^b	NA	25	0	90

Source: Table 1 of Study Report THR-1442-N-367

a MX is predicted to be an interfering compound based on mass analysis indicating presence of nitrogen

b Result is abnormal, and an error might have occurred during sample incubation.

Data are chromatogram selected ion currents × 10⁻⁴

Abbreviations: CYP, cytochrome P450 isoenzyme; SIM, selected ion monitoring.

14.1.6. In Vitro Metabolism by Human Liver Microsomes and Recombinant UGT (Study THR-1474-N-377)

Methods: The human liver microsome incubations were conducted at a microsomal protein concentration of 2 mg/mL and a single concentration of bexagliflozin (1mM) for 2 h; NADPH (2.0mM when present), UDPGA (2.0mM when present), magnesium chloride (10mM), and EDTA (2mM) in a total volume of 0.5 mL PBS buffer (100mM, pH 7.4) were also added to the reaction system. Reactions were terminated by adding ice-cold acetonitrile to the reaction mixtures.

Reaction mixtures containing 50mM Tris (pH 7.5), 10mM MgCl₂, 5mM UDP-glucuronic acid, 0.025 mg/ml alamethicin, 0.35 μg/μl protein of different human recombinant UGT membrane preparations (UGT1A4, UGT1A6, UGT1A9, UGT1A10, UGT2B7), and 100μM bexagliflozin were incubated at 37°C for 120 min in 200 μl volume. Reactions were terminated by the addition of 100 μl of acetonitrile, centrifuged at 10,000 g for 3 min and the supernatants were transferred to fresh tubes.

The incubation samples were analyzed by a developed HPLC-PDA/MS method.

Results:

- In human liver microsomes incubations containing solely UDPGA, the only glucuronide conjugate of bexagliflozin detected was metabolite M5 (EGT0002149).
- Following incubation with human liver microsomes fortified with UDPGA and NADPH, three additional metabolites M1 (EGT0001301), M² (EGT0001494) and M4 (EGT0001663) were characterized in addition to M5. M5 was also identified following incubation with UDPGA and recombinant UGT1A9.

Conclusion: UGT1A9 is the major UGT isoform for glucuronidation in vitro.

14.1.7. In Vitro CYP and UGT Phenotyping by Recombinant Human CYP and UGT Enzymes (Study THR-1442-N-440)

Methods: For phase I metabolism, bexagliflozin (10 and 100 μ M) was incubated for 30 minutes with a panel of recombinant human CYP enzymes (rCYPs, namely rCYP1A2, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C19, rCYP2D6 and rCYP3A4, 10 pmol/incubation) and two negative controls (Bactosome control and reductase control). For phase II metabolism, bexagliflozin (10 and 100 μ M), was incubated with two recombinant human UGT enzymes (rUGTs, namely rUGT1A1 and rUGT2B7) and negative control (insect cell control). Metabolite production was monitored using an LC/MS/MS method that was transferred and modified for concentrations of the metabolites ranging from 10 to 1000 ng/mL. Positive controls were conducted in parallel using prototype substrates for each respective enzyme.

Results:

Recombinant Human CYP Enzymes

- From an initial concentration of 10 μ M bexagliflozin, CYP3A4 caused 16% depletion and CYP2D6 approximately 12% depletion. From an initial concentration of 100 μ M bexagliflozin, depletion greater than 10% was only observed in incubations with CYP3A4 (approximately 17%). Depletion by less than 10% was observed for the other recombinant CYP enzymes evaluated (data not shown).
- Bexagliflozin was metabolized in vitro by recombinant human CYP enzymes (predominantly by CYP3A4, with minor contributions from CYP2C8 and 2D6) to EGT0001301 and EGT0001685 ([Table 80](#)).

Table 80. Metabolism of Bexagliflozin in Recombinant Human CYP Enzymes

Substrate Bexagliflozin (μM)	Test system	EGT0001301 detected (pmol)	EGT0001494 detected (pmol)	EGT0001685 detected (pmol)
10	Bactosome Control	8.85	NC	NC
	Reductase Control	9.01	NC	NC
	CYP1A2	8.76	NC	NC
	CYP2B6 + b5	9.01	NC	NC
	CYP2C8 + b5	32.2	NC	NC
	CYP2C9	11.0	NC	NC
	CYP2C19	11.1	NC	NC
	CYP2D6	43.2	NC	5.36
	CYP3A4 + b5	432	NC	52.2
100	Bactosome Control	84.0	NC	NC
	Reductase Control	77.0	NC	NC
	CYP1A2	89.2	NC	NC
	CYP2B6 + b5	86.4	NC	NC
	CYP2C8 + b5	288	NC	NC
	CYP2C9	86.9	NC	NC
	CYP2C19	94.9	NC	NC
	CYP2D6	274	NC	NC
	CYP3A4 + b5	3910	169	522

Source: Tables 1-3 of Study Report THR-N-440.

Values are the mean of duplicate determinations unless indicated otherwise and are rounded to three significant figures (LLOQ: 4.7 pmol per incubation). NC: Not calculated (value was < lowest standard of 11.4 pmol per incubation); CYP2B6, CYP2C8 and CYP3A4 were expressed with cytochrome b5;

Abbreviations: CYP; cytochrome P450 isoenzyme.

Recombinant Human UGT Enzymes:

- After 60-minute incubation, less than 10% of bexagliflozin was lost for the recombinant enzymes evaluated (data not shown).
- Neither UGT1A1 nor UGT2B7 play a major role in the conversion of bexagliflozin to the O-glucuronides, EGT0002148 and EGT0002149, at C_{max} concentrations ($\leq 0.5 \mu\text{M}$) anticipated for the intended human dose ([Table 81](#)).

Table 81. Metabolism of Bexagliflozin in Recombinant Human UGT Enzymes

Substrate concentration	Incubation	Rate of Formation in $\text{pmol (mg protein)}^{-1} \text{min}^{-1}$ ^a			
		EGT0002147	EGT0002148	EGT0002149	4-MU ^b
10 μM	Control	-	-	-	
	UGT1A1	-	1.47	1.90	
	UGT2B7	-	-	-	
100 μM	Control	-	-	-	
	UGT1A1	-	-	13.7	5010
	UGT2B7	-	-	-	5250

^a - signifies result below limit of quantification

^b 4-MU: 4-methylumbelliferone (positive control, incubated at 1 mM substrate concentration)

Source: Tables 7-9 of Study Report THR-N-440.

Abbreviations: UGT, uridine diphosphate glucuronosyltransferase

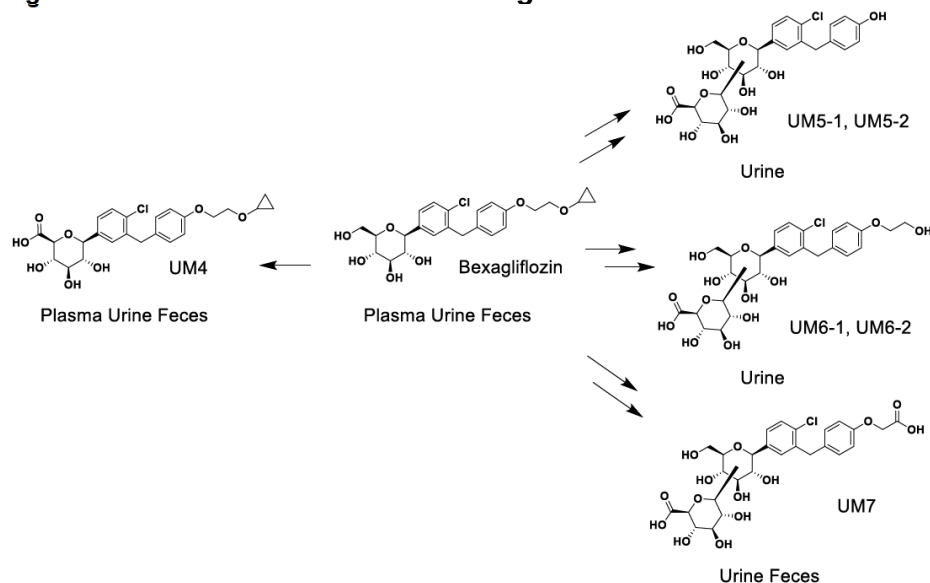
14.1.8. Identification of Additional Metabolites (Study THR-1474-N-382)

Methods: Bioanalyses performed on plasma, urine, and fecal samples collected from subjects after administration of a single oral dose of bexagliflozin (150 mg, cohort 6) in Trial C-328. The metabolites of bexagliflozin in human urine, feces, and plasma were also identified and characterized using an ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC/Q-TOF MS) via positive and negative scan modes in SCDMPK.

Results:

- In addition to the six known metabolites (three oxidative metabolites: EGT0001301, EGT0001494 and EGT0001663, and three bexagliflozin glucuronides), six additional minor metabolites were identified and partially characterized ([Figure 20](#)).
 - In plasma, two additional metabolites were found: UM4, the product of oxidation of the bexagliflozin glucose 6' carbon to a carboxylic acid (bexagliflozin glucuronic acid) and UM6-2, a glucuronide of EGT0001301.
 - In urine, six additional metabolites were found: UM4, described above, UM5-1 and -2, two glucuronides of the phenol resulting from abstraction of the bexagliflozin ethyloxycyclopropyl moiety, UM6-1 and -2, two glucuronides of EGT0001301, and UM7, a glucuronide of EGT0001494.
 - In feces, UM4 was also found.

Figure 20. Minor Metabolites of Bexagliflozin



Source: Figure 2.7.2-7 Summary of Clinical Pharmacology Studies

FDA Reviewer Comment: None of the metabolites contribute to the pharmacological activity of bexagliflozin.

14.1.9. In Vivo Metabolic Profiling Study of Bexagliflozin Metabolites (Study THR-1442-N-403)

Methods: In this study, the major metabolites of bexagliflozin following a single oral dose of 100 mg or 17 mg in healthy subjects (Trial C-328) were profiled and quantified in plasma and urine using a developed LC/MS/MS method.

Results:

- Bexagliflozin is extensively metabolized to oxidation products and glucuronides.
- The principal metabolite is the 3'-O-glucuronide EGT0002149.
- In this study, EGT0001301 was not detected in plasma but was found in urine.

Table 82. Detected Plasma and Urine Metabolites Following Oral Administration 100 mg Bexagliflozin

Human (100 mg)			Human (Day 1, 17 mg)			Human (Day 8, 17 mg)	
AUC _{0-∞}	*M/P Ratio		AUC _{0-∞}	*M/P Ratio		AUC _{0-∞}	*M/P Ratio
(nM·h)	(%)		(nM·h)	(%)		(nM·h)	(%)
EGT0001442	13031 ± 2443	100	EGT0001442	1863 ± 576	100	2387 ± 691	100
EGT0001301	NA	NA	EGT0001301	NA	NA	NA	NA
EGT0001494	625 ± 200	4.8 ± 1.5	EGT0001494	NA	NA	NA	NA
EGT0001685	364 ± 115	2.8 ± 0.9	EGT0001685	NA	NA	NA	NA
EGT0002147	518 ± 136	4.0 ± 1.0	EGT0002147	NA	NA	NA	NA
EGT0002148	263 ± 55.5	2.0 ± 0.4	EGT0002148	NA	NA	NA	NA
EGT0002149	4114 ± 1278	31.6 ± 9.8	EGT0002149	571 ± 208	30.7 ± 11.2	627 ± 301	26.3 ± 12.6

Human urine (100 mg)				
0-12 h	12-24 h	24-36 h	36-48 h	
*M/P Ratio (%)				
EGT0001442	100	100	100	100
EGT0001301	15.5 ± 7.5	16.7 ± 13.4	19.4 ± 17.5	28.3 ± 23.7
EGT0001494	158 ± 74.3	219 ± 155	245 ± 195	282 ± 200
EGT0001685	23.8 ± 8.8	40.7 ± 15.0	40.3 ± 19.2	39.2 ± 23.1
EGT0002147	173 ± 34.2	120 ± 58.5	195 ± 71.8	142 ± 55.0
EGT0002148	37.6 ± 5.6	38.1 ± 13.7	56.4 ± 17.2	42.4 ± 11.1
EGT0002149	498 ± 61	780 ± 192	1509 ± 455	1131 ± 321

Source: Table 47 of Study THR-1442-N-403

*: Metabolite to parent AUC_{0-∞} ratio

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity

14.1.10. Inhibitory Effect of Bexagliflozin on CYP450 Activities (Study THR-1474-N-346)

Methods: The inhibitory potential of eight concentrations (0.0229, 0.0686, 0.206, 0.617, 1.85, 5.56, 16.7, and 50.0 µM) of EGT0001474 (bexagliflozin: L-proline 1:2 cocrystal) were evaluated with pooled human liver microsomes. These concentrations approximated and significantly exceeded the plasma concentrations anticipated in humans. The six CYP isoenzymes monitored in the study were CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Control

incubations were performed for each assay with appropriate positive inhibitory controls. Time-dependent inhibition was evaluated by preincubating the test article in the presence of the microsomes and NADPH for 30 minutes prior to adding the probe substrate.

Results:

- EGT0001474 at concentrations up to 50 μM did not inhibit enzyme assays specific to CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 by 50% or more.
- EGT0001474 had a weak inhibitory effect on CYP2B6 as the half maximal inhibitory concentration (IC_{50}) value was more than 50 μM ([Table 83](#)).

Table 83. Summary of Inhibition Assays

Isoform	Probe Substrate	Pre-Incubated Samples		Co-Incubated Samples	
		EGT0001474 IC_{50} (μM)	Positive Control IC_{50} (μM)	EGT0001474 IC_{50} (μM)	Positive Control IC_{50} (μM)
CYP1A2	Phenacetin	NI	0.58	NI	1.7
CYP2B6	Bupropion	>50	0.089	>50	0.20
CYP2C9	Diclofenac	NI	0.061	NI	0.66
CYP2C19	S-Mephenytoin	NI	1.5	NI	2.5
CYP2D6	Dextromethorphan	NI ^a	0.14	NI	1.3
CYP3A4	Testosterone	NI	13	NI	>100

Source: Table 6 of Study THR-1474-N-346

^a The test article exhibited apparent heterotropic positive cooperativity to enhance metabolism of the probe substrate.

Abbreviations: CYP, cytochrome P450 isoenzyme; IC_{50} , half maximal inhibitory concentration; NI, no significant inhibition observed.

FDA Reviewer Comment: Given CYP2B6 is primarily expressed in the liver and bexagliflozin plasma concentrations ($\sim 0.4\mu\text{M}$) are much smaller than the IC_{50} of $50\mu\text{M}$ at the proposed dose of 20 mg, overall, this study suggests that bexagliflozin is unlikely to inhibit enzyme activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 at the clinically relevant dose.

14.1.11. Induction Effect of Bexagliflozin on CYP450 Activities (Study THR-1474-N-347)

Methods: Plated cryopreserved human hepatocytes were separately incubated with 0.05, 0.50, and 5.0 μM solutions of EGT0001474 in supplemented William's E media for 48 hours. The selected concentrations were expected to approximate and significantly exceed the anticipated clinical exposure conditions. Controls of 1 μM 3-methylcholanthrene, 10 μM rifampicin, and 25 μM rifampicin in the same media were used to establish positive induction responses for CYP1A2, CYP2C19, and CYP3A4, respectively. The activities of CYP1A2, CYP2C19, and CYP3A4 were determined by incubating the cells with solutions of phenacetin, S-mephenytoin, and testosterone, respectively, in the same media. Samples of the media were removed, extracted, and analyzed for the metabolites of the probe substrate using HPLC in conjunction with LC/MS/MS.

Results:

- Exposure of human hepatocytes to 0.05, 0.5, and 5 μ M bexagliflozin did not result in notable induction of enzyme activities associated with CYP1A2, CYP2C19, or CYP3A4 isoforms in vitro ([Table 84](#)).

Table 84. Impact of Bexagliflozin on Enzyme Activities of CYP1A2, 2C19 and 3A4

Substrate	Donor	Positive Control	Bexagliflozin		
			50 nM	500 nM	5000 nM
		Fold Induction of CYP1A2			
Acetaminophen	GCP	13.0	0.946	1.00	0.977
	OSI	7.76	1.29	1.02	1.04
	KQG	31.0	0.969	0.963	1.19
		Fold Induction of CYP2C19			
Hydroxymephenytoin	GCP	2.16	1.05	0.693	1.118
	OSI	1.16	1.06	1.06	1.05
	KQG	3.27	1.00	1.10	1.04
		Fold Induction of CYP3A4			
Hydroxytestosterone	GCP	8.06	0.989	0.934	0.913
	OSI	3.35	0.98	1.00	1.10
	KOG	43.4	1.09	1.19	1.26

Source: Tables 2-4 of Study THR-1474-N-347
Abbreviations: CYP, cytochrome P450 isoenzyme.

FDA Reviewer Comment: Per drug-drug interaction (DDI) Guidance (January 2020), a compound that produces a change that is equal to or greater than 40% of the positive control can be considered an enzyme inducer in vitro. Based on this criterion, bexagliflozin (as EGT0001474) did not produce effects reflective of CYP450 enzyme induction.

14.1.12. Inhibitory Effect of Bexagliflozin on CYP2C8 Activity (Study THR-1442-N-439)

Methods: To evaluate bexagliflozin as a direct, time-dependent, and metabolism-dependent inhibitor of CYP2C8 activity, human liver microsomes from a pool of sixteen individuals were incubated with the marker substrate in the presence or absence of bexagliflozin. To distinguish between time-dependent and metabolism-dependent inhibition, bexagliflozin was preincubated with human liver microsomes for 30 minutes without and with an NADPH-generating system, respectively, prior to incubation with the marker substrate. Known direct and metabolism-dependent inhibitors of CYP2C8 were included as positive controls, and negative controls included the absence of bexagliflozin.

Results:

- Under the experimental conditions examined, there was little or no evidence of direct, time-dependent, or metabolism-dependent inhibition of CYP2C8 by bexagliflozin. Bexagliflozin is unlikely to inhibit CYP2C8 at the clinically relevant dose.

Table 85. Potential of Bexagliflozin as an Inhibitor of Human CYP2C8

Enzyme	Test reaction	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		No preincubation		30-min preincubation without NADPH		30-min preincubation with NADPH		Potential for metabolism-dependent inhibition ^c
		IC ₅₀ (μM) ^a	Inhibition observed at 50 μM (%) ^b	IC ₅₀ (μM) ^a	Inhibition observed at 50 μM (%) ^b	IC ₅₀ (μM) ^a	Inhibition observed at 50 μM (%) ^b	
CYP2C8	Amodiaquine <i>N</i> -dealkylation	> 50	6.3	> 50	13	>50	19	Little or no

Source: Tables 3 of Study THR-1474-N-439

^a Average data obtained from duplicate samples for each test article concentration were used to calculate IC₅₀ values.

^b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures): Inhibition observed (%) = 100% – Percent solvent control.

^c Metabolism-dependent inhibition was determined by comparison of IC₅₀ values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC₅₀ plots.

Abbreviations: CYP, cytochrome P450 isoenzyme; IC₅₀, half maximal inhibitory concentration.

14.1.13. In Vitro Permeation of Bexagliflozin Through Caco-2 Monolayers (Study THR-1442-N-431)

Methods: Bidirectional transport experiments were conducted in 21-day Caco-2 monolayer cultures. Bexagliflozin and (b) (4) (internal standard for high permeability) were dissolved in HBG buffer and added to the donor chamber of the filter at the desired concentrations (10 μM and 100 μM for bexagliflozin, 100 μM for (b) (4)). The transport experiments were conducted bidirectionally in duplicate. Samples in the receiver chamber were collected at multiple time points after the addition of the test articles.

Results:

- An active efflux process favors basolateral to apical transport of bexagliflozin at an efflux ratio >2 (mean value of 7.4). Further in vitro studies are needed to determine the efflux transporters involved in this process.

Table 86. Papp and Efflux Ratio of Bexagliflozin and Internal Standard (×10⁻⁶ cm/s)

Exp.	EGT0001442						(b) (4)		
	100 μM			10 μM			100 μM		
	P _{app} A>B	P _{app} B>A	R _E	P _{app} A>B	P _{app} B>A	R _E	P _{app} A>B	P _{app} B>A	R _E
1	2.6	14.9	5.8	3.8	16.4	4.3	7.0	34.9	5.00
2	2.1	23.6	11.4				8.3	45.7	5.5
3	2.8	13.6	4.8				6.7	37.3	5.6
Mean	2.5	17.4	7.4				7.3	39.3	5.4
SD	0.4	5.4	3.6				0.9	5.6	0.3

Source: Tables 2 of Study THR-1474-N-431

Abbreviations: P_{app}, apparent permeability; R_E, efflux ratio.

14.1.14. P-gp Substrate and Inhibitory Potential (Study THR-1442-N-432)

Methods: For bidirectional transport assays, Caco-2 cells were grown to confluence for 14 to 21 days on 1.0 µm BD Falcon filters in 24-well plates. Monolayer integrity was confirmed by transepithelial electrical resistance values greater than 400 ohms-cm² prior to assay initiation and monitored during the studies by Lucifer yellow transfer. The bidirectional apparent permeability coefficients (Papp) and efflux ratio were determined for 1 to 100µM bexagliflozin using 20-minute sampling intervals over 2 hours. For P-gp inhibitor assays, transport of [³H] Digoxin transport was assessed in the presence of 100µM bexagliflozin.

Results:

- The efflux ratios were 13, 6.7, and 5.4 for 1, 10, and 100 µM bexagliflozin, respectively. The inclusion of 20 µM cyclosporin A (a potent inhibitor of P-gp) with 10 µM bexagliflozin reduced the efflux ratio to 1.9, indicating that bexagliflozin is a potential P-gp substrate.
- The presence of 100 µM bexagliflozin reduced the efflux ratio for [³H]-digoxin from 10.3 to 3.5 suggesting that bexagliflozin at 100 µM is a potential inhibitor of P-gp but is not as potent as 20 µM cyclosporin A, which reduced the efflux ratio for [³H]-digoxin to 1.5. Calculation of the half-maximal inhibition constant (IC₅₀) for this interaction based on efflux ratio yielded an estimated value of 3.7 µM (2.3 to 6 µM range).

FDA Reviewer Comment: The determined IC₅₀ is much higher than the C_{max} of bexagliflozin following the oral dose of 20 mg with calculated R1 < 1.02. R1 in the gut is estimated to be about 6 and is less than the cut-off value of 11 in the DDI Guidance (January 2020). Therefore, bexagliflozin is unlikely to be a significant P-gp inhibitor in the clinical setting. Nonetheless, the Applicant conducted a clinical DDI study and demonstrated the lack of significant effect of bexagliflozin on the pharmacokinetics (PK) of the sensitive P-gp substrate digoxin.

14.1.15. Inhibitory Effect of Bexagliflozin on Transporters (Study THR-1442-N-441)

Methods: Vesicles or cells transfected with control vectors were used as negative controls and the validity of each assay was confirmed with a positive control inhibitor for each transporter. Bidirectional apparent permeability coefficients, the resulting efflux ratios (for breast cancer resistance protein [BCRP]), and the cleared volume (for BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) were quantified using transporter specific substrates in the presence and absence of bexagliflozin at 1 and 100 µmol L⁻¹. Each assay was conducted in duplicate and mean values were reported for each assay. For BCRP, OATP1B1, and OATP1B3, which were inhibited significantly by 100 µM bexagliflozin, IC₅₀ values were determined.

Results:

- At concentrations up to 100µM, bexagliflozin did not inhibit BSEP, OAT1, OAT3, OCT1, and OCT2 ([Table 87](#)).

- The rank order for inhibition at 100 μM bexagliflozin was OATP1B1>OATP1B3>BCRP. However, the IC_{50} values were high multiples of the expected C_{max} produced by the 20 mg bexagliflozin tablet (0.38 μM).
- Therefore, no meaningful inhibition on BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2 is expected from the plasma levels produced by the intended dosage strength.

Table 87. Inhibitory Effect of Bexagliflozin on Drug Transporters BCRP, BSEP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2

Transporter	BCRP	BSEP	OAT1	OAT3
Substrate	Prazosin	Taurocholate	Aminohippuric acid	Estrone sulfate
Inhibitor	Ko143	Cyclosporin A	Probenecid	Probenecid
Cell lines/vesicles	LLC-PK1	vesicles	S2	S2
100 μM Effect	25.9%	175.4%	71.0%	45.2%
IC_{50} (μM)	79.2	> 100	> 100	~ 100
Transporter	OATP1B1	OATP1B3	OCT1	OCT2
Substrate	Estradiol glucuronide	Estradiol glucuronide	Tetraethyl-ammonium	Metformin
Inhibitor	Rifampicin	Rifampicin	Quinidine	Quinidine
Cell lines/vesicles	293	293	293	293
100 μM Effect	5.6%	34.1%	61.8%	108.4%
IC_{50} (μM)	34.8	57.5	> 100	> 100

Source: Tables 1-8 of Study THR-1474-N-441

Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; IC_{50} , half maximal inhibitory concentration; OAT, organic anion transporter; OCT, organic cation transporter.

FDA Reviewer Comment: As BCRP is also expressed in the GI tract, the R1 gut value was calculated. As the value (1.2) is less than the cut-off of 11, bexagliflozin is unlikely to inhibit BCRP activity at the clinically relevant dose.

14.1.16. Transporters Substrate and Inhibitory Potential (Study THR-1442-N-491)

Methods and Results:

Inhibition:

- Bexagliflozin is an inhibitor of MATE1 with an IC_{50} value of 45.5 μM , but not an inhibitor of MATE2-K ([Table 88](#)).

Table 88. Inhibitory Effect of Bexagliflozin and Its Metabolite EGT0002149 on MATE1 and MATE2-K

Test article	Transporter	Test system	Substrate	Test article concentrations (μM)	IC_{50} (μM)
Bexagliflozin	MATE1	HEK293 cells	$[^{14}\text{C}]$ -Metformin (10 μM)	0.1, 0.3, 1, 3, 10, 30, 100	45.5
	MATE2-K				> 100
EGT0002149	MATE1				> 100
	MATE2-K				> 100

Source: Tables 1-2 of Study THR-1442-N-491

Abbreviations: IC_{50} , half maximal inhibitory concentration; MATE, multidrug efflux transporters.

Substrate:

- Bexagliflozin is a substrate of BCRP (Table 89).
- No definitive conclusion could be made on SLC transporters due to the high permeability of bexagliflozin in the parental cell line for the transporter cell lines.
- Glucuronide metabolite EGT0002149 is a substrate of OATP1B1, OATP1B3, and OAT3, but not for BCRP, OAT1, OCT2, MATE1, and MATE2-K.

Table 89. Substrate Determination for Bexagliflozin and its Metabolite EGT0002149

Test article	Transporter	Test system	Test article concentration (μM)	Potential substrate (uptake or efflux ratio ≥ 2 and reduced in presence of inhibitor)
Bexagliflozin	BCRP	MDCKII cells	10	Yes
	OATP1B1	HEK293 cells		Inconclusive
	OATP1B3			Inconclusive
	OAT1			Inconclusive
	OAT3			Inconclusive
	OCT2			Inconclusive
	MATE1			Inconclusive
	MATE2-K			Inconclusive
EGT0002149	BCRP	MDCKII cells		No
	OATP1B1	HEK293 cells		Yes
	OATP1B3			Yes
	OAT1			No
	OAT3			Yes
	OCT2			No
	MATE1			No
	MATE2-K			No

Source: Tables 3-20 of Study THR-1442-N-491

Abbreviations: OAT, organic anion transporter; OCT, organic cation transporter; MATE, multidrug efflux transporters.

FDA Reviewer Comment: Although substrate status of bexagliflozin for SLC transporters is inconclusive, active renal secretion via these SLC transporters, such as OATs, OCTs, MATE1, and MATE2-K, are unlikely to affect bexagliflozin PK. This is based on the observation from the mass balance study where only 2% of administered dose was found as the parent drug (bexagliflozin) in urine.

14.2. In Vivo Studies

14.2.1. Single and Multiple Dose in Healthy Subjects (Trial C-328)

Study Design

This was a phase 1, double-blind, placebo-controlled, dose-escalation study conducted in 78 healthy male and female subjects to assess the safety, tolerability, PK, and pharmacodynamics (PD) (24 hours urinary glucose excretion [UGE]) of rising single and multiple oral doses of bexagliflozin. In the study, bexagliflozin was administered as an L-proline: bexagliflozin 2:1 cocrystal (EGT0001474) formulated in neat-filled hypromellose capsules. Therefore, EGT0001474 doses of 2.5 mg to 150 mg listed below are cocrystal doses and are equivalent to bexagliflozin doses of 1.67 to 100 mg.

- In Part 1: subjects were randomized to receive either a single oral dose of placebo or EGT0001474 at 2.5 mg, 5 mg, 10 mg, 25 mg, 75 mg, or 150 mg in the fasted state.

Subjects in the food effect cohort received a second dose of placebo or 25 mg EGT0001474 after a standard high fat breakfast.

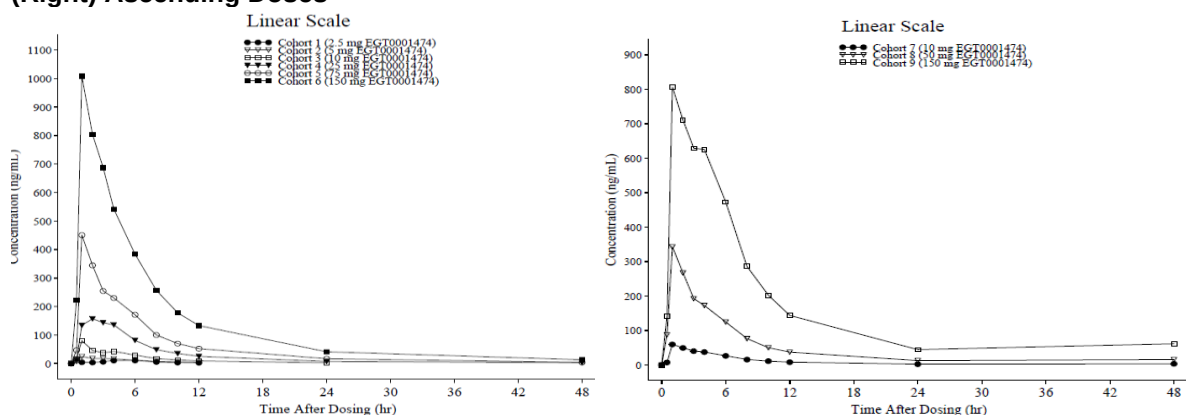
- In Part 2: subjects received single oral daily doses of placebo or EGT0001474 at 10 mg, 50 mg, or 150 mg in the fasted state for 14 days.

Serial PK, safety, and PD evaluations were performed at prespecified times throughout the study.

Results

- Following the oral administration of bexagliflozin capsules, peak plasma concentrations of bexagliflozin reached between 2 to 4 hours postdose ([Figure 21](#)).
- Based on data from the single ascending dose (SAD) portion of the study, bexagliflozin exhibits a linear PK (as assessed by C_{max} and AUC) in EGT0001474 doses ranging from 2.5 mg to 150 mg (equivalent to 1.7 mg to 100 mg bexagliflozin, [Table 90](#)).
- Food delayed T_{max} by 1 to 2 hours and decreased the mean C_{max} and AUC_{0-inf} by approximately 34% and 10%, respectively, when compared to the fasted state.
- Based on data from the multiple ascending dose (MAD) portion of the study, there is no significant accumulation after multiple doses of bexagliflozin capsules once daily for 14 days at 6.7 mg to 100 mg with accumulation ratios ranging from 1.10 to 1.17 ([Table 90](#)).
- Bexagliflozin increased UGE in healthy subjects in a dose-dependent and saturable manner with plateau between 16.7 mg and 50 mg of bexagliflozin ([Figure 22](#)).

Figure 21. Mean Concentration-Time Profiles for Bexagliflozin Following Single (Left) and Multiple (Right) Ascending Doses



Source: Figures 11-1 and 11-2 of Study Report HR-1474-C-328

Table 90. Summary of Mean (SD) Bexagliflozin PK Parameters Following Single and Multiple Doses of EGT0001474

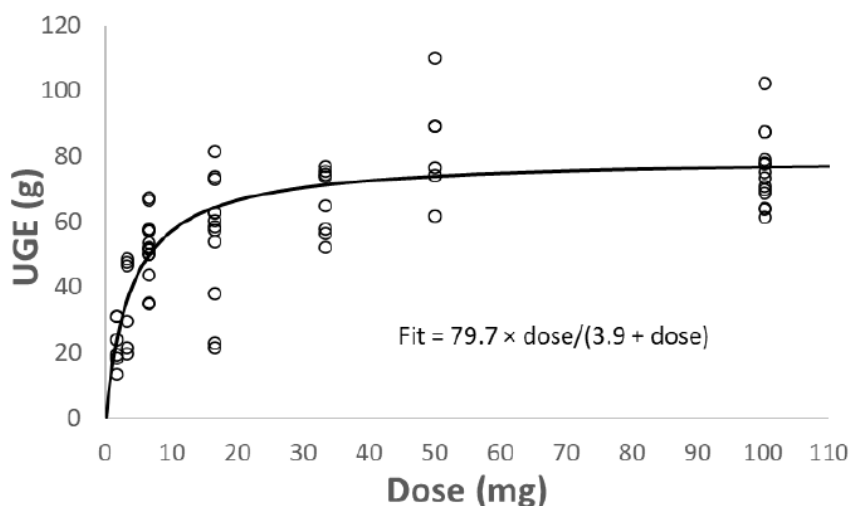
Parameter	Units	Single Dose of EGT0001474						
		Cohort 1 2.5 mg	Cohort 2 5 mg	Cohort 3 10 mg	Cohort 4 Fasted 25 mg	Cohort 5 75 mg	Cohort 6 150 mg	Cohort 4 Fed 25 mg
C_{max}	ng/mL	12.7 (1.08)	28.0 (10.2)	90.7 (31.7)	194 (53.3)	537 (198)	1183 (434)	129 (37.0)
T_{max}^a	hr	4.00 (4.00, 6.00)	2.01 (1.00, 4.00)	1.00 (1.00, 4.00)	2.00 (1.00, 4.00)	1.51 (1.00, 6.00)	1.50 (1.00, 3.00)	5.02 (2.00, 10.0)
AUC_{0-t}	ng•hr/mL	67.4 (13.9)	126 (33.8)	388 (108)	1200 (320)	2564 (607)	6412 (1179)	1081 (293)
AUC_{0-inf}	ng•hr/mL	87.1 (9.07)	148 (33.7)	412 (109)	1246 (321)	2628 (580)	6639 (1176)	1122 (292)
AUC_{0-24}	ng•hr/mL	85.6 (9.67)	145 (34.4)	392 (99.8)	1121 (264)	2383 (527)	5828 (1080)	1004 (236)
$t_{1/2}$	hr	3.66 (0.559)	4.19 (1.30)	5.81 (1.38)	9.71 (3.28)	9.27 (1.60)	11.4 (2.49)	7.01 (2.53)
λ_z	L/hr	0.193 (0.0314)	0.177 (0.0456)	0.126 (0.0373)	0.0799 (0.0308)	0.0765 (0.0117)	0.0637 (0.0158)	0.109 (0.0340)
CL/F	L/hr	28.9 (2.89)	35.3 (8.24)	25.9 (7.59)	21.2 (5.18)	30.1 (8.51)	23.1 (3.67)	23.7 (6.39)
V_z/F	L	154 (37.1)	222 (121)	208 (49.5)	287 (105)	398 (109)	385 (121)	234 (98.9)

Parameter	Units	Multiple Dose of EGT0001474					
		Cohort 7 10 mg Day 1	Cohort 8 50 mg Day 1	Cohort 9 150 mg Day 1	Cohort 7 10 mg Day 14	Cohort 8 50 mg Day 14	Cohort 9 150 mg Day 14
C_{max}	ng/mL	70.5 (25.3)	405 (161)	941 (316)	85.7 (27.9)	465 (126)	1202 (345)
T_{max}^a	hr	1.50 (1.00, 4.00)	1.01 (1.00, 4.00)	2.01 (1.00, 6.00)	1.00 (1.00, 6.05)	1.00 (1.00, 1.00)	1.02 (1.00, 6.00)
AUC_{0-t}	ng•hr/mL	360 (59.8)	1807 (265)	5968 (1333)	432 (89.5)	2146 (539)	7733 (1957)
AUC_{0-inf}	ng•hr/mL	387 (65.1)	1945 (298)	6402 (1523)	NA	NA	NA
AUC_{0-24}	ng•hr/mL	363 (54.3)	1807 (265)	5968 (1333)	412 (73.8)	1983 (443)	6939 (1675)
$t_{1/2}$	hr	6.33 (1.65)	7.34 (1.01)	6.58 (0.889)	9.03 (1.44)	9.02 (2.38)	10.3 (1.98)
λ_z	L/hr	0.118 (0.0370)	0.0958 (0.0122)	0.107 (0.0146)	0.0783 (0.0117)	0.0818 (0.0230)	0.0697 (0.0143)
CL/F ^b	L/hr	26.6 (4.72)	26.3 (4.76)	24.4 (4.70)	24.9 (4.45)	26.4 (6.49)	22.6 (4.67)
V_z/F^b	L	235 (44.0)	277 (50.2)	229 (40.7)	319 (39.3)	327 (54.2)	333 (84.2)
RA		NA	NA	NA	1.17 (0.0515)	1.10 (0.105)	1.16 (0.0679)

Source: Tables 11-6 and 11-7 of Study Report HR-1474-C-328

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from 0 to 24 hours; AUC_{0-t} , area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; C_{max} , maximum plasma concentration; $t_{1/2}$, half life; T_{max} , time to maximum plasma concentration; V_z/F , apparent volume of distribution; λ_z , elimination rate constant.

Figure 22. 24-Hour Urinary Glucose Excretion (UGE) as a Function of Bexagliflozin Dose



Source: Figures 11-4 and 11-5 of Study Report HR-1474-C-328
Pooled data from Part 1 Day 1 and Part 2 Day 1; converted from cocrystal dose to Bexa dose
The solid line is the model best fit. The maximum UGE was estimated at 79.7 g per day (95% CI, 73.8, 85.5), and the ED50 was 3.9 mg (95% CI, 2.6, 5.3).

Conclusion

- Bexagliflozin was well tolerated up to 100 mg per day for 14 days.
- Bexagliflozin, administered as oral capsules, was rapidly absorbed, and resulted in dose-dependent increases in systemic exposure and dose-related saturable glucosuria.

FDA Reviewer Comment: Linear PK in the dose range of 1.7 mg to 100 mg is based on C_{max} and AUC values. The terminal $t_{1/2}$ values appear to increase with increasing bexagliflozin doses. Nonetheless, based on limited accumulation between 6.7 and 100 mg, the effective $t_{1/2}$ may be comparable among the doses. Based on data from Part 2, after 14 days of repeat dosing, UGE declined by about 13% in the 100 mg bexagliflozin/day cohort and 26% in the 16.7 mg bexagliflozin/day cohort when compared to the UGE values measured on Day 1 in the same cohort.

14.2.2. SAD Study in Patients With Type 2 Diabetes (Trial C-396)

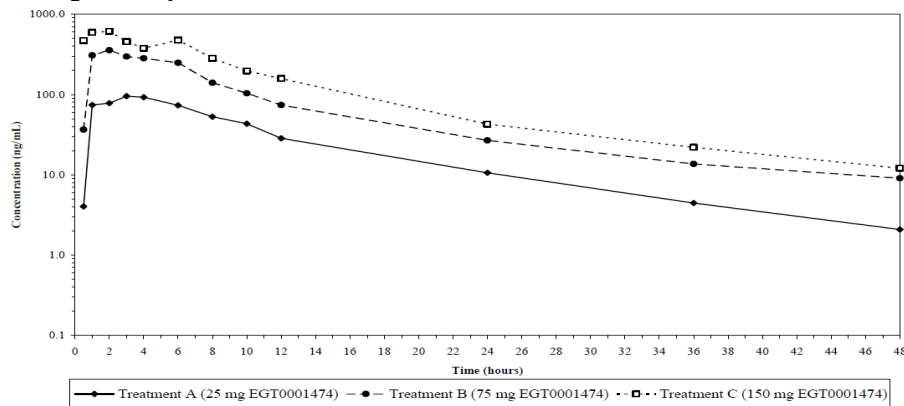
Study Design

This was a phase 1, single-dose, double-blind, placebo-controlled study to assess the PK, PD (UGE), and safety tolerability of bexagliflozin following the oral administration of 25 mg, 75 mg, and 150 mg EGT0001474 (capsules; equivalent to 16.7, 50, and 100 mg bexagliflozin) in subjects with T2DM. During the study, 24 subjects (3 cohorts of 8 subjects per cohort) were randomized in a ratio of 3:1 to bexagliflozin or placebo groups. Serial PK, safety, and PD evaluations were performed at prespecified times throughout the study.

Results

- Upon absorption, the maximum plasma concentration ($C_{\max}$) of bexagliflozin was reached at 2 to 3 hours postdose (range 0.5 to 8 hours) ([Figure 23](#)).
- Systemic exposures ($C_{\max}$ and AUC) of bexagliflozin showed a linear dose proportionality in the studied dose range of 16.7 mg and 100 mg ([Table 91](#)).
- Although the amount of UGE increased significantly compared to that measured in subjects taking placebo, the increase (24 hour UGE between 90 to 120 g) was comparable at the studied doses of 16.7 mg and 100 mg ([Table 92](#)).
- Single doses of bexagliflozin decreased the fasting plasma glucose (FPG) levels by 29 mg/dL, 27 mg/dL, and 26 mg/dL, respectively, 24 hours after bexagliflozin administration at the doses of 16.7 mg, 50 mg, and 100 mg ([Table 93](#)).

Figure 23. Mean Bexagliflozin Concentration-Time Profiles Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin)



Source: Figure 11.4-2 of Study Report THR-1474-C-396 (b) (4) R09-0580

Table 91. Mean Bexagliflozin PK Parameters Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin) in Subjects With T2DM

Parameter (units)	Arithmetic Mean (%CV) Median (Range) for T _{max}		
	EGT0001474, 25 mg (1 x 25 mg capsule) (N=6)	EGT0001474, 75 mg (3 x 25 mg capsules) (N= 6)	EGT0001474, 150 mg (6 x 25 mg capsules) (N= 6)
AUC _{0-t} (ng·hr/mL)	1103.89 (42.60)	3370.29 (14.82)	6177.80 (27.37)
AUC _{inf} (ng·hr/mL)	1165.59 (41.17)	3532.02 (14.86)	6399.55 (27.13)
AUC ₀₋₂₄ (ng·hr/mL)	987.30 (37.29)	2990.63 (15.42)	5584.72 (27.16)
C _{max} (ng/mL)	157.23 (48.50)	518.67 (34.00)	1014.00 (36.75)
t _{max} (hr)	3.00 (1.00 -8.00)	2.00 (1.00 -6.00)	2.00 (0.50 – 6.00)
λ _z (1/hr)	0.0741 (28.99)	0.0613 (27.36)	0.0622 (31.44)
t _{1/2} (hr)	10.10 (31.80)	12.18 (31.90)	12.15 (32.42)
CL/F (mL/hr)	25059.67 (38.44)	21616.42 (14.40)	24996.33 (28.04)
V _z /F (mL)	355114.57 (44.29)	382783.75 (36.30)	435944.78 (41.25)

Source: Table 11.4-1 of Study Report THR-1474-C-396 (b) (4) R09-0580)

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from 0 to 24 hours; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; C_{max}, maximum plasma concentration; %CV, coefficient of variation; t_{1/2}, half life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

Table 92. Mean UGE Values at Baseline and Different Time Intervals Following Oral Administration of a Single Dose of 25 mg, 75 mg, and 150 mg EGT0001474 (Equivalent to 16.7 mg, 50 mg, and 100 mg Bexagliflozin) in Subjects With T2DM

Parameters (units)	Placebo	EGT0001474, 25 mg (1 x 25 mg capsule) (N=6)	EGT0001474, 75 mg (3 x 25 mg capsules) (N= 6)	EGT0001474, 150 mg (6 x 25 mg capsules) (N= 6)
Pre-dose (-12 – 0 h)				
Glucose (mg/dL)	271.83	135.83	183.50	113.50
Urine vol. (mL)	1206.67	2011.83	1226.50	1155.17
UGE (mg)	3313.93	2703.46	2562.75	1291.90
Post-dose (0-12 h)				
Glucose (mg/dL)	815.33	2630.17	2674.83	2641.33
Urine vol. (mL)	1679.83	2338.33	1903.00	2389.83
UGE (mg)	9932.15	62662.91	49526.23	62560.58
Post-dose (12-24 h)				
Glucose (mg/d)	400.20	2969.67	3247.50	4170.50
Urine vol. (mL)	1304.60	1039.67	1224.00	1305.50
UGE (mg)	5667.32	31220.45	40704.85	57079.55
Post-dose (24-36 h)				
Glucose (mg/dL)	735.83	2835.50	2906.00	4244.50
Urine vol. (mL)	1648.67	1961.00	1761.33	1518.67
UGE (mg)	10393.35	52588.20	45280.92	62986.45
Post-dose (36-48 h)				
Glucose (mg/dL)	485.50	1983.50	2759.67	3365.33
Urine vol. (mL)	1351.50	1419.17	1045.00	1395.67
UGE (mg)	6772.04	23484.69	27013.90	41356.56

Source: Table 11.4-2 of Study Report THR-1474-C-396 (b) (4) R09-0580)

Abbreviations: UGE, urinary glucose excretion; T2DM, type 2 diabetes mellitus.

Table 93. Effects on FPG in Subjects With T2DM

Study Day ¹	Statistics	Fasting Glucose (mg/dL): (normal range 70-100 mg/dL)			
		Placebo	EGT0001474		
		(N=6)	25 mg (N=6)	75 mg (N=6)	150 mg (N=6)
Day 1	Mean	174.67	183.17	183.33	159.67
	(SD)	(58.37)	(46.12)	(45.37)	(35.11)
Day 2	Mean	179.50	154.00	156.17	133.33
	(SD)	(61.72)	(28.78)	(42.08)	(19.50)
Change from Day 1	Mean	4.83	-29.17	-27.17	-26.33
	(SD)	(13.30)	(23.40)	(7.28)	(23.07)
T-test P value	---	0.41	0.03	0.00	0.04

Source: Table 11.4-3 of Study Report THR-1474-C-396 ((b) (4) R09-0580)
Abbreviations: FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.

Conclusion

- A single dose of bexagliflozin up to 100 mg (or 150 mg EGT0001474) is well tolerated in subjects with T2DM.
- Bexagliflozin doses ≥ 16.7 mg (or 25 mg EGT0001474) produced significant glucosuria and induced significant reduction in fasting plasma glucose compared to placebo in T2DM patients.

14.2.3. SAD and MAD Study in Healthy Subjects and Patients With T2DM (Trial C-445)

Study Design

This was a phase 1, double-blind, placebo-controlled, dose escalation study to assess the safety, tolerability, PK, and PD of bexagliflozin (EGT0002142 sustained release (SR) tablet) in Japanese healthy subjects and patients with T2DM. The treatment plan is described below:

Table 94. Description of Treatment Plan, Trial C-445

	Group	Study Drug	Treatment Group	Methodology
Single Dose	1	EGT0001442 SR tablets, 3 mg: 6 subjects; placebo: 2 subjects	3 mg group (fed state)	Single dose
Single Dose and Food Effect	2	EGT0001442 SR tablets, 10 mg: 6 subjects; placebo: 2 subjects	10 mg group (fed and fasted)	Cross over; 2 doses
Single Dose and Food Effect	3	EGT0001442 SR tablets, 30 mg: 6 subjects; placebo: 2 subjects	30 mg group (fed and fasted)	Cross over; 2 doses
Single Dose	4	EGT0001442 SR tablets, 90 mg: 6 subjects; placebo: 2 subjects	90 mg group (fed state)	Single dose
Multiple Dose	5	EGT0001442 SR tablets, 3 mg: 8 subjects; placebo: 2 subjects	3 mg group (fed state)	7 daily doses
Multiple Dose	6	EGT0001442 SR tablets, 10 mg: 8 subjects; placebo: 2 subjects	10 mg group (fed state)	7 daily doses
Multiple Dose	7	EGT0001442 SR tablets, 30 mg: 8 subjects; placebo: 2 subjects	30 mg group (fed state)	7 daily doses

Source: Table 9.1-1 of Study Report THR-1442-C-445
Abbreviations: SR, sustained release.

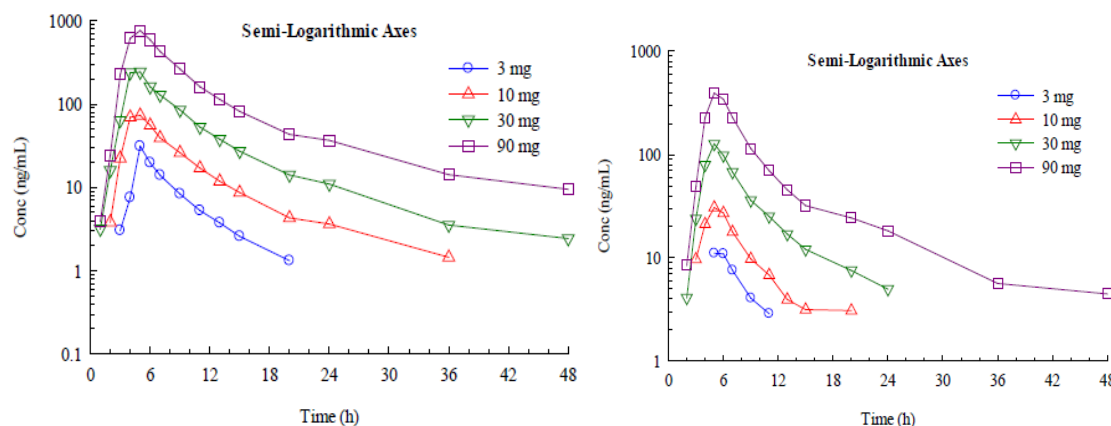
Serial PK, safety, and PD evaluations were performed at prespecified times up to 48 hours postdose.

Results

Part 1: SAD in Healthy Japanese Subjects

- Following a single dose oral administration of bexagliflozin tablets, a dose-proportional increase in C_{max} and AUC of bexagliflozin was observed in the studied dose range of 3 mg to 90 mg. The percentage of dose excreted in urine (Fe %dose) as bexagliflozin was 2.17 to 2.76% of the dose and thus, renal clearance (CL_r) was a minor component of the total clearance ([Figure 24](#) and [Table 95](#)).
- A dose-proportional increase in C_{max} and AUC of metabolite EGT0002149 was observed. The Fe %dose as metabolite EGT0002149 was 28.4 to 34.8% of the dose and thus, CL_r was a significant component of the total clearance of the metabolite ([Figure 24](#) and [Table 96](#)).
- For bexagliflozin, subjects dosed in the fed state exhibited a higher C_{max} compared to subjects dosed in the fasted state. The terminal elimination constant (λ_z) and T_{max} were unaffected by food consumption. There was no impact on the PK of the metabolite (data not shown).
- Consistent with the study results in American subjects, UGE in Japanese subjects increased in a dose-dependent manner after administration of 3 mg through 30 mg. The UGE was essentially the same in the 30 and 90-mg dose groups ([Table 97](#)).

Figure 24. Geometric Mean Plasma Concentrations of Bexagliflozin (Left) and Its Metabolite EGT0002149 (Right) After Oral Administration of a Single Dose of Bexagliflozin to Healthy Japanese Subjects in the Fed State



Source: Figures 11.1-1 and 11.1-3 of Study report THR-1442-C-445

Table 95. Summary of Bexagliflozin PK Parameters After Oral Administration of a Single Dose to Healthy Japanese Subjects in the Fed State

Parameter*	Dose			
	3 mg	10 mg	30 mg	90 mg
C _{max} (ng/mL)	36.1 ± 2.95 (6) [35.6; 19.3]	99.3 ± 4.98 (6) [98.7; 11.9]	283 ± 26.7 (6) [277; 24.5]	1,004 ± 95.2 (6) [982; 23.3]
T _{max} (h)	5.0 (6)	4.0 (6)	4.0 (6)	4.5 (6)
AUC _(0-t) (h×ng/mL)	151 ± 15.7 (6) [147; 25.4]	517 ± 34.2 (6) [511; 17.8]	1,656 ± 130 (6) [1,632; 18.3]	5,298 ± 324 (6) [5,252; 14.4]
AUC _(inf) (h×ng/mL)	160 ± 17.3 (6) [156; 26.2]	539 ± 30.4 (6) [535; 14.7]	1,697 ± 143 (6) [1,670; 19.5]	5,620 ± 389 (5) [5,570; 14.9]
λ _z (1/h)	0.1290 ± 0.0174 (6) [0.1216; 41.4]	0.0947 ± 0.0103 (6) [0.0921; 25.9]	0.0790 ± 0.0146 (6) [0.0736; 41.3]	0.0612 ± 0.0099 (5) [0.0587; 30.9]
t _{1/2} (h)	6.13 ± 1.14 (6) [5.70; 41.4]	7.73 ± 0.76 (6) [7.53; 25.9]	9.99 ± 1.41 (6) [9.42; 41.3]	12.2 ± 1.33 (5) [11.8; 30.9]
CL/F (L/h)	19.8 ± 1.99 (6) [19.2; 26.2]	18.9 ± 1.19 (6) [18.7; 14.7]	18.2 ± 1.33 (6) [18.0; 19.5]	16.3 ± 1.03 (5) [16.2; 14.9]
V _z /F (L)	160 ± 12.9 (6) [158; 19.1]	212 ± 25.5 (6) [203; 34.7]	254 ± 26.8 (6) [244; 33.6]	284 ± 34.4 (5) [275; 30.7]
A _e (μg)	79.9 ± 10.5 (6) [75.9; 38.2]	222 ± 19.65 (6) [216.9; 25.0]	839 ± 58.0 (6) [828; 18.0]	2,326 ± 127 (6) [2,308; 13.7]
F _e (% Dose)	2.66 ± 0.35 (6) [2.53; 38.2]	2.22 ± 0.20 (6) [2.17; 25.0]	2.80 ± 0.19 (6) [2.76; 18.0]	2.58 ± 0.14 (6) [2.56; 13.7]
CL _r (mL/min)	8.77 ± 0.79 (6) [8.60; 22.5]	7.10 ± 0.34 (6) [7.05; 12.2]	8.60 ± 0.71 (6) [8.46; 19.6]	7.45 ± 0.61 (6) [7.33; 20.2]
CL _{nr} (L/h)	19.2 ± 2.00 (6) [18.7; 27.1]	18.4 ± 1.20 (6) [18.3; 15.1]	17.7 ± 1.31 (6) [17.5; 19.8]	15.9 ± 1.00 (5) [15.7; 14.9]

*Arithmetic mean ± standard error (N) [Geometric mean: geometric %CV] except T_{max} for which the median (N) is reported.

Source: Table 11.1-4 of Study report THR-1442-C-445

Abbreviations: A_e, amount excreted; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; CL_{nr}, non-renal clearance; CL_r, renal clearance; C_{max}, maximum plasma concentration; %CV, coefficient of variation; F_e, fraction excreted unchanged; PK, pharmacokinetics; t_{1/2}, half life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant.

Table 96. Summary of Metabolite EGT0002149 PK Parameters After Oral Administration of a Single Dose of Bexagliflozin to Healthy Japanese Subjects in the Fed State

Parameter*	Dose			
	3 mg	10 mg	30 mg	90 mg
C _{max} (ng/mL)	13.9 ± 1.45 (6) [13.5; 26.2]	42.4 ± 3.79 (6) [41.3; 26.2]	138 ± 15.6 (6) [134; 27.6]	467 ± 72.1 (6) [438; 42.5]
T _{max} (h)	5.0 (6)	4.5 (6)	5.0 (6)	5.0 (6)
AUC _(0-t) (h×ng/mL)	50.1 ± 5.91 (6) [48.2; 32.2]	183 ± 17.1 (6) [179; 26.4]	722 ± 62.4 (6) [708; 22.5]	2,541 ± 362 (6) [2,402; 38.9]
AUC _(inf) (h×ng/mL)	59.6 ± 6.33 (6) [57.7; 28.9]	192 ± 35.2 (3) [185; 37.3]	788 ± 76.2 (5) [772; 23.5]	2,477 ± 512 (4) [2,316; 44.8]
λ _z (1/h)	0.2991 ± 0.0414 (6) [0.2823; 40.4]	0.1902 ± 0.0536 (3) [0.1705; 68.1]	0.0970 ± 0.0090 (5) [0.0952; 21.9]	0.0594 ± 0.0035 (4) [0.0590; 12.3]
t _{1/2} (h)	2.62 ± 0.45 (6) [2.46; 40.4]	4.66 ± 1.81 (3) [4.07; 68.1]	7.42 ± 0.74 (5) [7.28; 21.9]	11.8 ± 0.75 (4) [11.7; 12.3]
CL/F (L/h)	39.0 ± 4.74 (6) [37.7; 28.9]	41.1 ± 9.23 (3) [39.3; 37.3]	28.8 ± 3.20 (5) [28.2; 23.5]	30.1 ± 6.18 (4) [28.2; 44.8]
V _z /F (L)	140 ± 17.5 (6) [134; 34.7]	254 ± 74.1 (3) [230; 61.3]	307 ± 42.4 (5) [296; 31.0]	504 ± 97.0 (4) [477; 39.7]
A _e (μg)	1,303 ± 132 (6) [1,270; 24.9]	4,332 ± 210 (6) [4,308; 11.7]	14,447 ± 625 (6) [14,378; 10.8]	35,405 ± 1,454 (6) [35,240; 10.9]
Fe (% Dose)	31.5 ± 3.19 (6) [30.7; 24.9]	31.4 ± 1.52 (6) [31.2; 11.7]	34.9 ± 1.51 (6) [34.8; 10.8]	28.5 ± 1.17 (6) [28.4; 10.9]
CL _r (mL/min)	441 ± 36.2 (6) [433; 22.3]	449 ± 106 (3) [426; 40.7]	342 ± 31.4 (5) [337; 19.9]	278 ± 53.0 (5) [260; 43.1]
CL _{nr} (L/h)	12.5 ± 3.92 (6) [7.95; 205]	14.2 ± 3.33 (3) [13.4; 43.7]	8.28 ± 1.58 (5) [7.72; 44.2]	12.5 ± 2.28 (4) [11.8; 39.6]

*Arithmetic mean ± standard error (N) [Geometric mean; geometric %CV] except T_{max} for which the median (N) is reported.

Source: Table 11.1-10 of Study report THR-1442-C-445

Abbreviations: A_e, amount excreted; AUC_{0-inf}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; CL_{nr}, non-renal clearance; CL_r, renal clearance; C_{max}, maximum plasma concentration; %CV, coefficient of variation; Fe, fraction excreted unchanged; PK, pharmacokinetics; t_{1/2}, half life; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant

Table 97. Summary of UGE Rate (mg/min) After Oral Administration of a Single Dose to Healthy Japanese Subjects

Study Day*	Dose				
	Placebo	3 mg	10 mg	30 mg	90 mg
1	0.053 ± 0.005 (8) [0.052; 28.4]	24.6 ± 1.42 (6) [24.3; 14.5]	31.7 ± 1.51 (6) [31.5; 11.5]	51.7 ± 3.45 (6) [51.2; 15.9]	50.7 ± 2.01 (6) [50.5; 9.85]

*Arithmetic mean ± standard error (N) [Geometric mean; geometric %CV]

Source: Table 11.1-16 of Study report THR-1442-C-445

Abbreviations: %CV, coefficient of variation; UGE, urinary glucose excretion.

Part 2: MAD in Japanese Subjects With T2DM

- The systemic exposures of bexagliflozin and its metabolite are dose-proportional at the doses ranging from 3 to 30 mg.
- Upon once daily dosing, there was no significant accumulation of bexagliflozin or its metabolite ([Table 98](#) and [Table 99](#)).
- As shown in [Table 100](#), although the UGE rate was greater for treated subjects than placebo subjects on Days 1 and 7, the UGE rate geometric means were comparable among 3 mg, 10 mg, and 30-mg dose groups.

- Bexagliflozin reduced FPG in Japanese subjects with T2DM at all dose levels ([Table 101](#)). A statistically significant FPG reduction was observed at 10 mg and 30 mg bexagliflozin doses.

Table 98. Summary of Bexagliflozin PK Parameters After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State

Parameter*	Dose					
	3 mg		10 mg		30 mg	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C _{max} (ng/mL)	27.3 ± 2.71 (8) [26.4; 27.0]	27.2 ± 2.16 (8) [26.6; 22.5]	111 ± 7.97 (8) [108; 22.5]	117 ± 9.20 (8) [114; 23.8]	266 ± 17.2 (8) [262; 19.3]	357 ± 44.2 (8) [337; 39.0]
T _{max} (h)	4.50 (8)	4.00 (8)	5.00 (8)	4.50 (8)	5.00 (8)	4.00 (8)
AUC _(0-t) (h×ng/mL)	131 ± 9.32 (8) [129; 20.2]	156 ± 13.6 (8) [151; 24.9]	540 ± 42.6 (8) [528; 23.4]	762 ± 72.7 (8) [738; 27.7]	1,273 ± 87.6 (8) [1,249; 21.6]	1,792 ± 149 (8) [1,742; 26.7]
AUC ₍₀₋₂₄₎ (h×ng/mL)	131 ± 9.32 (8) [129; 20.2]	151 ± 11.2 (8) [148; 21.4]	540 ± 42.6 (8) [528; 23.4]	650 ± 59.5 (8) [631; 26.0]	1,273 ± 87.6 (8) [1,249; 21.6]	1,557 ± 119 (8) [1,521; 24.6]
λ _z (1/h)	0.1182 ± 0.0336 (3) [0.1086; 54.8]	0.0716 ± 0.0079 (6) [0.0698; 24.1]	0.0681 ± 0.0103 (5) [0.0643; 41.5]	0.0505 ± 0.0066 (7) [0.0480; 35.3]	0.0757 ± 0.0064 (6) [0.0741; 23.4]	0.0577 ± 0.0082 (8) [0.0537; 42.2]
t _{1/2} (h)	6.96 ± 2.01 (3) [6.38; 54.8]	10.1 ± 0.86 (6) [9.93; 24.1]	11.6 ± 2.38 (5) [10.8; 41.5]	15.2 ± 1.93 (7) [14.4; 35.3]	9.57 ± 1.00 (6) [9.35; 23.4]	13.8 ± 1.99 (8) [12.9; 42.2]
CL/F (L/h)	—†	20.7 ± 1.53 (8) [20.3; 21.4]	—†	16.3 ± 1.47 (8) [15.8; 26.0]	—†	20.3 ± 1.92 (8) [19.7; 24.6]
V _z /F (L)	—†	309 ± 42.2 (6) [293; 38.0]	—†	331 ± 37.8 (7) [316; 37.1]	—†	387 ± 43.4 (8) [367; 38.9]
A _e (μg)	55.8 ± 12.7 (8) [48.3; 59.2]	79.7 ± 17.9 (8) [69.2; 59.0]	180 ± 18.8 (8) [174; 30.1]	233 ± 24.6 (8) [222; 35.8]	574 ± 59.2 (8) [552; 31.5]	707 ± 57.4 (8) [691; 23.0]
Fe (% Dose)	1.86 ± 0.42 (8) [1.61; 59.2]	2.66 ± 0.60 (8) [2.31; 59.0]	1.80 ± 0.19 (8) [1.74; 30.1]	2.33 ± 0.25 (8) [2.22; 35.8]	1.91 ± 0.20 (8) [1.84; 31.5]	2.36 ± 0.19 (8) [2.30; 23.0]
CL _r (mL/min)	7.15 ± 1.44 (8) [6.26; 59.3]	8.83 ± 1.75 (8) [7.81; 56.2]	5.61 ± 0.49 (8) [5.47; 22.9]	6.17 ± 0.76 (8) [5.86; 34.7]	7.71 ± 0.86 (8) [7.36; 34.2]	7.92 ± 0.96 (8) [7.58; 31.8]
CL _{nr} (L/h)	—†	20.2 ± 1.53 (8) [19.8; 22.1]	—†	15.9 ± 1.45 (8) [15.5; 26.3]	—†	19.8 ± 1.88 (8) [19.3; 24.7]

Source: Table 11.2-4 of study report THR-1442-C-445

Abbreviations: A_e, amount excreted; AUC₀₋₂₄, area under the curve from zero to 24 hours; AUC_{0-t}, area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; CL_{nr}, non-renal clearance; CL_r, renal clearance; C_{max}, maximum plasma concentration; %CV, coefficient of variation; Fe, fraction excreted unchanged; PK, pharmacokinetics; t_{1/2}, half life; T2DM, type 2 diabetes mellitus; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant

Table 99. Summary of Metabolite EGT0002149 PK Parameters After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State

Parameter*	3 mg		10 mg		30 mg	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C _{max} (ng/mL)	31.1 ± 3.93 (8) [29.5; 35.3]	29.6 ± 3.85 (8) [28.2; 33.0]	110 ± 9.32 (8) [107; 24.6]	122 ± 15.1 (8) [115; 39.7]	293 ± 27.2 (8) [284; 27.7]	324 ± 35.1 (8) [311; 31.7]
T _{max} (h)	5.00 (8)	4.00 (8)	5.00 (8)	5.00 (8)	5.00 (8)	5.00 (8)
AUC _(0-t) (h×ng/mL)	148 ± 22.9 (8) [136; 46.6]	164 ± 25.4 (8) [150; 46.5]	659 ± 62.8 (8) [639; 27.3]	824 ± 98.0 (8) [787; 33.0]	1,501 ± 167 (8) [1,435; 33.6]	2,026 ± 287 (8) [1,875; 45.4]
AUC ₍₀₋₂₄₎ (h×ng/mL)	148 ± 22.9 (8) [136; 46.6]	164 ± 25.4 (8) [150; 46.5]	659 ± 62.8 (8) [639; 27.3]	721 ± 78.5 (8) [692; 30.8]	1,501 ± 167 (8) [1,435; 33.6]	1,755 ± 234 (8) [1,638; 42.5]
λ _z (1/h)	0.2338 ± 0.0534 (5) [0.2020; 74.7]	0.1102 ± 0.0383 (5) [0.0810; 119]	0.0639 ± 0.0074 (4) [0.0627; 22.6]	0.0528 ± 0.0072 (5) [0.0511; 28.4]	0.0531 ± 0.0059 (4) [0.0522; 22.1]	0.0555 ± 0.0148 (4) [0.0505; 51.9]
t _{1/2} (h)	4.20 ± 1.52 (5) [3.43; 74.7]	12.1 ± 4.79 (5) [8.56; 119]	11.3 ± 1.19 (4) [11.1; 22.6]	14.0 ± 1.56 (5) [13.6; 28.4]	13.5 ± 1.43 (4) [13.3; 22.1]	14.9 ± 3.21 (4) [13.7; 51.9]
CL/F (L/h)	—†	21.7 ± 3.32 (8) [19.9; 46.5]	—†	15.0 ± 1.54 (8) [14.4; 30.8]	—†	19.7 ± 2.94 (8) [18.3; 42.5]
V _z /F (L)	—†	295 ± 106 (5) [240; 75.9]	—†	307 ± 41.2 (5) [298; 27.0]	—†	397 ± 110 (4) [362; 50.3]
A _e (μg)	1,406 ± 82.2 (8) [1,392; 15.3]	1,390 ± 67.3 (8) [1,379; 13.7]	4,089 ± 402 (8) [3,974; 24.9]	4,524 ± 364 (8) [4,425; 22.7]	12,199 ± 474 (8) [12,134; 11.1]	13,235 ± 684 (8) [13,115; 14.4]
Fe (% Dose)	34.0 ± 1.99 (8) [33.6; 15.3]	33.6 ± 1.63 (8) [33.3; 13.7]	29.7 ± 2.92 (8) [28.8; 24.9]	32.8 ± 2.64 (8) [32.1; 22.7]	29.5 ± 1.15 (8) [29.3; 11.1]	32.0 ± 1.65 (8) [31.7; 14.4]
CL _r (mL/min)	185 ± 26.3 (8) [171; 47.7]	164 ± 21.5 (8) [153; 45.8]	108 ± 10.8 (8) [104; 30.5]	111 ± 11.2 (8) [107; 30.0]	146 ± 15.3 (8) [141; 29.8]	139 ± 15.8 (8) [133; 31.3]
CL _{nr} (L/h)	—†	11.8 ± 2.14 (8) [10.6; 51.1]	—†	8.38 ± 1.19 (8) [7.78; 44.0]	—†	11.4 ± 2.04 (8) [10.2; 54.0]

*Arithmetic mean ± standard error (N) [Geometric mean; geometric %CV] except T_{max} for which the median (N) is reported.

†Parameter cannot be estimated for day 1.

Source: Table 11.2-15 of study report THR-1442-C-445

Abbreviations: A_e, amount excreted; AUC₀₋₂₄, area under the curve from zero to 24 hours; AUC_{0-t}, area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; CL_{nr}, non-renal clearance; CL_r, renal clearance; C_{max}, maximum plasma concentration; %CV, coefficient of variation; Fe, fraction excreted unchanged; PK, pharmacokinetics; t_{1/2}, half life; T2DM, type 2 diabetes mellitus; T_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant

Table 100. Summary of UGE Rate After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State

Parameter*	Study Day	Dose			
		Placebo	3 mg	10 mg	30 mg
UGE Rate (mg/min)	0	25.8 ± 9.06 (6) [19.8; 91.4]	32.6 ± 7.74 (8) [22.9; 149]	16.1 ± 4.99 (8) [10.0; 188]	34.8 ± 13.1 (8) [22.4; 143]
	1	24.3 ± 6.02 (6) [20.1; 83.6]	85.9 ± 7.41 (8) [83.4; 27.2]	81.3 ± 11.8 (7) [77.3; 33.5]	107 ± 8.07 (8) [105; 20.9]
	7	16.1 ± 8.52 (6) [10.2; 118]	85.5 ± 5.92 (8) [84.1; 19.5]	75.3 ± 5.34 (8) [74.0; 20.1]	97.9 ± 9.62 (8) [94.9; 27.0]

*Arithmetic mean ± standard error (N) [Geometric mean; geometric %CV]

Source: Table 11.2-6 of Study Report THR-1442-C-445

Abbreviations: %CV, coefficient of variation; T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion

Table 101. Summary of FPG (mg/dL) After Oral Administration Once Daily for 7 Days to Japanese Subjects With T2DM in the Fed State

Study Day*	Dose			
	Placebo	3 mg	10 mg	30 mg
0	185 ± 9.35 (6) [184; 12.5]	201 ± 5.27 (8) [201; 7.37]	184 ± 10.2 (8) [182; 15.2]	183 ± 10.4 (8) [181; 16.2]
1	182 ± 9.51 (6) [181; 12.7]	209 ± 9.38 (8) [207; 12.3]	189 ± 10.6 (8) [187; 16.0]	184 ± 10.9 (8) [182; 15.8]
7	165 ± 14.5 (6) [162; 19.8]	153 ± 9.46 (8) [151; 17.9]	127 ± 4.86 (8) [126; 11.0]	129 ± 8.03 (8) [127; 16.6]

*Arithmetic mean ± standard error (N) [Geometric mean; geometric %CV]

Source: Table 11.2-10 of Study Report THR-1442-C-445

Abbreviations: %CV, coefficient of variation; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.

Conclusion:

- Administration of bexagliflozin up to 90 mg to Japanese subjects was safe and well tolerated.
- Prior consumption of food was not found to markedly change the PK parameters observed following administration of the 10 and 30 mg bexagliflozin tablets.
- Bexagliflozin at the studied doses of 3 mg to 90 mg increased UGE in both healthy subjects and subjects with T2DM.
- Bexagliflozin significantly reduced FPG in Japanese subjects with T2DM at 10 mg and 30-mg doses.

14.2.4. Mass Balance Study (Trial C-410)

Study Design

This was an open-label, radiolabeled mass balance study conducted in six healthy male subjects to determine absorption, routes of elimination, and circulatory and excretory metabolites of bexagliflozin. During the study, subjects received a single oral dose of 50 mg of bexagliflozin (with approximately 100 μ Ci of [^{14} C]-bexagliflozin) in an aqueous solution. Plasma and whole blood samples were collected for at least 48 hours after dosing. Urine and feces samples were collected for up to 9 days or to when the total excreted radioactivity levels had exceeded 90% of the administered radioactivity, whichever occurred first.

Results

Plasma:

- Mean $C_{\max}$ and $AUC_{\inf}$ values for total radioactivity in plasma were approximately 2-fold higher than those for total radioactivity in whole blood, indicating that most of the total radioactivity resides in the plasma compartment of blood and is not highly associated with blood cells.
- The $t_{1/2}$ of unchanged parent drug in plasma from humans was 5.6 hours after oral dosing.
- In plasma, 55% of the circulating radioactivity was associated with unchanged bexagliflozin. EGT0002149, an O-glucuronide, was the major circulating metabolite in plasma contributing to 32% of parent AUC and 18% of total radioactivity AUC. Other metabolites identified in plasma were the O-glucuronide conjugates EGT0002147 and EGT0002148; and the phase 1 metabolites EGT0001301 (M1), EGT0001494 (M²), and EGT0001684. All other metabolites were <10% of parent AUC and total radioactivity AUC ([Table 102](#)). A metabolism diagram is provided in [Figure 25](#).

Table 102. PK Parameters for [¹⁴C] Bexagliflozin and Metabolites in Plasma

Metabolite Identification	C _{max} (ng equiv/g)	t _{max} (h)	t _{1/2} (h)	AUC _(0-t) (ng equiv-h/g)	AUC _(0-∞) (ng equiv-h/g)	% AUC of Parent ^a	% AUC of Total Radioactivity ^b
Total Radioactivity	1070	1.0	6.7	4558	4816	NA	100
EGT0001301	28.8	1.0	2.1	105	111	4.16	2.30
EGT0001494	28.4	2.0	5.0	171	176	6.78	3.75
EGT0002147	33.3	1.0	NR	60.5	NR	2.40	1.33
EGT0001684	14.2	2.0	1.9	78.9	83.7	3.13	1.73
EGT0002148	5.10	2.0	NR	30.3	NR	1.20	0.66
EGT0002149	231	1.0	6.9	813	855	32.2	17.8
EGT0001442 (parent)	692	0.5	5.6	2523	2604	NA	55.3

equiv = Equivalents
h = Hours

NR = Not reported, due to an indiscernible elimination phase

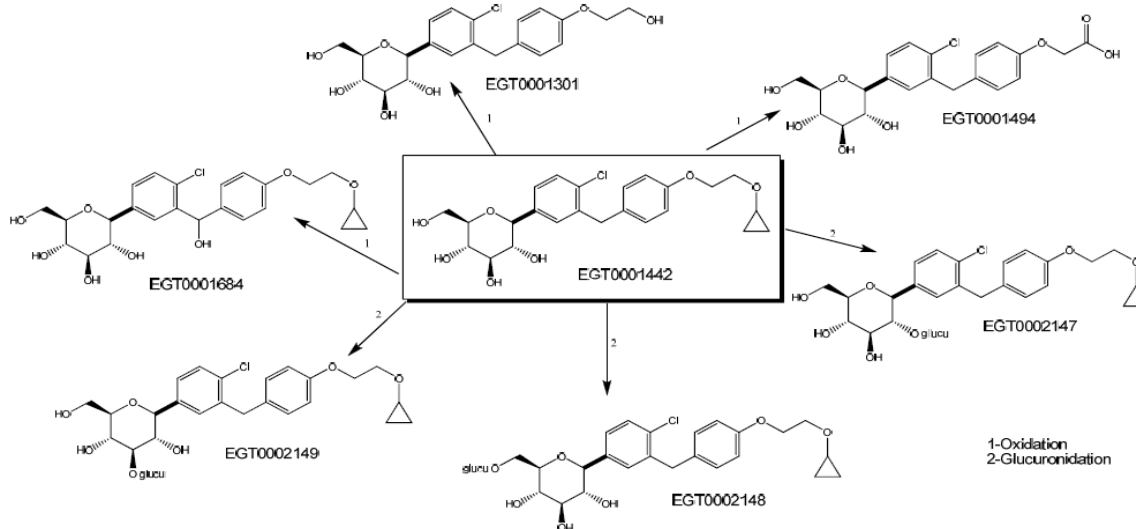
^a % of AUC calculated by: AUC_{0-t} (metabolite peak)/AUC₀₋₂₄ (parent)*100%.

^b % of AUC calculated by: AUC_{0-t} (metabolite peak)/AUC₀₋₂₄ (plasma total radioactivity area, TRA)*100%.

Source: Table 11-3 of Study Report THR-1442-C-410

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-∞}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time; C_{max}, maximum plasma concentration; PK, pharmacokinetics; t_{1/2}, half life; t_{max}, time to maximum plasma concentration

Figure 25. Proposed Biotransformation Pathway of [¹⁴C] Bexagliflozin in Humans



Source: Figure 11-1 of Study Report THR-1442-C-410

Urine and Feces:

- Total recovery of radioactivity in urine and feces combined was approximately 91.6% over the 192-hour postdose assessment period, representing 51.1% mean recovery in feces and 40.5% mean recovery in urine.
- Most of the radioactivity excreted in urine was associated with EGT0002149, accounting for 30.1% of the administered dose through 96 hours post dosing, of which the majority was excreted within the first 12 hours.

- For minor metabolites, 1.69% EGT0001301 (M1), 3.88% EGT0001494 (M²), 1.63% EGT0002147, and 0.45% EGT0002148 were also identified in urine.
- Unchanged parent drug in urine accounted for 1.50% of the dose through 96 hours postdose.
- Most of the radioactivity in feces was associated with the unchanged parent drug, accounting for 28.7% of the administered dose through 144 hours postdose.
- In feces, EGT0001301 (M1) and EGT0001494 (M²) were the major metabolites and accounted for 8.03 and 10.1% of the dose, respectively, through 144 hours postdose. EGT0001684 was also identified in feces.

Conclusions

- Most of the total radioactivity was in plasma and was not highly associated with blood cells.
- Bexagliflozin was metabolized in humans via oxidation and glucuronidation with 55.3% of the circulating radioactivity associated with the parent drug.
- EGT0002149 (glucuronide metabolite) was the major circulating metabolite in plasma.
- Mean total recovery of radioactivity was 91.6%, with a mean of 51.1% of the dose excreted in feces and 40.5% excreted in urine through 192 hours postdose.
- In urine, most of the radioactivity (30.1% of the dose) was associated with EGT0002149.
- In feces, most of the radioactivity (28.7% of the dose) was associated with unchanged parent drug.
- Bexagliflozin was safe and well tolerated in this group of healthy male subjects.

14.2.5. Food Effect Study (Trial C-481)

Study Design

This was a phase 1, open-label, two-treatment, two-period crossover study designed to assess the effects of a high-fat meal on the PK of orally administered bexagliflozin tablets in 18 healthy adults. Subjects were randomized 1:1 to receive bexagliflozin tablets with a high-fat meal on Day 1 and without a meal on Day 8 after an overnight fast or to receive bexagliflozin tablets without a meal on Day 1 after an overnight fast and with a high-fat meal on Day 8. Blood and urine samples were collected at prespecified time points up to 48 hours postdose.

Results

- High fat, high calorie meal did not affect the extent of bexagliflozin absorption with both AUC parameters entirely contained within the 80% to 125% margins ([Table 103](#)).
- Intake of a high-fat, high-calorie meal increased bexagliflozin C_{max} by approximately 30% and delayed the median T_{max} by 1.5 hours (5.0 and 3.5 hours for fed and fasted states, respectively).
- Intrasubject variability was low (<30%) for the primary PK parameters AUC_{0-t}, AUC_{0-∞}, and C_{max}.

- The elimination half-life is 11.7 h or 10.1 h following dosing in the fasted or fed states, respectively.
- Administration of bexagliflozin was well tolerated under both fasted and fed conditions.

Table 103. Bexagliflozin PK Parameters Following Oral Administration Bexagliflozin Tablets, 20 mg Under Fasted Versus Fed Condition

Pharmacokinetic Parameter	Geometric LSM (CV%)		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability
	Fed	Fasted			
Fed vs. Fasted, n	24	23			
AUC _{0-t} (h*ng/mL)	1198.6 (6.2)	1086.8 (6.2)	110.29	103.91, 117.06	11.5%
AUC _{0-∞} (h*ng/mL)	1258.7 (5.8)	1161.8 (5.7)	108.34	102.48, 114.54	10.7%
C _{max} (ng/mL)	176.1 (7.4)	134.0 (7.3)	131.41	117.03, 147.56	22.8%

Abbreviations: AUC_{0-∞} = area under the plasma concentration-time curve from Time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time t (time of last quantifiable plasma concentration); C_{max} = maximum observed plasma concentration; LSM = least squares means.

¹ Ratio (expressed as %) of exponentiated mean difference of log-transformed pharmacokinetic parameter for treatment A vs. treatment B.

² Confidence interval (expressed as %) from ANOVA (linear mixed-effects model) with treatment, period, and sequence as fixed effects, and subject as a random effect.

Source: Table 11 of Study Report THR-1442-c-481

Abbreviations: ANOVA, analysis of variance; CV%, coefficient of variation; PK, pharmacokinetics.

Conclusion

No significant food effect was observed for bexagliflozin 20-mg tablet.

14.2.6. Formulation Development (Trial CLR-002)

Study Design:

This was a phase 1, open-labeled, crossover (Part 1) and parallel (Part 2) study to assess the PK and PD of multiple oral doses of bexagliflozin sustained release (SR) tablets in healthy male subjects.

- In Part 1, a crossover design was used. Twenty eligible subjects were dosed in a randomized sequence with each of 4 formulations of bexagliflozin in 15-mg formulations of bexagliflozin SR tablets (SR11, SR8, and SR5) and 20 mg bexagliflozin capsule.
- In Part 2, three bexagliflozin formulations (SR5 and additional formulations of 10 and 30 mg) were administered orally under fasting condition on Day 1 and 2 and 30 minutes after a standard meal on Day 3.

Serial PK, safety, and PD evaluations were performed at prespecified times up to 48 hours postdose.

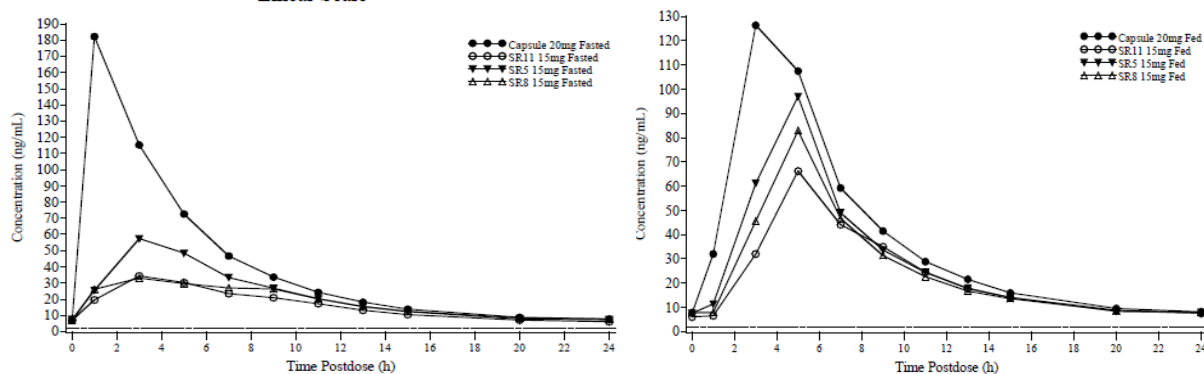
Results:

- Median T_{max} values were 1 hour for the capsule formulation and 3 hours for all SR tablet formulations ([Figure 26](#)). Administration of the SR formulations in the fed state resulted

in an increase in exposure of 17% to 45% and 71% to 97%, for $AUC_{0-\infty}$ and C_{max} , respectively, compared to administration in the fasted state ([Table 104](#)).

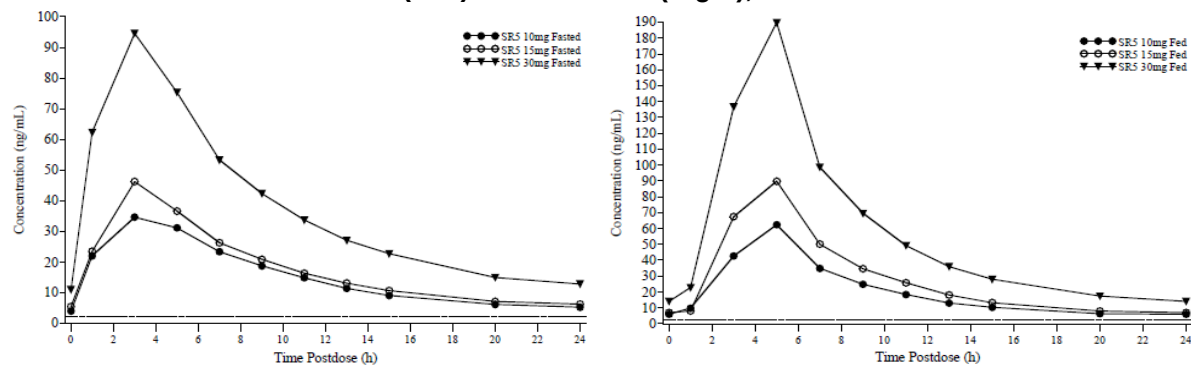
- SR5 formulation showed the largest systemic exposures of the SR formulations and was selected to be studied in Part 2.
- In Part 2, bexagliflozin exposures (AUC_{0-24} and C_{max}) generally increased in a dose-proportional manner over the dose range of 10 to 30 mg of the SR5 formulation ([Figure 27](#) and [Table 105](#)).
- There was no apparent difference in UGE between formulations in Part 1 (data not shown). In Part 2 (SR5 formulation), UGE_{0-24} values were comparable between 10 and 15-mg dose groups, both of which were slightly lower than that from the 30-mg dose group ([Table 106](#)).

Figure 26. Geometric Mean Plasma Concentration Time Profiles of Bexagliflozin From All Formulations in the Fasted State (Left) and Fed State (Right), Trial CLR-002 Part 1



Source: Figures 11.1 and 11.2 of Study Report THR100-CLR-002

Figure 27. Geometric Mean Plasma Concentration Time Profiles of Bexagliflozin From SR5 formulation in the Fasted State (Left) and Fed State (Right), Trial CLR-002 Part 2



Source: Figures 11.3 and 11.4 of Study Report THR100-CLR-002

Table 104. Summary PK Parameters for Bexagliflozin, Trial CLR-002 Part 1

Parameter	EGT0001442 Formulation							
	SR11 15 mg		SR8 15 mg		SR5 15 mg		Capsule 20 mg	
	Fasted	Fed	Fasted	Fed	Fasted	Fed	Fasted	Fed
AUC ₀₋₂₄ (ng•hr/mL)	409 (51.0) [n=15]	609 (32.8) [n=18]	497 (40.6) [n=14]	633 (31.3) [n=18]	562 (38.4) [n=18]	723 (18.9) [n=18]	1019 (23.0) [n=19]	1025 (18.3) [n=19]
AUC ₀₋₄ (ng•h/mL)	410 (45.9) [n=19]	600 (32.5) [n=19]	467 (43.3) [n=19]	634 (30.4) [n=19]	562 (37.2) [n=19]	720 (18.4) [n=19]	1018 (23.0) [n=19]	1023 (18.3) [n=19]
AUC _{0-∞} (ng•h/mL)	497 (49.6) [n=14]	720 (32.8) [n=17]	628 (34.4) [n=11]	741 (29.8) [n=18]	700 (27.2) [n=16]	822 (17.6) [n=16]	1111 (21.7) [n=19]	1118 (18.7) [n=19]
C _{max} (ng/mL)	44.2 (63.3) [n=19]	85.0 (36.5) [n=19]	48.5 (60.1) [n=19]	95.6 (30.5) [n=19]	68.9 (62.2) [n=19]	118 (20.7) [n=19]	204 (47.3) [n=19]	174 (24.5) [n=19]
t _{max} ^a (h)	3.00 (1.00 – 11.00) [n=19]	5.00 (3.00 – 9.00) [n=19]	3.00 (1.00 – 9.00) [n=19]	5.00 (3.00 – 5.05) [n=19]	3.00 (1.00 – 9.00) [n=19]	5.00 (3.00 – 5.00) [n=19]	1.00 (1.00 – 5.00) [n=19]	3.00 (1.00 – 5.00) [n=19]
t _{1/2} (h)	8.27 (22.8) [n=14]	8.25 (22.8) [n=17]	8.45 (37.5) [n=11]	9.05 (19.8) [n=18]	8.31 (22.7) [n=16]	7.81 (19.6) [n=16]	8.06 (15.3) [n=19]	7.47 (21.2) [n=19]
λ _z (1/h)	0.0838 (22.8) [n=14]	0.0840 (22.8) [n=17]	0.0821 (37.5) [n=11]	0.0766 (19.8) [n=18]	0.0834 (22.7) [n=16]	0.0887 (19.6) [n=16]	0.0860 (15.3) [n=19]	0.0928 (21.2) [n=19]
CL/F (L/hr)	36.7 (51.0) [n=15]	24.6 (32.8) [n=18]	30.2 (40.6) [n=14]	23.7 (31.3) [n=18]	26.7 (38.4) [n=18]	20.8 (18.9) [n=18]	19.6 (23.0) [n=19]	19.5 (18.3) [n=19]
V _z /F (L)	420 (58.3) [n=14]	286 (42.5) [n=17]	345 (84.0) [n=11]	310 (43.2) [n=18]	296 (50.5) [n=16]	231 (32.4) [n=16]	228 (33.4) [n=19]	210 (28.9) [n=19]

Geometric mean (CV%); n = number of subjects included in the analysis

^aMedian (min – max)

Source: Table 11.1 of Study Report THR100-CLR-002

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity; AUC₀₋₂₄, area under the curve from zero to 24 hours; AUC_{0-t}, area under the concentration-time curve from 0 to time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV%, coefficient of variation; PK, pharmacokinetics; t_{1/2}, half life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant.

Table 105. Summary PK Parameters for Bexagliflozin, Trial CLR-002 Part 2

Parameter	EGT0001442 – SR5 Tablet					
	10 mg		15 mg		30 mg	
	Fasted	Fed	Fasted	Fed	Fasted	Fed
AUC ₀₋₂₄ (ng•hr/mL)	411 (31.6) [n=6]	523 (30.5) [n=10]	445 (43.3) [n=9]	704 (15.8) [n=10]	1090 (27.9) [n=7]	1461 (23.7) [n=10]
AUC ₀₋₄ (ng•h/mL)	386 (25.9) [n=10]	523 (30.4) [n=10]	455 (41.5) [n=10]	704 (15.8) [n=10]	939 (39.6) [n=10]	1461 (23.7) [n=10]
AUC _{0-∞} (ng•h/mL)	465 (26.2) [n=6]	606 (25.1) [n=10]	583 (21.7) [n=8]	783 (15.2) [n=9]	1246 (28.9) [n=7]	1572 (23.2) [n=9]
C _{max} (ng/mL)	41.0 (44.2) [n=10]	85.9 (37.2) [n=10]	56.7 (69.1) [n=10]	106 (20.4) [n=10]	102 (52.0) [n=10]	236 (21.8) [n=10]
t _{max} ^a (h)	3.00 (1.00 – 7.00) [n=10]	3.00 (1.00 – 5.02) [n=10]	3.01 (1.00 – 5.00) [n=10]	5.00 (2.95 – 7.00) [n=10]	3.00 (1.00 – 5.00) [n=10]	5.00 (3.00 – 5.05) [n=10]
t _{1/2} (h)	7.80 (35.9) [n=6]	8.94 (24.2) [n=10]	9.71 (24.8) [n=9]	7.57 (12.3) [n=9]	8.16 (16.9) [n=7]	8.02 (15.0) [n=9]
λ _z (1/h)	0.0889 (35.9) [n=6]	0.0775 (24.2) [n=10]	0.0714 (24.8) [n=9]	0.0916 (12.3) [n=9]	0.0850 (16.9) [n=7]	0.0865 (15.0) [n=9]
CL/F (L/hr)	24.3 (31.6) [n=6]	19.1 (30.5) [n=10]	33.7 (43.3) [n=9]	21.3 (15.8) [n=10]	27.5 (27.9) [n=7]	20.5 (23.7) [n=9]
V _z /F (L)	274 (72.5) [n=6]	247 (54.8) [n=10]	472 (72.9) [n=9]	231 (27.0) [n=9]	324 (29.1) [n=7]	244 (32.7) [n=9]

Geometric mean (CV%); n = number of subjects included in the analysis

^aMedian (min – max)

Source: Table 11.2 of Study Report THR100-CLR-002

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity; AUC₀₋₂₄, area under the curve from zero to 24 hours; AUC_{0-t}, area under the concentration-time curve from 0 to time; CL/F, apparent clearance; C_{max}, maximum plasma concentration; CV%, coefficient of variation; PK, pharmacokinetics; t_{1/2}, half life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution; λ_z, elimination rate constant.

Table 106. Summary UGE Parameters (mg), Trial CLR-002 Part 2

Treatment	Parameter		
	UGE ₀₋₁₂	UGE ₁₂₋₂₄	UGE ₀₋₂₄
EGT0001442 SR5 Tablet – 10 mg			
Fasted Loading Dose (n=10)	32208 (16.5)	19573 (31.0)	52113 (19.3)
Fasted Dose (n=10)	40342 (25.9)	22788 (33.9)	64013 (23.9)
Fed Dose (n=10)	37432 (26.1)	22324 (22.8)	59980 (22.9)
EGT0001442 SR5 Tablet – 15 mg			
Fasted Loading Dose (n=10)	35589 (28.9)	20258 (23.2)	56319 (23.5)
Fasted Dose (n=10)	35562 (15.0)	19086 (26.1)	55084 (13.6)
Fed Dose (n=10)	34548 (21.2)	21552 (30.4)	57107 (14.3)
EGT0001442 SR5 Tablet – 30 mg			
Fasted Loading Dose (n=10)	40788 (41.1)	27750 (16.8)	69771 (25.4)
Fasted Dose (n=10)	39971 (27.7)	26609 (19.8)	67286 (17.8)
Fed Dose (n=10)	45434 (9.91)	30019 (26.0)	75866 (14.5)

Geometric mean (CV%): n = number of subjects included in the analysis
Source: Table 11.5 of Study Report THR100-CLR-002
Abbreviations: CV%, coefficient of variation; UGE, urinary glucose excretion.

Conclusions

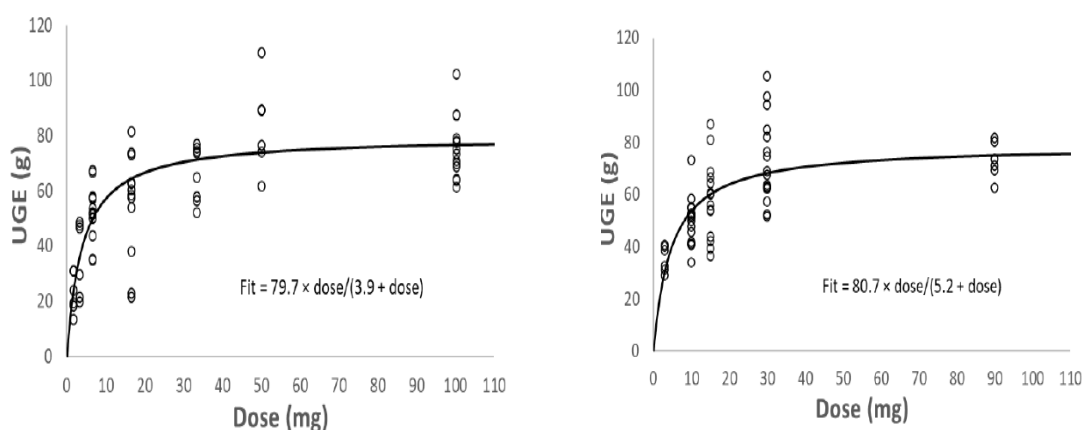
- Administration of 10 to 30 mg of bexagliflozin from SR5 formulation was safe and well tolerated in this group of healthy male subjects.
- Based on the PK and PD data from this study, SR5 formulation was selected as the formulation for further clinical trials.

FDA Reviewer Comment: Per the Applicant, the prolonged release profile of bexagliflozin from the SR5 formulation is mediated by (b) (4) excipients that promote gastric retention. In Part 1 of the study, PK exposure of bexagliflozin was compared between 20 mg prolonged release tablet formulation (SR5) and 15 mg immediate release capsule formulation in a crossover manner. Based on the demonstrated dose proportionality of bexagliflozin in the range of 1.67 to 100 mg, bexagliflozin exposures were normalized by the studied doses to assess the relative bioavailability between capsule and tablet (SR5) formulations. The results showed that the prolonged release tablet formulation (SR5) had about 16% lower AUC and 55% lower C_{max} compared to the immediate release capsule formulation.

FDA Reviewer's Note:

- Subsequent to Trial C-445, three changes were made to the formulation to improve the manufacturing process. (b) (4)
- Seven phase 3 clinical trials and six clinical pharmacology studies were conducted using the modified SR5 formulation.
- The PD (UGE) activities of bexagliflozin are comparable between the capsule and tablet formulations ([Figure 28](#)). PK and PD information was used to support the dosage form designation as immediate release tablet by the biopharmaceutical reviewer (See. Dr. Joan Zhao's review for details).

Figure 28. UGE as a Function of Dose for Capsule (Left) and Tablet Formulations (Right)



Source: Figures 2.7.2-16 and 2.7.2-17 Summary of Clinical Pharmacology
Abbreviations: UGE, urinary glucose excretion

14.2.7. Effect of Hepatic Impairment (Trial C-455)

Study Design

This was a phase 1, open-label, parallel-group study to assess the effect of moderate hepatic impairment on the PK and PD of orally administered bexagliflozin tablets. A total of 16 subjects comprising 8 with moderate hepatic impairment (Child-Pugh total score 7 to 9) and 8 healthy, matched controls, were enrolled and received a single oral dose of bexagliflozin tablets, 20 mg, after an overnight fast. Blood samples were collected prior to dosing, and at multiple time points for up to 48 hours postdose. The unbound fraction of bexagliflozin at 24 hours postdose and at the maximum plasma concentration for each subject was determined by equilibrium dialysis. Urine samples for PD analysis were collected for the 12 hour interval preceding dosing and 48 hours following dosing. Plasma concentrations of bexagliflozin were determined by a validated LC-MS/MS assay.

Results

- Bexagliflozin $AUC_{0-\infty}$ and C_{max} were about 28 to 32% and 6 to 10% higher, respectively, in subjects with moderate hepatic dysfunction compared to subjects with normal function. ([Table 107](#) and [Table 108](#)).
- Plasma protein binding were minimally affected by moderate hepatic impairment.
- $T_{1/2}$ values were comparable between subjects with moderate hepatic impairment (11.2 ± 4.16 hrs) and subjects with normal hepatic function (12.3 ± 6.56 hrs).
- Urinary glucose excretion was lower in the group with reduced hepatic function, with 24 hour collection values of 58.5 and 46.8 g for subjects with normal and moderately diminished function, respectively. The corresponding values for the creatinine normalized urinary glucose excretion over the 24 hours postdose was 67.38 (19.0) and 74.69 (35.2) g for subjects with normal or moderately diminished function, respectively, and were consistent with the substantially lower creatinine excretion displayed by the impaired cohort.

- Bexagliflozin was well tolerated, treatment-emergent adverse events (TEAEs) were mild in severity and no subject experienced a death, serious TEAE, or TEAE leading to withdrawal from the study.

Table 107. Comparison of Total Bexagliflozin PK Parameters by Hepatic Function Group

Pharmacokinetic Parameter	Normal Hepatic Function		Moderate Hepatic Impairment		Point Estimate (%) ¹	90% Confidence Interval ²
	n	Geometric LSM	n	Geometric LSM		
AUC _{0-t} (ng·h·mL ⁻¹)	8	653.9	8	836.7	127.94	99.03, 165.28
AUC _{0-∞} (ng·h·mL ⁻¹)	8	695.8	8	893.0	128.34	99.98, 164.73
C _{max} (ng·mL ⁻¹)	8	90.8	8	96.5	106.22	78.34, 144.02

Abbreviations: AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time t; C_{max} = maximum observed plasma concentration; LSM = least squares means.

¹. Estimated ratio (expressed as %) of exponentiated mean difference of log-transformed PK parameter from ANOVA.

². Confidence interval (expressed as %) from ANOVA (linear mixed-effects model) with hepatic function group as a fixed effect, and subject as a random effect.

n = number of subjects with data

Source: Table 11 of Study Report THR-1442-C-455

Abbreviations: ANOVA, analysis of variance; PK, pharmacokinetics

Table 108. Comparison of Free Bexagliflozin PK Parameters by Hepatic Function Group

Pharmacokinetic Parameter	Normal Hepatic Function		Moderate Hepatic Impairment		Point Estimate (%) ¹	90% Confidence Interval ²
	n	Geometric LSM	n	Geometric LSM		
AUC _{0-t} (ng·h·mL ⁻¹)	8	45.4	8	58.4	128.70	94.16, 175.91
AUC _{0-∞} (ng·h·mL ⁻¹)	7	47.9	8	63.3	132.16	96.46, 181.08
C _{max} (ng·mL ⁻¹)	8	6.0	8	6.6	110.84	75.34, 163.06

Abbreviations: AUC_{0-∞} = area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time t; C_{max} = maximum observed plasma concentration; LSM = least squares means.

¹. Estimated ratio (expressed as %) of exponentiated mean difference of log-transformed PK parameter from ANOVA.

². Confidence interval (expressed as %) from ANOVA (linear mixed-effects model) with hepatic function group as a fixed effect, and subject as a random effect.

n = number of subjects with data

Source: Table 12 of Study Report THR-1442-C-455

Abbreviations: ANOVA, analysis of variance; PK, pharmacokinetics

Conclusions

- Moderate hepatic impairment slightly increased bexagliflozin exposures (~30% for AUC). No significant impact on UGE was observed after correcting by the renal function.
- An adjustment of dosage for patients with mild to moderate hepatic impairment is not considered necessary in light of the wide safety margins observed in the bexagliflozin development program.

14.2.8. Effect of Renal Impairment (Trial C-424)

Study Design

This was a phase 1, open-label, parallel-group study to assess the effect of mild, moderate, and severe renal impairment on the PK and PD of orally administered bexagliflozin capsules in subjects with T2DM. During the study, subjects received a single dose of 20 mg bexagliflozin

capsules, administered orally after overnight fast. Four cohorts of 6 to 9 subjects were enrolled, representing individuals with normal ($\text{GFR} \geq 90 \text{ mL min}^{-1} \text{ per } 1.73 \text{ m}^2$, $n=8$), mildly impaired ($60 \leq \text{GFR} < 90$, $n=8$), moderately impaired ($30 \leq \text{GFR} < 60$, $n=9$) or severely impaired ($\text{GFR} < 30$, $n=6$) renal function. Timed blood and urine specimens for PK and PD analysis were collected.

Results

Parent Drug PK

- Systemic exposure ($\text{AUC}_{0-\infty}$) of bexagliflozin was significantly increased in subjects with moderate and severe renal impairment, with a mean ratio of 1.34 and 1.54, respectively, as compared to subjects with normal renal function. $\text{AUC}_{0-\text{inf}}$ was similar between the groups with normal renal function and mild renal impairment ([Figure 29](#) and [Table 109](#)).
- The percent of plasma protein binding was not affected by declining renal function, with mean values of 88.23%, 87.99%, 89.38%, and 85.97% in the normal renal function, mildly, moderately, and severely impaired groups, respectively.
- Elimination half-life was slightly increased in subjects with renal impairment (7.3 to 7.9 hours) but was not significantly different from the group with normal renal function (6.7 hours).
- The percent of parent drug excreted in urine gradually decreased with declining renal function: 1.25% was excreted in urine in the group with mild impairment, 0.91% in the group with moderate impairment, and 0.51% in the group with severe impairment.

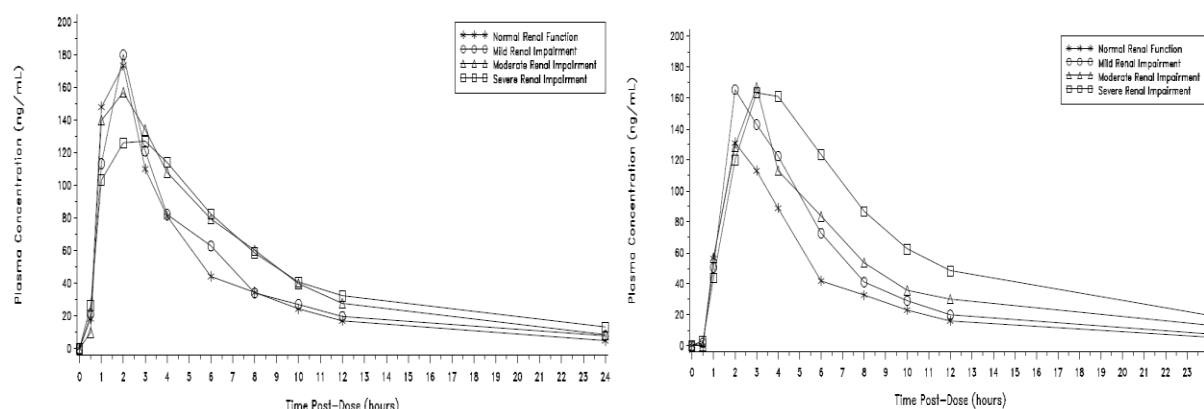
Metabolite PK

- For metabolite EGT0002149, its systemic exposures increased with increasing kidney disease severity suggesting reduced renal clearance. Compared to subjects with normal renal function, $\text{AUC}_{0-24\text{h}}$ was comparable in subjects with mild renal impairment, 1.6-fold, and 2.2-fold higher in subjects with moderate and severe renal impairment, respectively ([Figure 29](#)).
- As renal clearance is a significant route of elimination for the glucuronide, renal excretion was incrementally reduced with increasing kidney disease severity, from 32.9% to 21.5%, 15.6%, and 6.3% of dose in normal renal function and mild, moderate, and severe impairment, respectively.
- As a result of decreased renal elimination of the glucuronide, metabolite to parent AUC ratios were incrementally higher with increasing severity of renal impairment (geometric means 69.4%, 76.2%, and 98.2% in mild, moderate, and severe renal impairment, respectively).

PD (UGE)

- Consistent with the mechanism of action of bexagliflozin, the urinary excretion of glucose highly depends on the renal function. In patients with moderate and severe renal impairment, UGE values were reduced by 60% and 80% compared to patients with normal renal function ([Table 110](#)).

Figure 29. Median Plasma Concentrations of Bexagliflozin (Left) and Its Metabolite EGT0002149 (Right) Over Time in Subjects With Normal Renal Function and Subjects With Mild, Moderate, and Severe Renal Impairment



Source: Figures 11-1 and 11-6 of Study Report THR-1442-C-424

Table 109. PK Parameters of Bexagliflozin by Renal Function Group, PK Population

Statistic	PK Parameter			
	Renal Function Group			
	Normal n=8	Mild n=8	Moderate n=9	Severe n=6
C_{max} (ng/mL)				
Geometric Mean	185.410	162.990	187.775	160.506
Mean (SD)	196.250 (72.2847)	179.588 (80.3261)	191.556 (39.9221)	167.167 (54.0904)
Median	190.000	180.000	204.000	149.500
t_{max} (h)				
Geometric Mean	2.1	1.9	2.0	1.9
Mean (SD)	2.3 (0.89)	2.0 (0.76)	2.1 (0.78)	2.2 (1.17)
Median	2.0	2.0	2.0	2.0
λ_z (1/h)				
Geometric Mean	0.106	0.092	0.095	0.090
Mean (SD)	0.109 (0.0276)	0.093 (0.0143)	0.096 (0.0129)	0.092 (0.0213)
Median	0.100	0.093	0.094	0.092
$t_{1/2}$ (h)				
Geometric Mean	6.529	7.530	7.275	7.745
Mean (SD)	6.710 (1.6540)	7.622 (1.3297)	7.341 (1.0855)	7.934 (1.9253)
Median	6.932	7.488	7.390	7.529
CL/F (mL/min)				
Geometric Mean	341.468	319.717	255.205	221.970
Mean (SD)	347.127 (65.4007)	326.804 (73.5820)	262.583 (63.9676)	231.272 (61.2121)
Median	354.045	306.379	260.950	254.657
Vz/F (mL)				
Geometric Mean	192973.644	208381.411	160714.719	148805.609
Mean (SD)	200265.409 (56648.5873)	211900.724 (42265.4885)	166506.459 (48532.1618)	153666.844 (44730.6498)
Median	204780.820	205218.211	145823.558	143881.787
AUC_{0-inf} (h*ng/mL)				
Geometric Mean	976.177	1042.588	1306.140	1501.703
Mean (SD)	993.243 (202.6604)	1065.211 (232.5337)	1346.811 (365.6970)	1589.572 (681.3523)
Median	948.258	1089.099	1277.386	1310.475

NDA 214373
Brenzavvy (bexagliflozin)

AUC ₀₋₂₄ (h*ng/mL)				
Geometric Mean	917.957	960.440	1204.188	1314.479
Mean (SD)	932.792 (181.1405)	980.788 (214.6931)	1238.435 (319.7872)	1373.039 (501.4911)
Median	913.038	955.970	1198.843	1197.020
Fe (%)				
Geometric Mean	1.545	1.253	0.908	0.513
Mean (SD)	1.604 (0.4535)	1.337 (0.5164)	0.945 (0.3035)	0.547 (0.1842)
Median	1.704	1.168	0.764	0.595
Ae _[0-24] (mg)				
Geometric Mean	0.309	0.251	0.182	0.103
Mean (SD)	0.321 (0.0907)	0.267 (0.1033)	0.189 (0.0607)	0.109 (0.0368)
Median	0.341	0.234	0.153	0.119
CL _R (mL/min)				
Geometric Mean	5.611	4.349	2.513	1.300
Mean (SD)	5.758 (1.2976)	4.920 (2.6337)	2.774 (1.4630)	1.358 (0.4141)
Median	5.763	4.145	2.335	1.396
CL _{NR} (mL/min)				
Geometric Mean	335.647	315.057	252.589	220.576
Mean (SD)	341.369 (65.2251)	321.884 (71.6997)	259.809 (62.8258)	229.914 (61.1376)
Median	347.672	300.763	258.840	252.943

Source: Table 14-3 of Study Report THR-1442-C-424

Abbreviations: Ae, amount excreted; AUC_{0-inf}, area under the curve from zero to infinity; AUC₀₋₂₄, area under the curve from zero to 24 hours; CL/F, apparent clearance; CL_{nr}, non-renal clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; Fe, fraction excreted unchanged; PK, pharmacokinetics; t_{1/2}, half life; t_{max}, time to maximum plasma concentration; V_Z/F, apparent volume of distribution; λ_z, elimination rate constant

Table 110. Summary of 24-hr UGE (g) in T2DM Patients With Normal Renal Function, Mild, Moderate, and Severe Renal Impairment

Renal Function	N	Mean (SD)
Normal renal function	8	99.6 (45.4)
Mild renal impairment	8	83.0 (35.8)
Moderate renal impairment	9	39.7 (21.2)
Severe renal impairment	6	16.9 (6.5)

Source: Table 14-46 of Study Report THR-1442-C-424

Abbreviations: T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion

Conclusion

- Bexagliflozin exposures increased with increasing severity of renal impairment, with a 54% increase in bexagliflozin AUC for subjects with severe renal impairment.
- In patients with moderate and severe renal impairment, UGE values reduced by 60% and 80% compared to patients with normal renal function.

FDA Reviewer Comment: *Per the Applicant “Because only a very small fraction of bexagliflozin is found in urine, the increase in systemic exposure with decreasing renal function substantially implicates the kidney as an important organ for metabolism of bexagliflozin. However, exposure to both the principal glucuronide and the most prominent oxidative metabolite increased with decreasing renal function, suggesting that the reduction in elimination falls more rapidly than the reduction in capacity to metabolize bexagliflozin.”*

14.2.9. Effect of Probenecid, Rifampin, and Verapamil on PK/PD of Bexagliflozin (Trial C-454)

Study Design

This was a phase 1, open-label, nonrandomized, fixed sequence composite study to assess the effects of probenecid, rifampin, and verapamil on the PK and PD of orally administered bexagliflozin tablets in 48 healthy subjects (N=16 per cohort).

Cohort 1: Bexagliflozin/Probenecid (UGT Inhibitor):

- On Day 1, subjects took one 20 mg bexagliflozin tablet; on Days 3 to 4 subjects took probenecid tablets, 500 mg (twice daily [BID]); on Day 5 subjects took one bexagliflozin tablet (once daily [QD]) + probenecid tablets, 500 mg (BID); and on Day 6 subjects took probenecid tablets, 500 mg (BID).

Cohort 2: Bexagliflozin/Rifampin (CYP3A/UGT Inducer)

- On Day 1, subjects took one bexagliflozin tablet, 20 mg; on Days 3 to 5 subjects took 600 mg of rifampin (2 x 300 mg capsules) QD; on Day 6 subjects took one bexagliflozin tablet, 20 mg, and 600 mg of rifampin; and on Day 7 subjects took 600 mg of rifampin.

Cohort 3: Bexagliflozin/Verapamil (P-gp Inhibitor)

- On Day 1, subjects took one bexagliflozin tablet, 20 mg; and on Day 4 subjects took one verapamil tablet, 120 mg, 1 hour before taking one bexagliflozin tablet, 20 mg.

Multiple PK and urine samples were collected for 48 hours after administration of bexagliflozin on Day 1 (bexagliflozin alone) and Day 4/5/6 (bexagliflozin + perpetrator drug).

Results

- *Cohort 1:* Previous studies have indicated that bexagliflozin is cleared predominantly by metabolism to an inactive metabolite, bexagliflozin 3'-O-glucuronide (EGT0002149), by UGT1A9. When bexagliflozin was coadministered with probenecid, a nonspecific UGT inhibitor, 39% and 44% increases in AUC of bexagliflozin and EGT0002149, respectively, were observed ([Table 111](#)). Postdose UGE for each 12-hour collection interval was similar for both treatments, indicating that the inhibitory effect on bexagliflozin exposure by probenecid had no effect on UGE.
- *Cohort 2:* Rifampin is a strong inducer of CYP3A4 and several UGT enzymes, including UGT1A9. When bexagliflozin was coadministered with rifampin, its AUC_{0-t} decreased by 14% and C_{max} increased by 20% ([Table 111](#)). This was accompanied by a decreased bexagliflozin t_{1/2} from 12.9 hours to 5.9 hours. Coadministration with rifampin led to 90% (90% CI: 145%, 250%) and 54% (90% CI: 119%, 199%) increases in EGT0002149 C_{max} and AUC, respectively. UGE_{0-24h} was comparable between treatments.
- *Cohort 3:* Verapamil is a P-glycoprotein (P-gp) inhibitor. The point estimate and the 90% CI for both C_{max} and AUC were entirely contained within the range of 80 to 125%, indicating that there was no interaction between bexagliflozin and verapamil ([Table 111](#)).

Table 111. Bexagliflozin PK Parameters When Administered Alone or With Probenecid, Rifampin, and Verapamil

Investigational Product		PK Parameters (%CV) of Substrate Drug				GMR (90% CI)	
Substrate Drug	Interacting Drug	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (ng h/mL)	t _{1/2} (h)	C _{max}	AUC _{0-t}
Bexa 20 mg	-	162 (28.7)	2.0	1056 (24.3)	12.1 (36.0)		
Bexa 20 mg	Probenecid 500 mg bid × 2 days	193 (22.1)	3.0	1471 (23.3)	13.9 (24.8)	1.19 (1.11, 1.27)	1.39 (1.30, 1.49)
Bexa 20 mg	-	97.8 (53.9)	2.0	698.3 (43.9)	12.2 (37.0)		
Bexa 20 mg	Rifampin 600 mg × 3 days	117 (60.1)	2.0	601 (49.9)	5.3 (49.7)	1.20 (0.94, 1.52)	0.86 (0.70, 1.06)
Bexa 20 mg	-	159 (35.4)	3.0	969 (26.0)	10.7 (44.1)		
Bexa 20 mg	Verapamil 120 mg	169 (24.7)	3.0	9356 (22.1)	11.7 (48.2)	1.06 (0.89, 1.27)	0.96 (0.88, 1.06)

Source: Tables 13, 16, 17, 18, 21, 22, 23 and 24 of Study Report THR-1442-C-454

Abbreviations: AUC_{0-t}, area under the concentration-time curve from 0 to time t; Bexa, bexagliflozin; %CV, coefficient of variation; bid, twice daily; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetics; t_{1/2}, half life; t_{max}, time to maximum plasma concentration

Conclusions

Bexagliflozin is not expected to interact to a clinically relevant extent with other drugs that are inhibitors of P-gp and UGTs.

***Reviewer' Comment:** Coadministration with UGT inhibitor probenecid is expected to decrease the concentrations of EGT0002149, a UGT metabolite of bexagliflozin. The unexpected 40% increase of this metabolite is likely because it is also subject to active transport by uptake transporters such as OAT3, which are inhibited by probenecid.*

In this study, rifampin was only dosed for 3 days before coadministration with bexagliflozin. The current study may not adequately capture the worst-case scenario of enzyme induction.

14.2.10. Effect of Exenatide on Bexagliflozin (Trial C-458)

Study Design

This was a phase 1, open-label, two-period, two-treatment crossover study to assess the effects of exenatide injection on the PK and PD of orally administered bexagliflozin tablets. Twenty eligible healthy subjects were randomly assigned to one of two groups (N=10 per group). Each group received both the treatments, alternately, in a crossover fashion, with the two treatment periods separated by a 7-day washout period.

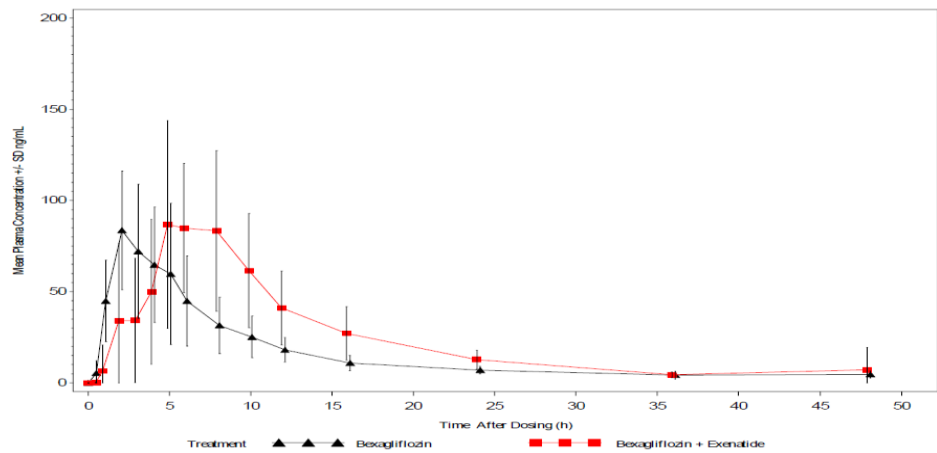
- A single oral dose of 20 mg bexagliflozin administered 30 minutes after breakfast
- Exenatide at 10 µg BID with an initial dose 30 minutes prior bexagliflozin administration, and 1 hour before breakfast, followed by the second dose of exenatide alone 1 hour prior to the evening meal

Blood and urine samples were collected at multiple timepoints for up to 48 hours postdose.

Results

- Absorption was delayed when bexagliflozin was administered 30 minutes after exenatide injection as evident in the time-concentration profile and a prolonged T_{max} of 5.00 hours postdose compared to 2.00 hours postdose for administration of bexagliflozin alone (Figure 30). Additionally, AUC_{0-t} and C_{max} of bexagliflozin were increased by approximately 48% and 25%, respectively, compared to bexagliflozin administration alone (Table 112).
- UGE during the first 12 hours after dosing was lower in subjects administered bexagliflozin + exenatide (26 g) compared to when subjects were administered bexagliflozin alone (38 g), with comparable UGE observed between treatments for the subsequent postdose collection intervals (Table 113).
- Approximately 65% of the total UGE was excreted in the first 24 hours for each treatment dosing period.

Figure 30. Geometric Mean ($\pm$ SE) Plasma Concentration-Time Profile of Bexagliflozin With or Without Exenatide



Source: Figure 1 in Study Report THR-1442-C-458

Table 112. Comparison of Bexagliflozin PK Parameters for Bexagliflozin vs. Bexagliflozin + Exenatide

Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM	90% Confidence Interval	Intra- subject variability
	Bexagliflozin	Bexagliflozin + Exenatide			
Bexagliflozin vs. Bexagliflozin + Exenatide, n					
AUC _{0-t} (hr*ng/mL)	706.4	1042.0	147.50	130.23, 167.07	21.3%
AUC _{0-inf} (hr*ng/mL)	780.8	1074.0	137.56	122.28, 154.75	18.6%
C _{max} (ng/mL)	96.4	120.8	125.27	104.45, 150.24	31.7%

Source: Table 11 in Study Report THR-1442-C-458

Abbreviations: AUC_{0-inf} , area under the curve from zero to infinity; AUC_{0-t} , area under the concentration-time curve from 0 to time t; C_{max} , maximum plasma concentration; LSM, least square means; PK, pharmacokinetics.

Table 113. Mean Urinary Glucose Excretion

Timeframe	Bexagliflozin, 20 mg (N=19)		Bexagliflozin, 20 mg + Exenatide 10 µg bid (N=17)	
	n	Mean ± SD	n	Mean ± SD
Pre-dose (-12 to 0 hours)	18	0.07 ± 0.140	16	0.05 ± 0.100
0 to 12 hours post-dose	19	38.32 ± 8.705	17	26.38 ± 8.347
12 to 24 hours post-dose	19	26.89 ± 7.833	16	28.95 ± 6.812
24 to 36 hours post-dose	19	21.93 ± 6.934	17	22.16 ± 6.845
36 to 48 hours post-dose	19	9.56 ± 6.283	17	9.21 ± 6.499
0 to 24 hours post-dose	19	65.21 ± 15.035	16	55.65 ± 12.123
0 to 48 hours post-dose	19	96.70 ± 25.080	16	88.11 ± 20.525

N = number of subjects in the PD Population.
n = number of subjects with data in the specific category.
Source: Table 13 in Study Report THR-1442-C-458

Conclusion

No clinically significant DDI was observed when bexagliflozin was administered with exenatide.

FDA Reviewer Comment: Rationale of DDI study: Exenatide is one of most prescribed GLP-1 receptor agonists and is administered subcutaneously (SC) BID because of its relatively short half-life of 2.4 hours. Exenatide is primarily eliminated by glomerular filtration and subsequent proteolytic degradation, thus, interactions involving CYP450 isoenzymes or enzymes responsible for phase 2 metabolism are not expected. However, because exenatide slows gastric emptying, the rate of absorption for concurrent orally administered medications may be altered.

Exenatide increased bexagliflozin AUC and C_{max} by 30 to 40%. Given metabolism based DDI is not likely, the increased exposures of bexagliflozin are likely due to prolonged GI emptying, a mechanism similar to the observed higher bioavailability from the delayed release formulation than the immediate release formulation. Nonetheless, the 30 to 40% increase in bexagliflozin is not considered clinically relevant in terms of safety.

Exenatide induces glucose-dependent insulin secretion and suppresses postprandial glucagon release and therefore may accelerate the absorption of glucose in peripheral tissue via insulin action. This mechanism likely reduces the filtered glucose in the kidney and results in reduced glucose. The observed ~30% reduction in first 0- to 12-hour UGE when bexagliflozin was administered with exenatide may not be clinically relevant.

14.2.11. Effect of Bexagliflozin on the PK of Metformin, Glimepiride or Sitagliptin (Trial C-453)

Study Design

This was a phase 1, open-label, three-period, three-treatment crossover study designed to assess the effects of bexagliflozin on the PK of metformin, glimepiride, and sitagliptin. Fifty-four eligible healthy subjects were randomly assigned to one of three groups (N=18 per group).

- Group 1: bexagliflozin /metformin
- Group 2: bexagliflozin /glimepiride
- Group 3: bexagliflozin /sitagliptin

For each group, every subject received a single dose of bexagliflozin tablet, 20 mg, alone, a single dose of an oral hypoglycemic agent (OHA: 1000 mg metformin, 2 mg glimepiride, or 100 mg sitagliptin) alone, and the combination of both (bexagliflozin tablet and OHA) alternately in a crossover fashion, with three treatment periods separated by a washout period of at least 7 days. PK and urine samples were collected for up to 48- and 72-hours postdose for groups 1 and 2, and group 3, respectively.

Results

- The Impact of Metformin, Glimepiride, and Sitagliptin on Bexagliflozin PK

The estimated geometric mean ratios and 90% CI of bexagliflozin AUC were within the 80% to 125%, when taken with metformin, glimepiride, or sitagliptin ([Table 114](#)). The point estimate and 90% CI of bexagliflozin C_{max} slightly fell outside of the bounds of 80-125%, when taken with sitagliptin and glimepiride. Nonetheless, the extent of exposure change is not considered as clinically significant.

- The Impact of Bexagliflozin on the PK of Metformin, Glimepiride, and Sitagliptin

There was no impact on the PK of metformin or sitagliptin when taken with bexagliflozin, as the point estimate and corresponding 90% CI for C_{max} and AUC were entirely contained within the 80-125% margins ([Table 115](#)). Glimepiride AUC_{0-t} increased by 27% (90% CI: 10%, 48%) in the presence of bexagliflozin. The extent of exposure increase in glimepiride is not clinically relevant.

- UGE values of bexagliflozin were slightly lower when administered with other antidiabetic agents but were not statistically significantly different.

Table 114. Bexagliflozin PK Parameters When Taken With or Without Metformin, Glimepiride, and Sitagliptin

Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Bexagliflozin	Bexagliflozin + Metformin			
Bexagliflozin, n	18	18			
AUC _{0-t} (h*ng/mL)	1101.1	971.0	88.19	80.20, 96.97	16.4
AUC _{0-∞} (h*ng/mL)	1154.4	1008.6	87.36	80.02, 95.38	15.1
C _{max} (ng/mL)	124.6	135.5	108.73	94.35, 125.30	24.6
Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Bexagliflozin	Bexagliflozin + Glimepiride			
Bexagliflozin, n	17	18			
AUC _{0-t} (h*ng/mL)	1167.8	1121.8	96.07	80.74, 114.30	29.4
AUC _{0-∞} (h*ng/mL)	1230.4	1162.2	94.46	80.34, 111.06	27.3
C _{max} (ng/mL)	160.7	143.7	89.44	70.39, 113.65	41.7
Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Bexagliflozin	Bexagliflozin + Sitagliptin			
Bexagliflozin, n	18	18			
AUC _{0-t} (h*ng/mL)	957.9	1095.1	114.33	108.86, 120.08	8.4
AUC _{0-∞} (h*ng/mL)	1024.0	1158.1	113.09	107.61, 118.86	8.2
C _{max} (ng/mL)	117.1	148.3	126.68	112.08, 143.17	21.2

Source: Tables 15, 19 and 23 in Study Report THR-1442-C-453

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time t; C_{max}, maximum plasma concentration; LSM, least square means; PK, pharmacokinetics

Table 115. PK Parameters of Metformin, Glimepiride, and Sitagliptin When Taken With or Without Bexagliflozin

Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Metformin	Bexagliflozin + Metformin			
Metformin, n	18	18			
AUC _{0-t} (h*ng/mL)	13180.1	13540.5	102.73	93.62, 112.73	16.0
AUC _{0-∞} (h*ng/mL)	13351.9	13784.6	103.24	94.59, 112.68	15.1
C _{max} (ng/mL)	2067.6	1965.2	95.05	84.73, 106.63	19.9
Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Glimepiride	Bexagliflozin + Glimepiride			
Glimepiride, n	18	18			
AUC _{0-t} (h*ng/mL)	476.9	608.0	127.49	110.01, 147.74	25.6
AUC _{0-∞} (h*ng/mL)	486.2	618.4	127.19	110.33, 146.62	23.0
C _{max} (ng/mL)	59.9	67.1	111.95	97.02, 129.19	24.9

Pharmacokinetic Parameter	Geometric LSM		Ratio of Geometric LSM ¹	90% Confidence Interval ²	Intra-subject variability (ISCV%)
	Sitagliptin	Bexagliflozin + Sitagliptin			
Sitagliptin, n	18	18			
AUC _{0-t} (h*ng/mL)	3521.1	3623.7	102.91	98.85, 107.14	6.9
AUC _{0-∞} (h*ng/mL)	3579.6	3692.8	103.16	99.30, 107.17	6.5
C _{max} (ng/mL)	356.6	351.2	98.48	84.90, 114.23	25.8

Source: Tables 16, 20 and 24 in Study Report THR-1442-C-453

Abbreviations: AUC_{0-∞}, area under the curve from zero to infinity; AUC_{0-t}, area under the concentration-time curve from 0 to time t; C_{max}, maximum plasma concentration; LSM, least square means; PK, pharmacokinetics

Conclusion

No clinically relevant DDIs were observed between bexagliflozin and metformin, glimepiride, or sitagliptin.

14.2.12. Dose-Finding Study Using FPG (Trial C-402)

Study Design

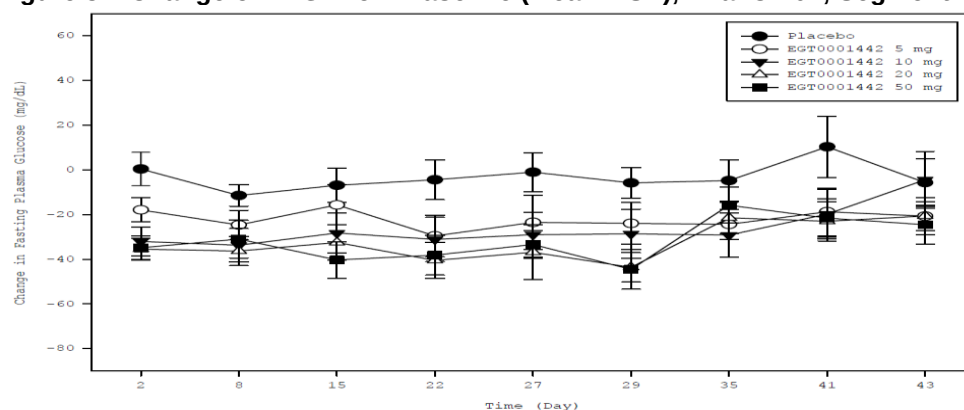
This was a phase 2 study to evaluate the efficacy of bexagliflozin based on FPG in patients with T2DM. The study included two segments:

- Segment 1: a single-center, open label, ascending dose study in four groups of diabetic subjects (5 per group) who received 5, 10, 20, or 50 mg of bexagliflozin capsules orally once daily for 28 days. The subjects were housed overnight in clinic for the first 3 days for safety and PK evaluation.
- Segment 2: a multicenter, double-blind, placebo-controlled parallel group study in five groups of diabetic subjects (25 per group) who receive oral bexagliflozin capsules at 5, 10, 20, or 50 mg/day or placebo once daily for 28 days in an outpatient setting.

Results

- PK: C_{max} and AUC were dose proportional over the dose range of 5 to 50 mg (data not shown).
- Reductions in FPG ranged from -24.25 to -41.64 mg/dL in the bexagliflozin treatment groups and was -6.63 mg/dL in the placebo group. Significant differences versus placebo were observed for both the 20 mg and 50 mg bexagliflozin groups.
- Increases in total UGE for all bexagliflozin treatment groups versus placebo were observed after one and 28 days of treatment. The change from baseline to Day 28 ranged from 18.71 to 26.80 g/24 h in the bexagliflozin cohorts versus -0.2 g/24 h with placebo (data not shown). The UGE values for all bexagliflozin cohorts were highly significant (p<0.0001).

Figure 31. Change of FPG From Baseline (Mean ± SE), Trial C-402, Segment 2



Note: Baseline is defined as the mean of FPG values on day -2 and day 1.

Source: Figure 4 of Study Report THR-1442-C-402

Abbreviations: FPG, fasting plasma glucose.

Table 116. Primary Efficacy Analysis: ANCOVA Results on Mean Change in FPG (mg/dL) From Baseline to End of Treatment, Trial C-402, Segment 2

Treatment	n	Mean (mg/dL)	SD	Median	LS Means	Difference vs Placebo		
						LS Means	95% CI	p-value
OVERALL	129							0.0333
Placebo	28	-6.63	33.51	-6.50	-12.595			
5 mg EGT0001442	24	-24.25	41.03	-32.00	-29.518	-16.923	-37.076, 3.230	0.0989
10 mg EGT0001442	23	-29.00	38.30	-30.00	-30.429	-17.834	-38.909, 3.242	0.0964
20 mg EGT0001442	28	-36.14	47.13	-43.00	-32.586	-19.991	-39.670, -0.312	0.0465
50 mg EGT0001442	26	-41.64	41.95	-39.50	-44.605	-32.010	-51.487, -12.533	0.0015

n: Number of subjects with data available in the specific treatment group

LSMeans: Least square means

Std Err LSMeans: Standard error of the LSMeans

CI: Confidence interval

Note: LSMeans, Std Err of LSMeans, 95% confidence intervals and p-values are based on an ANCOVA with change from baseline as dependent variable and treatment as fixed effect and baseline and center as covariate. P-values are from two-sided test at 5%-level.

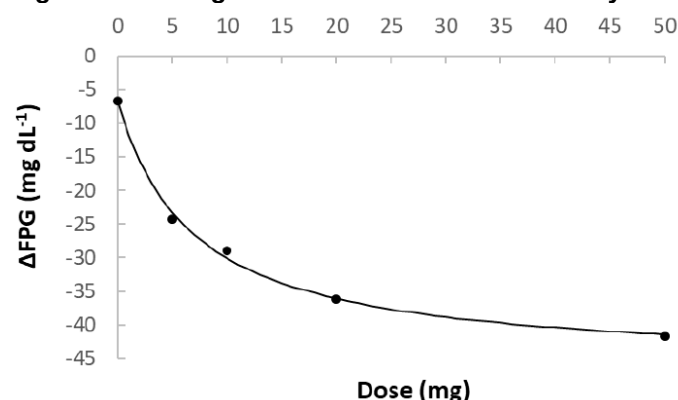
Note: Baseline is defined as the mean of FPG values on day -2 and day 1.

End of Treatment is defined as the mean of FPG values on day 27 and day 29.

Source: Table 9 of Study Report THR-1442-C-402

Abbreviations: ANCOVA, analysis of covariance; FPG, fasting plasma glucose.

Figure 32. Change in FPG From Baseline on Day 28



Source: Study THR-1442-C-402 Table 14.2.2; Solid line is $\Delta\text{FPG} = -6.77 - 39.4 \times \text{dose} / (6.90 + \text{dose})$

Abbreviations: FPG, fasting plasma glucose.

Conclusion

The changes in FPG were determined in T2DM patients at bexagliflozin doses ranging from 5 mg to 50 mg in a 28-day study ([Figure 32](#)). Based on the fitted $E_{\max}$ model, the 20-mg dose is expected to produce ~90% of the maximum effect in lowering FPG.

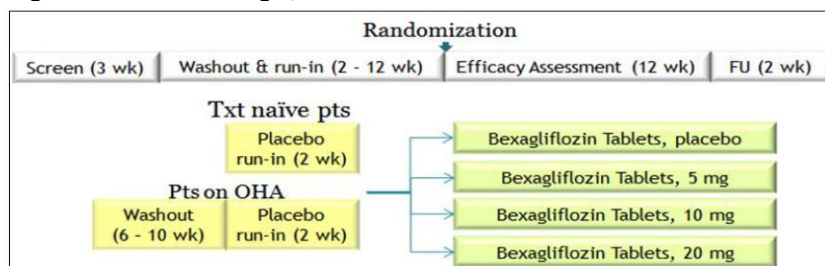
FDA Reviewer Comment: No apparent dose-response on UGE was observed in this study likely because of highly variable UGE among T2DM patients.

14.2.13. Dose-Finding Study by HbA1c (Trial C-449)

Study Design

The was a phase 2b multicenter, double-blind, placebo-controlled parallel group study to assess the effect of once daily bexagliflozin at doses ranging from 5-mg to 20-mg tablets for 12 weeks on HbA1c in either treatment-naïve T2DM subjects or in subjects who were treated with one oral antidiabetic agent. The primary efficacy endpoint was change from baseline in HbA1c after 12 weeks of placebo or bexagliflozin treatment. The secondary efficacy endpoint included FPG, seated systolic blood pressure (SBP) and diastolic blood pressure (DBP) and body weight.

Figure 33. Trial Design, Trial C-449

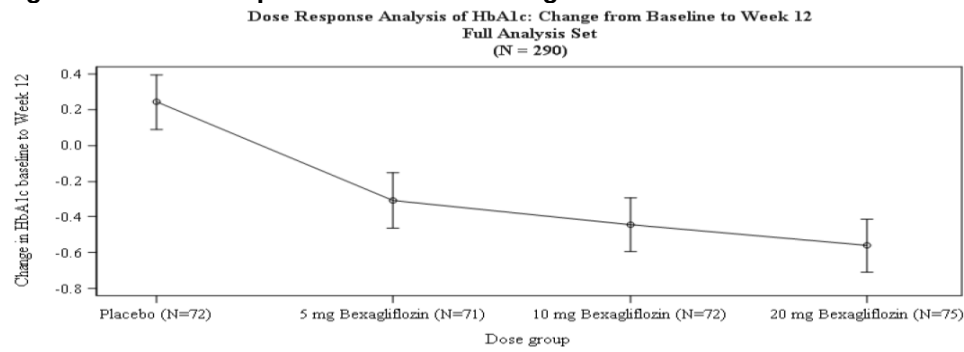


Source: Figure 1 of Study Report THR-1442-C-449
Abbreviations: FU, follow-up; OHA oral hypoglycemic agent; Txt, therapy.

Results

- A dose-dependent reduction in HbA1c over 12 weeks was observed with bexagliflozin doses ranging from 5 mg to 20 mg ([Figure 34](#)). All decreases in percent HbA1c were statistically significant and clinically meaningful.
- The proportions of subjects who achieved a postbaseline HbA1c <7% were 15% in placebo and 21%, 22%, and 36% in bexagliflozin 5 mg, 10 mg, and 20 mg treatment groups, respectively.
- A dose-dependent decrease in FPG from baseline to Week 12 was observed with the maximum mean decrease of -1.240 (SD 1.2305) mmol/L in the bexagliflozin 20 mg group.
- Daily dosing of bexagliflozin tablets for 12 weeks was well tolerated. Among all groups, subjects with related TEAEs were higher in the 20 mg bexagliflozin group (22.4%) compared to the related events in the 5 mg bexagliflozin (8.3%), 10 mg bexagliflozin (6.9%), or placebo (8.3%) groups ([Table 117](#))

Figure 34. Dose Response of HbA1c: Change From Baseline to Week 12



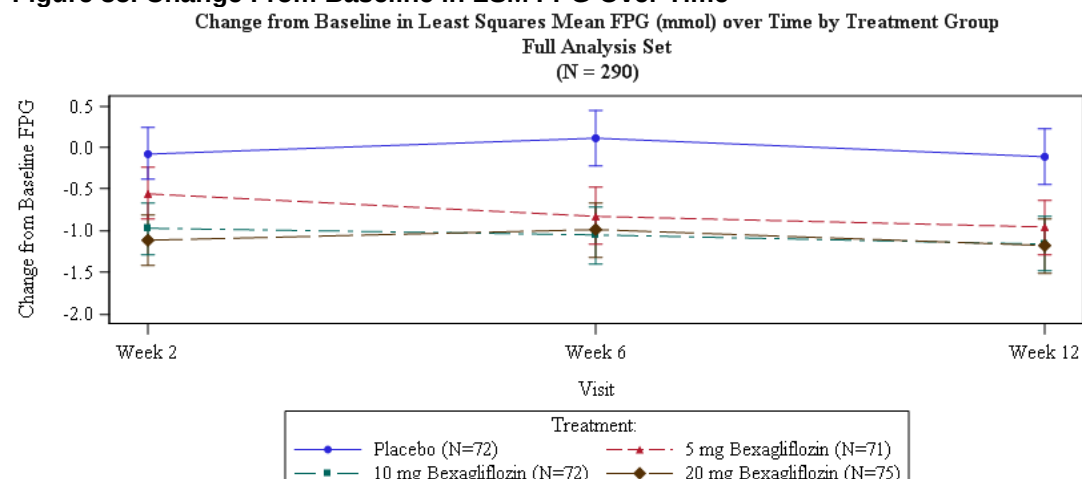
Note 1: Each error bar is constructed using ± 1 standard error from the mean.
2: Least squares means and the corresponding standard errors are derived based on MMRM ANCOVA that includes study center, treatment, visit and a treatment-by-visit interaction as fixed effects, with prior anti-diabetic treatment status and baseline HbA1c as covariates, and subject as a random effect. An unstructured covariance matrix is assumed.

Source: Figure 3 of Study Report THR-1442-C-449

Abbreviations: ANCOVA, analysis of covariance; HbA1c, hemoglobin A1c; MMRM, mixed model repeated measures

APPEARS THIS WAY ON ORIGINAL

Figure 35. Change From Baseline in LSM FPG Over Time



Note 1: Each error bar is constructed using ± 1 standard error from the mean.

2: Least squares means and the corresponding standard errors are derived based on MMRM ANCOVA that includes study center, treatment, visit and a treatment-by-visit interaction as fixed effects, with prior anti-diabetic treatment status and baseline fasting plasma glucose as covariates, and subject as a random effect. An unstructured covariance matrix is assumed.

Source: Figure 4 of Study Report THR-1442-C-449 Abbreviations: ANCOVA, analysis of covariance; FPG, fasting plasma glucose; LSM, least squares mean; MMRM, mixed model repeated measures.

Table 117. Overall Summary of Treatment-Emergent Adverse Events

	Placebo	Bexagliflozin			All (N=220) N (%)
	(N=72) N (%)	5 mg (N=72) N (%)	10 mg (N=72) N (%)	20 mg (N=76) N (%)	
Subjects with ≥ 1 TEAE	29 (40.3)	26 (36.1)	31 (43.1)	36 (47.4)	93 (42.3)
Subjects with ≥ 1 Severe TEAE	1 (1.4)	2 (2.8)	3 (4.2)	2 (2.6)	7 (3.2)
Subjects with ≥ 1 Related TEAE ¹	6 (8.3)	6 (8.3)	5 (6.9)	17 (22.4)	28 (12.7)
Subjects with ≥ 1 Serious TEAE	0	0	3 (4.2)	2 (2.6)	5 (2.3)
Subjects with ≥ 1 Serious Related TEAE ¹	0	0	0	1 (1.3)	1 (<1)
Subjects with ≥ 1 TEAE Leading to Study Drug Discontinuation	1 (1.4)	1 (1.4)	2 (2.8)	3 (3.9)	6 (2.7)
Subjects with ≥ 1 TEAE Leading to Study Withdrawal	1 (1.4)	0	1 (1.4)	2 (2.6)	3 (1.4)
Subjects with ≥ 1 TEAE Leading to Death	0	0	0	0	0

¹ Treatment-related TEAEs are events with a study drug causality of 'possible', 'probable' or 'definite.'

Source: Table 18 of Study Report THR-1442-C-449

Abbreviations: TEAE, treatment emergent adverse events.

Conclusion

Based on magnitude of HbA1c reduction and observed safety profile, the 20-mg dose has the most favorable risk/benefit assessment compared to the 5-mg and 10-mg doses.

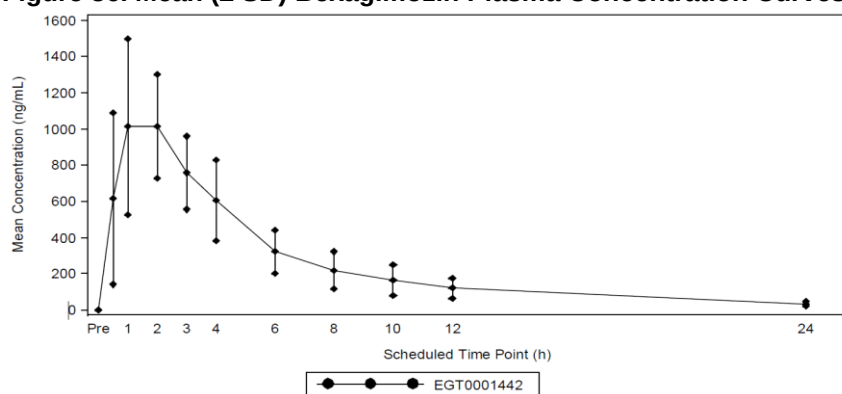
14.2.14. Effects on QT Prolongation (Trial C-428)

Study Design

This was a phase 1, single-center, randomized, partially double-blind, three-treatment, three-period study designed to assess the effects of a single dose of bexagliflozin capsule on QTc interval in 36 healthy male and female subjects. Subjects were assigned to receive single oral doses of placebo, 100 mg bexagliflozin, and 400 mg moxifloxacin in a randomized order (single dose of drug/placebo given during each treatment period), with a minimum 7-day washout interval between each drug administration. All three treatments were administered in the fasted state. Blood samples were collected for up to 24 hours.

Results

Figure 36. Mean ($\pm$ SD) Bexagliflozin Plasma Concentration Curves (ng/mL)



Source: Figure 14.2.1 of Study Report THR-1442-C-428

Table 118. Bexagliflozin PK Parameters Following Oral Administration of 100 mg Bexagliflozin Capsule

	C_{max} (ng/mL)	T_{max} (h)	λ_z (1/h)	$t_{1/2z}$ (h)	CL/F (L/h)	V_z/F (L)	AUC_{0-t}^a (h*ng/mL)	AUC_{0-inf} (h*ng/mL)	AUC_{0-24} (h*ng/mL)
n	37	37	37	37	37	37	37	37	37
Mean	1276	-	0.11	6.53	16.56	155.0	6064	6377	6057
SD	322.16	-	0.02	1.38	3.83	43.06	1547.3	1627.2	1545.5
CV (%)	25.25	-	17.64	21.17	23.15	27.78	25.52	25.52	25.51
Minimum	626	0.67	0.07	4.79	8.56	63.1	3471	3553	3468
Median	1250	2.15	0.11	6.18	15.75	151.2	5995	6349	5990
Maximum	1860	4.18	0.15	10.48	28.1	290	11083	11689	11070

CV=coefficient of variation; SD=standard deviation

Source: Table 14.2.1.2

^a the last blood collection time point was more than 24 hours for all subjects.

Source: Table 9 of Study Report THR-1442-C-428

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from 0 to 24 hours; AUC_{0-inf} , area under the curve from zero to infinity; AUC_{0-t} , area under the concentration-time curve from 0 to time t; CL/F, apparent clearance; C_{max} , maximum plasma concentration; PK, pharmacokinetics; $t_{1/2}$, half life; T_{max} , time to maximum plasma concentration; V_z/F , apparent volume of distribution; λ_z , elimination rate constant

FDA Reviewer Comment: The 24-hour sample collection may not accurately determine half-life but may have a reasonable estimation on the AUC of bexagliflozin. Based on Dr. Eliford Kitabi's IRT review in DARRTS dated on December 6, 2021, a single dose of 100 mg bexagliflozin (5 times the recommended dose) does not cause drug related QT prolongation.

14.3. Pharmacometrics Review

14.3.1. Review Summary

In general, the Applicant's population pharmacokinetic (popPK) analysis is considered acceptable for describing bexagliflozin PK (sustained-release or SR formulation for commercialization) in healthy subjects and those with T2DM. The final popPK model is adequate for assessing the impact of clinically relevant covariates on drug exposure and supporting labeling statements. The Applicant's popPK analyses were verified by the reviewer, with no significant discordance identified. More specifically, the developed covariate model was used to support the current submission as outlined in [Table 119](#).

Table 119. Specific Comments on Applicant's Final Population PK Model

	Utility of the final model		Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Section 12.3. "Based on a population pharmacokinetic analysis, age, body weight, sex and race do not have a clinically relevant effect on the pharmacokinetics of bexagliflozin."	The statement is acceptable. Covariate effects on CL/F and Vc/F are not considered to be clinically significant; therefore, no dose adjustment is needed based on PK
	Extrinsic factor	N/A	N/A

Source: Reviewer generated.

Abbreviations: CL/F, apparent clearance; PK, pharmacokinetics; Vc/F, apparent central volume of distribution.

14.3.2. Introduction

The primary objectives of Applicant's popPK analyses were to:

- Develop a popPK model for bexagliflozin SR formulation and quantify individual PK parameters
- Evaluate the impact of clinical covariates on bexagliflozin PK
- Describe the unexplained variability in bexagliflozin PK
- Support dosing recommendations for bexagliflozin

Of note, the bexagliflozin clinical program also studied essential hypertension (b) (4) in two phase 3 trials, and subjects with essential hypertension (with or without T2DM) were included in the popPK dataset per the population PK analysis plan. Population type as a categorical variable was not included in the final popPK model (refer to Section 5.2 of Applicant's PopPK Report on covariate analysis). (b) (4)

14.3.3. Model Development

Data

The popPK analysis was based on pooled PK data from 12 studies that administered the SR formulation. The pooled database included healthy volunteers, diabetic subjects (with or without essential hypertension), and subjects with hepatic impairment. The final NONMEM dataset for analysis contained 6247 PK observations from 884 unique subjects. Brief descriptions of the studies included are presented in [Table 120](#). [Table 121](#) provides a summary of the baseline demographics of the popPK populations.

Table 120. Summary of Studies With PK Sampling Included in Population PK Analysis

Study No	Duration	Description	Dose (mg)	PK Sampling
[Sites]	(N)		Prandial State	
THR100- CLR-002 [US]	NA (Ph1) (30†)	A phase 1, open-labeled, cross-over (part 1) or parallel group (part 2) study to evaluate the PK and PD of bexagliflozin in healthy volunteers	10, 15, 30 mg (part 2) fasted/fed	Predose, 1, 3, 5, 7, 9, 11, 13, 15, 20, 24 h postdose
THR- 1442-C- 419 [US, JP]	24 weeks (84)	A phase 3, randomized, double-blind, placebo-controlled study to evaluate bexagliflozin in subjects with T2DM not adequately controlled by metformin alone	20 mg left to subject discretion	During Week 6 or Week 12: Group 1: 0.25-1, 7-10, and 20-24 h post dose Group 2: 1.5-3, 3.5- 6.5, and 7-10 h postdose
THR- 1442-C- 445 [JP]	NA (Ph1) (48)	A phase 1, placebo-controlled, dose-escalation study to assess the safety, tolerability, PK, and PD of bexagliflozin in healthy Japanese volunteers and subjects with T2DM	3, 10, 30, 90 mg fasted/fed	SAD: predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, 24 (Day 2), 36 (Day 2), and 48 h (Day 3) postdose MAD: Day 1 at predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, and 24 (Day 2) h postdose, Day 4 at pre- dose only, and on Day 7 (last day of dosing) at predose and at 0.5, 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 15, 20, 24 (Day 8), 36 (Day 8), and 48 (Day 9) h postdose
THR- 1442-C- 448 [US, JP, FR, ES]	24 weeks (54)	A phase 3, double-blind, placebo-controlled study to evaluate the effect of bexagliflozin on HbA1c in patients with T2DM and moderate renal impairment	20 mg fasted	During Week 6 or Week 12: Group 1: 0.25-1, 7-10, and 20-24 h post dose Group 2: 1.5-3, 3.5- 6.5, and 7-10 h postdose

NDA 214373
Brenzavvy (bexagliflozin)

Study No	Duration	Description	Dose (mg)	Prandial State	PK Sampling
[Sites]	(N)				
THR-1442-C-449 [US, JP]	12 weeks (136)	A phase 2b, double-blind, placebo-controlled, dose range finding study to evaluate the effect of bexagliflozin on HbA1c in subjects with T2DM	5, 10, 20 mg	fasted	At weeks 2, 6, or 12: Group 1: 0.25-1, 7-10, and 20-24 h post dose Group 2: 1.5-3, 3.5-6.5, and 7-10 h postdose
THR-1442-C-453 [US]	NA (Ph1) (54)	A phase 1, open-label, randomized, three-period, crossover study to evaluate PK interaction between bexagliflozin and metformin, glimepiride, or sitagliptin in healthy subjects	20 mg	fasted	Predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose For bexagliflozin/sitagliptin DDI group, samples were also collected at 60 and 72 h postdose
THR-1442-C-454 [US]	NA (Ph1) (47††)	A phase 1, open-label, nonrandomized, fixed-sequence composite study to evaluate the effects of probenecid, rifampin, and verapamil on the PK and PD of bexagliflozin in healthy subjects	20 mg	fasted/fed	Predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose
THR-1442-C-455 [US]	NA (Ph1) (16)	A phase 1, open-label, parallel-group study to evaluate the effect of moderate hepatic impairment on the PK and PD of bexagliflozin	20 mg	fasted	Predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose
THR-1442-C-458 [US]	NA (Ph1) (20)	A phase 1, open-label, randomized, two-period, crossover study to evaluate the effect of exenatide on the PK and PD of bexagliflozin in healthy subjects	20 mg	fasted	Predose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose
THR-1442-C-476 [US, CA, PL, RU]	52 weeks (64)	A phase 3, double-blind, placebo-controlled study to evaluate the effects of bexagliflozin on HbA1c in patients with T2DM and increased risk of cardiovascular adverse events	20 mg	fasted	At weeks 6 or 12: Group 1: 0.25-1, 7-10, and 20-24 h post dose Group 2: 1.5-3, 3.5-6.5, and 7-10 h postdose
THR-1442-C-481 [US]	NA (Ph1) (25)	A phase 1, open-label, randomized, two-period, crossover study to evaluate the effect of a high-fat meal on the PK of bexagliflozin in healthy subjects	20 mg	fasted/fed	Predose and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h postdose

NDA 214373
Brenzavvy (bexagliflozin)

Study No [Sites]	Duration (N)	Description	Dose (mg) Prandial State	PK Sampling
THR-1442-C-603 [US]	36 weeks (306)	A phase 2/3, double-blind, placebo-controlled study to evaluate the efficacy and safety of bexagliflozin in patients with essential hypertension not adequately controlled by standard of care	20 mg fasted	At weeks 18 or 24: Group 1: 0.25-1, 7-10, and 20-24 h post dose Group 2: 1.5-3, 3.5-6.5, and 7-10 h postdose

Source: Applicant's PopPK Report THR-1442-C-447, Table 1, pages 19-20

†: THR100-CLR-002 included 50 subjects in total, in which 20 subjects received IR and exploratory SR formations. These subjects were removed from the PPK database.

††: THR-1442-C-454 (DDI study) included 48 subjects in total. After removing PK records with the concomitant DDI period, ID =400 (USUBJID = THR-1442-C-454- (b) (6)) did not have measurable PK records (all NAs); therefore, this subject was removed from the PPK database.

Abbreviations: CA, Canada; DDI, drug-drug interaction; ES, Spain; FR, France; h, hours; HbA1c, hemoglobin A1c; ID, identification; IR, immediate release; JP, Japan; MAD, multiple ascending dose; N, number of subjects; NA, not applicable; mg, milligrams; , PD, pharmacodynamics; Ph, phase; PL, Poland; PK, pharmacokinetics; RU, Russia; SAD, single ascending dose; SR, sustained release; T2DM, Type 2 Diabetes Mellitus; US, United States.

Table 121. Summary of Baseline Demographic Covariates for PopPK Analysis by Population

Demographic	All	Healthy	Diabetic	Hypertensive	Diabetic & Hypertensive	Hepatic Impairment
N	884	208	250	225	193	8
Variable, mean (SD)						
Age (years)	54.76 (14.84)	37.44 (12.59)	59.38 (10.63)	57.96 (12.19)	63.50 (8.88)	59.88 (4.58)
Weight (kg)	84.90 (21.81)	77.51 (13.65)	76.10 (19.18)	95.59 (23.34)	91.36 (22.77)	95.25 (20.72)
BMI (kg/m ²)	29.43 (6.45)	25.97 (3.60)	27.59 (5.73)	32.47 (7.26)	31.97 (6.12)	30.60 (4.69)
BSA (m ²)	1.99 (0.29)	1.92 (0.20)	1.86 (0.26)	2.12 (0.29)	2.06 (0.30)	2.15 (0.28)
Alb (g/dL)	43.47 (3.31)	41.97 (2.94)	44.61 (3.26)	43.71 (2.79)	43.67 (3.09)	35.50 (6.80)
ALT (U/L)	23.97 (14.71)	22.29 (11.34)	24.19 (17.50)	24.42 (14.67)	25.26 (14.11)	17.25 (7.27)
AST (U/L)	22.05 (9.82)	20.47 (6.57)	21.60 (10.39)	22.44 (10.21)	22.98 (10.29)	42.25 (15.54)
Bili (mg/dL)	9.57 (5.58)	11.62 (4.27)	8.67 (3.86)	8.78 (5.30)	8.23 (4.07)	38.26 (18.37)
CrCL (mL/min)	108.05 (39.63)	122.07 (24.82)	95.20 (40.42)	115.25 (46.34)	100.26 (36.15)	129.34 (39.69)
TPN (g/L)	71.46 (5.08)	70.99 (4.78)	73.17 (4.67)	70.91 (5.32)	70.58 (4.83)	67.38 (9.78)
Sex, n (%)						
Male	578 (65.4)	158 (76.0)	158 (63.2)	139 (61.8)	117 (60.6)	6 (75.0)
Female	306 (34.6)	50 (24.0)	92 (36.8)	86 (38.2)	76 (39.4)	2 (25.0)

NDA 214373
Brenzavvy (bexagliflozin)

Demographic	All	Healthy	Diabetic	Hypertensive	Diabetic & Hypertensive	Hepatic Impairment
Race, n (%)						
Caucasian	456 (51.6)	112 (53.8)	72 (28.8)	149 (66.2)	116 (60.1)	7 (87.5)
Black	181 (20.5)	63 (30.3)	20 (8.0)	65 (28.9)	33 (17.1)	0 (0.0)
Asian	226 (25.6)	27 (13.0)	154 (61.6)	4 (1.8)	41 (21.2)	0 (0.0)
Others	21 (2.4)	6 (2.9)	4 (1.6)	7 (3.1)	3 (1.6)	1 (12.5)

Source: Applicant's PopPK Report THR-1442-C-447, Table 3, page 25
Values reported are mean and standard deviation (SD) for continuous variables, count and % for categorical variables.
Abbreviations: N, n, number of subjects, ALB, albumin, ALT, alanine transaminase, AST, aspartate aminotransferase, BILLI, bilirubin, BMI, body mass index, BSA, body surface area, CrCL, creatinine clearance, popPK, population pharmacokinetics; TPN, serum total protein, WT, body weight.

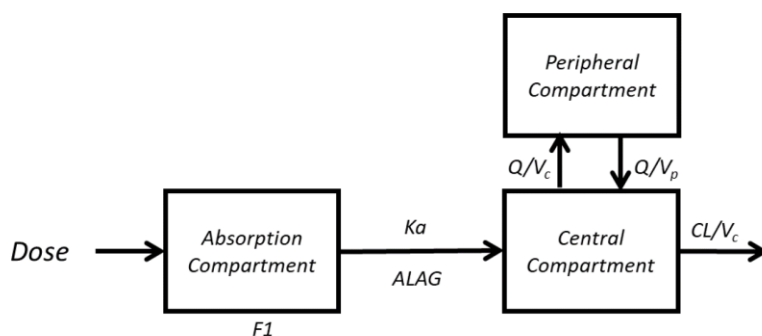
Base Model

A base 2-compartment model with first-order [absorption (K_a) with lag time (T_{lag})] and first-order elimination (CL) was developed to characterize bexagliflozin disposition. A schematic of the base structural model is shown in [Figure 37](#).

Interindividual variability (IIV) was modeled on primary PK parameters for patient level random effects in the base model. Residual variability was described using the proportional error model. Model selection from the base model was guided by change in objective function (OBJ), residual variance, IIV, and examination of diagnostic (e.g., goodness-of-fit) plots. Covariates for the final model were selected using the forward addition and backwards elimination approach using the base structural model.

Figure 37. Scheme of Base Model Structure

1st order absorption (K_a) + lag-time model:



Source: Applicant's PopPK Report THR-1442-C-447, Figure S1, page 4

Abbreviations: CL, clearance; K_a , absorption constant; Q , inter-compartmental clearance; V_c , central volume of distribution; V_p , peripheral volume of distribution.

FDA Reviewer Comment: The Applicant also tested the same structural model with transit compartments and considered it a better base model (without covariates); however, the 2-compartment model with K_a and T_{lag} appeared to describe the pooled PK of bexagliflozin adequately via diagnostic plots (reviewer noted obvious trends for creatinine clearance [CrCL] and body weight when plotted against ETA for CL, indicating further model refinement was needed). As such, the Applicant noted that structural model with K_a and T_{lag} was used for covariate selection because of less computational intensity, and final covariate model refinement was conducted with the transit model.

Covariate Analysis

Covariates shown in [Table 122](#) were evaluated in a forward-selection manner, and candidate models were evaluated based on OBJ reductions and PK parameter precision. The full model underwent backwards elimination. In addition, transit compartments were employed to describe the absorption profile as a candidate model, and an OMEGA block between CL and central compartment was also tested for the final covariate model. Refer to the Applicant's popPK report Section 5.2 for details on candidate models and results of backwards elimination.

Table 122. Covariates Tested for the Final PopPK Model

Parameter	Covariates
CL/F	Age, WT, BMI, BSA, ALT, AST, ALB, BILI, CRCL, TPN, Dose, Sex, Race, Population, Nation, Concomitant medications (hypoglycemic, hypotensive drugs etc.),
Vc/F	Age, WT, BSA, BMI, ALB, Sex, Race, Population
Q/F	WT, BSA, BMI, ALB, Sex – if feasible
Vp/F	WT, BSA, BMI, ALB, Sex – if feasible
Ka	Age, Food, Population
F	Food

ALB = albumin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = total bilirubin; BMI = body mass index, BSA = body surface area, CRCL = creatinine clearance; WT = weight; CL = clearance, Vc = volume of distribution in the central compartment, Q = intercompartmental clearance, Vp = volume of distribution in the peripheral compartment, Ka = absorption rate, F=bioavailability, TPN = serum total protein.

Source: Applicant's PopPK Report THR-1442-C-447, Table 5, page 33

14.3.4. Final Model

The final structural model including body weight, CrCL, Asian race, and food is described in [Figure 38](#). The final covariate model parameter estimates are listed in [Table 123](#). The goodness-of-fit plots are shown in [Figure 39](#). ETA versus continuous and categorical covariates are shown in [Figure 40](#) and [Figure 41](#), respectively. Visual predictive check (VPC) is shown in [Figure 42](#). Covariate effect is demonstrated in [Figure 43](#).

Figure 38. Final Model Structure

$$\begin{aligned}
 Kr &= \theta_1 * \theta_{31}^{FOOD=1} * \theta_{32}^{FOOD=2} * \exp(\eta_1) \\
 \frac{CL}{F} &= \theta_2 * \left(\frac{WT}{80}\right)^{\theta_8} * \left(\frac{CrCL}{100}\right)^{\theta_{12}} * \exp(\eta_2) \\
 \frac{Vc}{F} &= \theta_3 * \left(\frac{WT}{80}\right)^{\theta_{10}} * \theta_{21}^{RACE=3} * \exp(\eta_3) \\
 \frac{Vp}{F} &= \theta_4 \\
 \frac{Q}{F} &= \theta_5 \\
 F &= 1 * \theta_{34}^{FOOD=2}
 \end{aligned}$$

DOSE – Bexagliflozin dose, Kr – transit rate, CL – clearance, Vc – central volume, Vp – peripheral volume, Q – inter compartmental clearance, F – bioavailability, WT – body weight, RACE (3=Asian).

Source: Applicant's PopPK Report THR-1442-C-447, main text on page 44

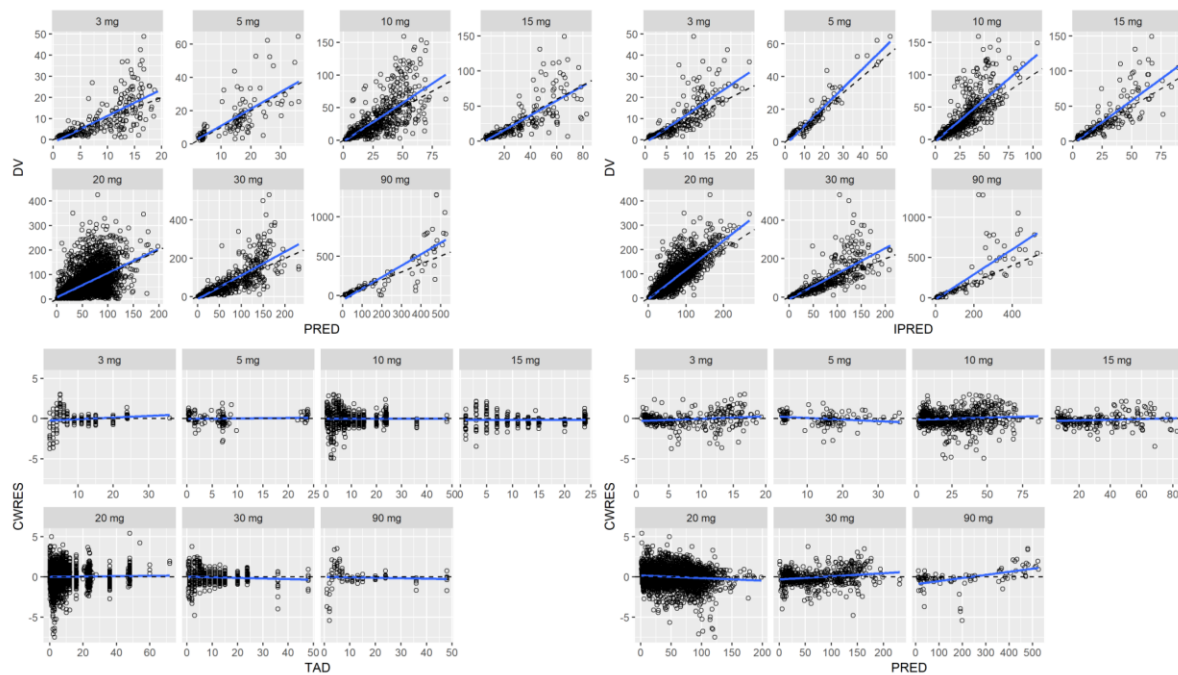
Table 123. Final PopPK Model Parameter Estimates

Parameter (Units)	Parameter	final model (OBJ= -1139.644)	
		Parameter estimate	RSE (%) for population parameter, Shrinkage (%) for IIV
Kr (1/h)	θ1	2.6	3.4
CL (L/h)	θ2	19.1	1.7
Vc (L)	θ3	146	4.9
Vp (L)	θ4	116	7.3
Q (L/h)	θ5	7.89	5.2
Residual Error (proportional) - (CV)	θ7	0.448	3.4
IIV Ka (CV%)	η1	45.8	31.2
IIV CL (CV%)	η2	38.5	15.1
IIV Vc (CV%)	η3	60.3	23.8
CL(η) - Vc(η)	σ _{2,3 -corr}	0.849	-
Covariate effects on clearance parameters (CL, Q)			
WT on CL	θ8	0.225	30.2
CrCL on CL	θ12	0.397	10.2
Covariate effects on volume parameters (Vc, Vp)			
WT on Vc	θ10	0.818	16.6
RACE=3 (Asian) on Vc	θ21	0.781	6.5
Covariate effects on absorption parameters (Kr, F)			
FOOD=1 (fed) on Kr	θ31	0.466	5.2
FOOD=2 (either) on Kr	θ32	0.443	8.3
FOOD=2 (either) on F	θ34	0.865	6.6

PPK – population pharmacokinetics, Kr – transit rate, CL – clearance from central compartment, L – liters, h – hour, Vc – central volume of distribution, Vp – peripheral volume of distribution, Q – inter-compartmental clearance, F – bioavailability, IIV – interindividual variability, θ – THETA (population value), η – ETA (the discrepancy of an individual parameter from the typical population value), CV – coefficient of variation, OBJ – objective function, RSE – relative standard error, WT – weight.

Source: Applicant's PopPK Report THR-1442-C-447, Table 9, page 45

Figure 39. Goodness-of-Fit Plots of the Final PopPK Model



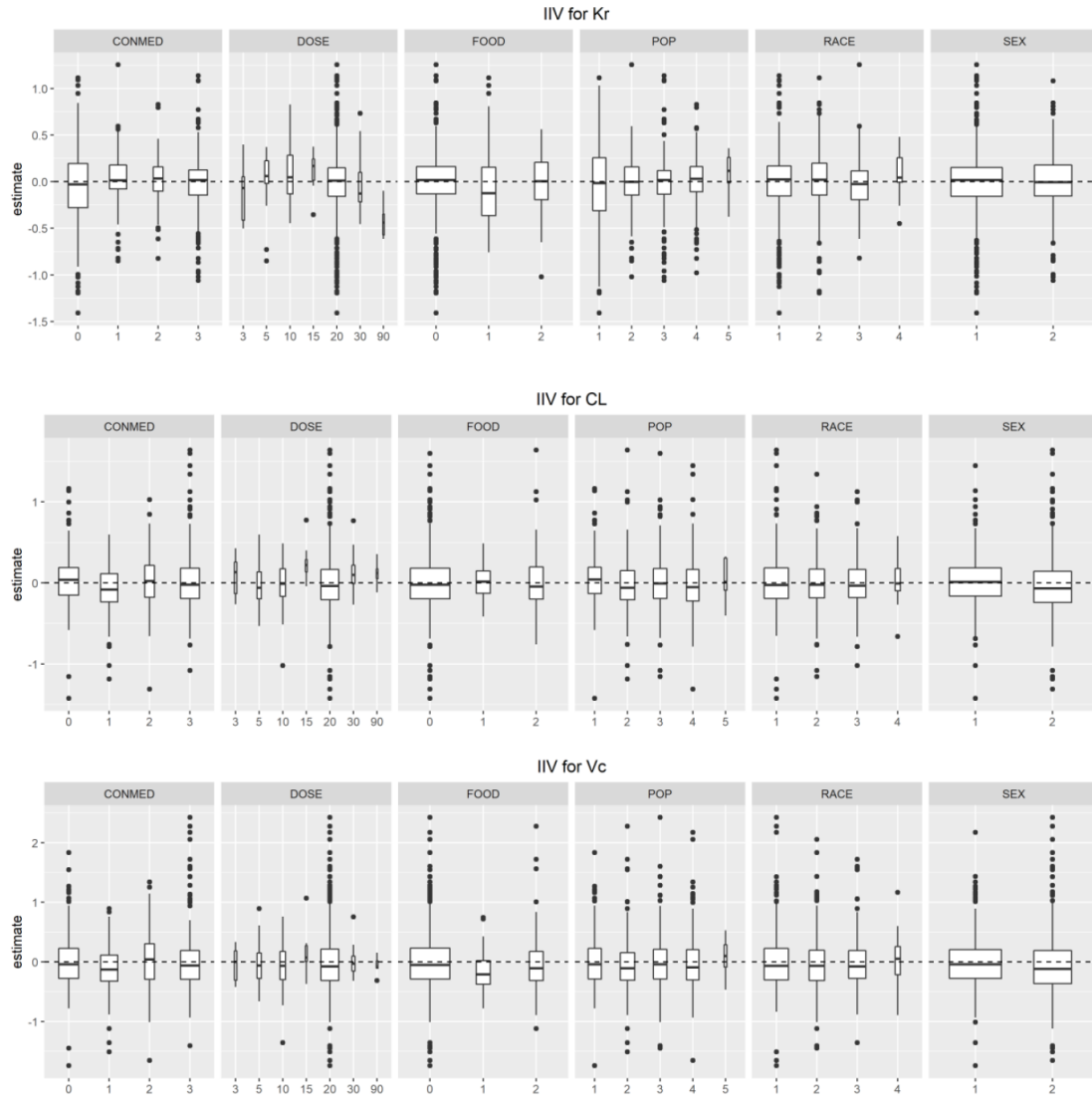
PPK – population pharmacokinetics, DV – dependent variable, PRED – predicted, IPRED – individual predicted, TAD – time after dose, CWRES – conditional weighted residuals. TAD is shown in hours, mg – milligrams.

Source: GOF_byDOSE_final_2cpt_transit3_omgblk.png

Note: The black open circles are observed data; the dashed black line is the line of unity or identity as appropriate; the blue line is a fitted linear or loess smooth lines.

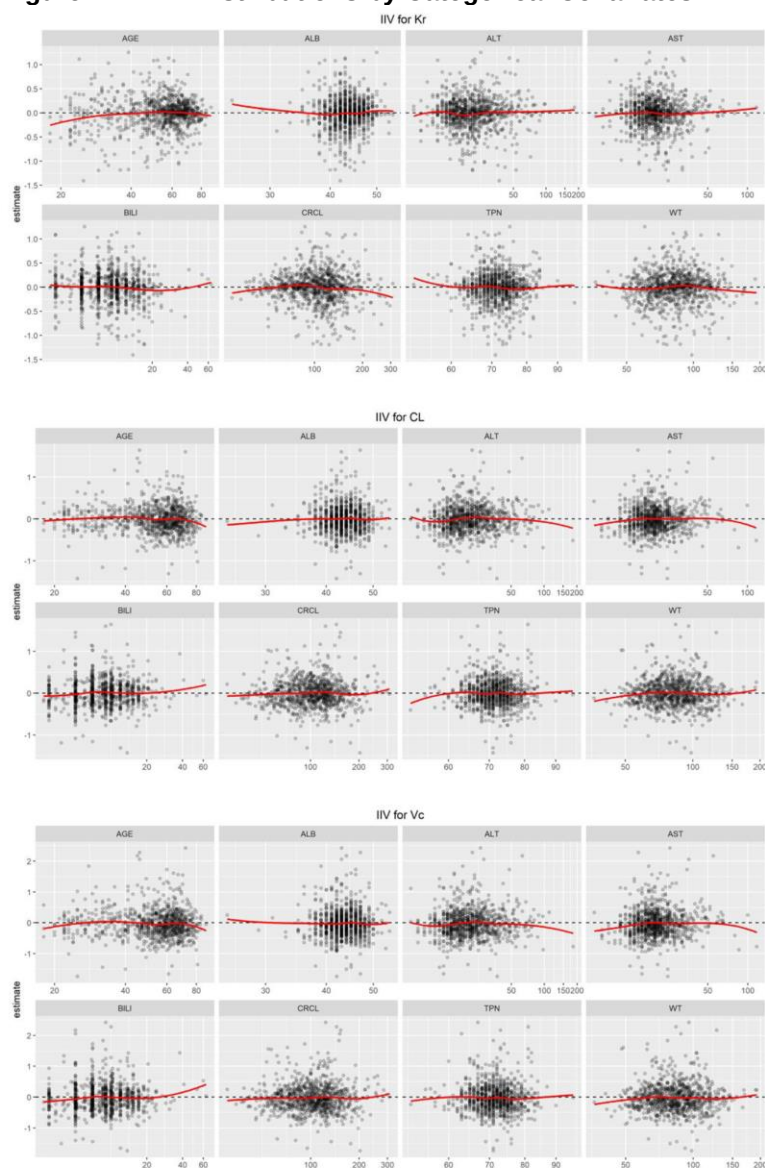
Source: Applicant's PopPK Report THR-1442-C-447, Figure 12, page 46

Figure 40. ETA Distributions by Continuous Covariates



IIV – interindividual variability, Kr – transit rate, CL – clearance, Vc – central volume of distribution, RACE– race (1=Caucasian, 2=Black, 3=Asian, 4=Others), SEX– sex (1=male, 2=female), FOOD – prandial state (0=fasted, 1=fed, 2=either: left to subject discretion), POP – population (1=healthy, 2=Type 2 diabetic mellitus, 3= hypertension, 4= Type 2 diabetic mellitus & hypertension, 5=hepatic impairment), CONMED – concomitant medication (0 = none, 1 = hypoglycemic agents; 2 = hypertensive agents; 3= both hypoglycemic & hypertensive), PPK – population pharmacokinetics, DOSE is in milligrams.
The size (width) of each box is proportional to the number of data records.
Source: Applicant's PopPK Report THR-1442-C-447, Figure 16, page 49

Figure 41. ETA Distributions by Categorical Covariates



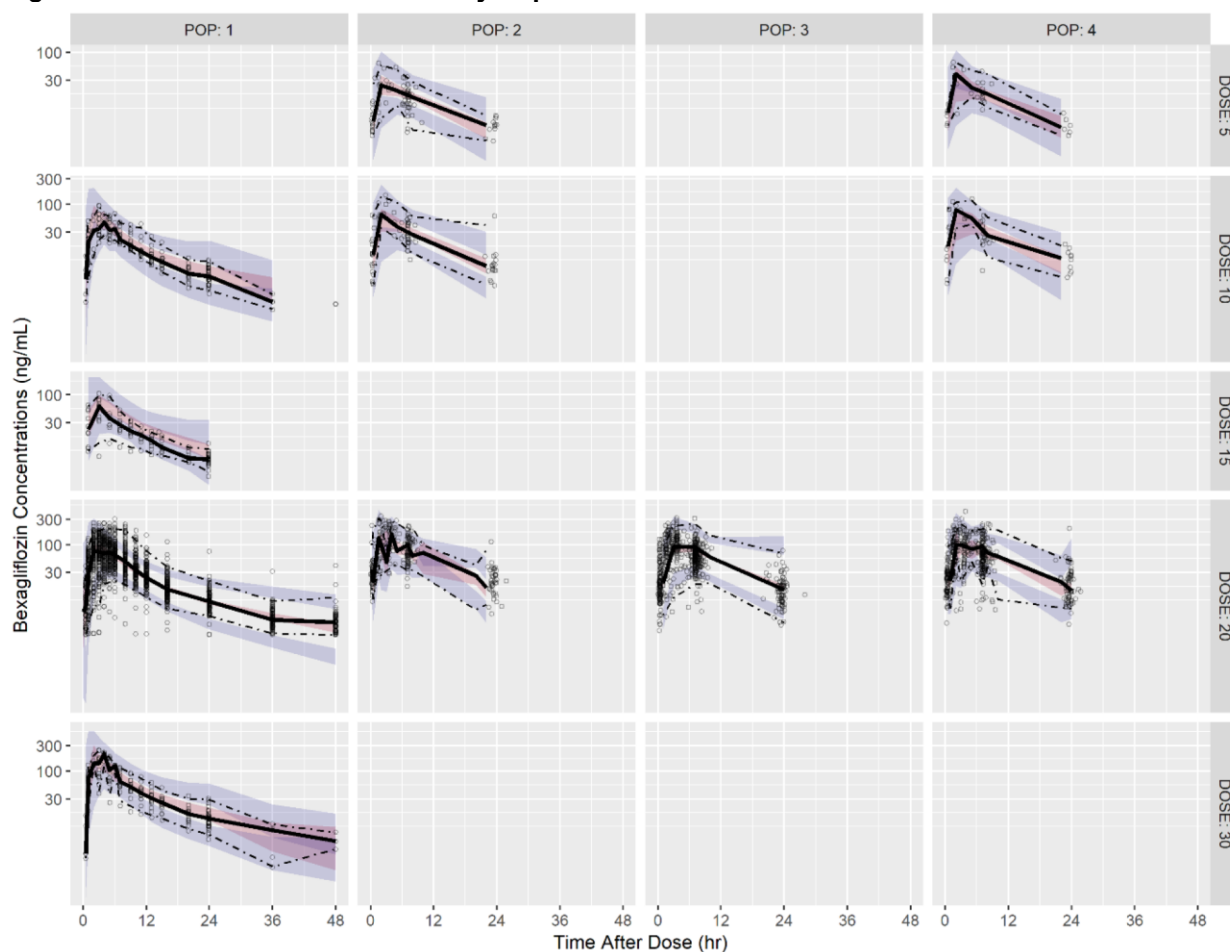
IIV – interindividual variability, Kr – transit rate, CL – clearance, Vc – central volume of distribution, PPK – population pharmacokinetics, AGE – age (years), ALB – albumin (g/dL), ALT – alanine transaminase (U/L), AST – aspartate aminotransferase (U/L), BILI – bilirubin (mg/dL), CRCL – creatinine clearance (mL/min), TPN – total protein (g/L), WT – weight (kg), g – grams, dL – deciliter, U – units, L – liters, mL – milliliter, min – minute, mg – milligrams, kg – kilograms. Red line: loess.

Source: Applicant's PopPK Report THR-1442-C-447, Figure 17, page 50

FDA Reviewer Comment: The reviewer was able to reproduce the base (base model parameter estimates not shown here) and final covariate model. The model parameters are precisely estimated (RSE generally below 25% with the exception of ETA Ka and weight exponent on CL at 31.2% and 30.2%, respectively). ETA shrinkages were low to moderate (15.1% to 31.2%). Based on the goodness-of-fit plots, the final model reasonably predicts the observed data. Although the individual predictions are slightly overpredicted, no overall systemic bias was observed based on the residual (CWRES) plots for time after dose and population predictions.

Between-subject variability of K_r , CL , and V_c are also randomly scattered around $y = 0$ without obvious trends.

Figure 42. Visual Predictive Checks by Population and Dose

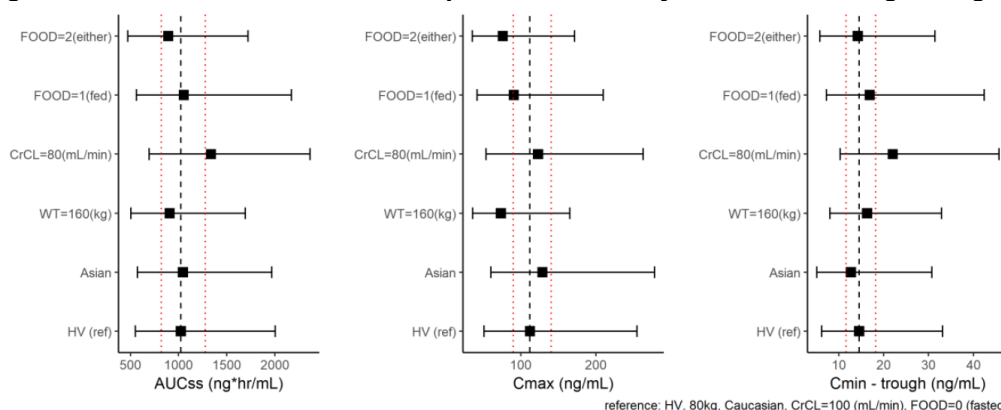


Source: Applicant's PopPK Report THR-1442-C-447, Figure 18, page 52

Fasted state; pop: 1 = healthy, 2 = diabetic, 3 = hypertensive, 4 = diabetic and hypertensive;

FDA Reviewer Comment: VPC plots (fed state not shown; refer to Applicant's popPK report) demonstrate that the model has slight overpredictions, and this is more notable for the lower prediction intervals (lower purple shaded areas). Generally, the central tendency of the PK data are adequately captured as shown in the pink median prediction intervals. VPC was also performed for bexagliflozin 20 mg with fasted condition by categorical body weight (≤ 80 kg versus > 80 kg) and by CrCL (≤ 100 mL/min versus > 100 mL/min) and no obvious misspecification was identified (figures not shown; refer to figures 21 and 22 in Applicant's popPK report). Overall, the population PK model is adequate in characterizing the disposition of bexagliflozin at 20 mg and in evaluating impacts of clinical covariates. Based on the Applicant's assessment of impacts of covariates and typical population factors on bexagliflozin exposure, no clinically meaningful difference was identified with regard to steady-state AUC, C_{max} , or C_{min} .

Figure 43. Effect of Covariates on Exposures at Steady-State With 20 mg Bexagliflozin



AUC_{ss} – area under the concentration time curve steady-state, ng – nanogram, mL – milliliter, C_{max} – maximum concentration, C_{min} – minimum concentration, hr – hours, WT – weight, kg – kilograms, HV – healthy volunteer, CrCL – creatinine clearance, min – minute, FOOD – prandial state (0=fasted, 1=fed, 2=either: left to subject discretion). ref - reference population: healthy volunteer, Caucasian, 20mg fasted (FOOD=0), male, 50 years old, body weight=80 kg, CrCL=100 mL/min.

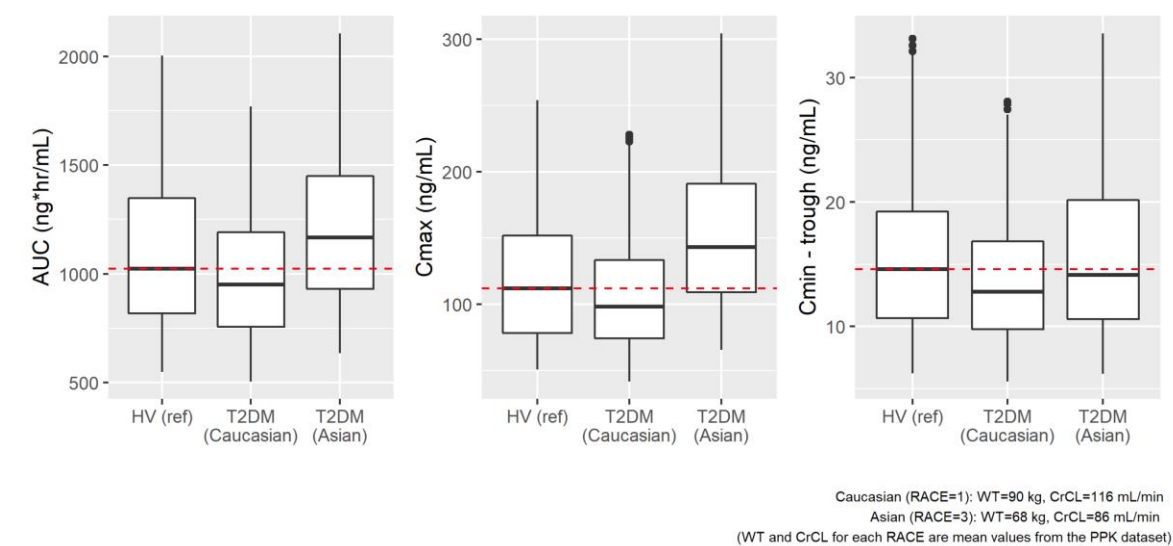
The plot shows median and 90% prediction intervals. Red dotted lines are 80% and 125% of reference values.

Source: Applicant's PopPK Report THR-1442-C-447, Figure 25, page 58

FDA Reviewer Comment: While food was significant and included in the popPK model, the estimated food effect (reduction in exposure with food versus fasted state) may be confounded by sparse sampling and other uncontrolled factors. Food effect was evaluated in a phase 1 crossover, dedicated food effect study (Trial C-481) in healthy volunteers. For food effect, refer to Therapeutic Individualization in Section 8.2.

The Applicant performed simulations (N=500 for each population) to further assess covariate effects with the final popPK model. For each simulated population, the covariates were set to mean population baseline values (see footnote in Figure 44). Since patient populations were not significant in the final model (based on stepwise covariate selection), simulation results for patients with hypertension or T2DM with hypertension were similar with T2DM below. The Applicant concludes that although Asian patients have slightly higher AUC and C_{max} than those of the Caucasian patients, C_{min} are overall similar. Generally, the ranges of exposure metrics overlap and no apparent differences were observed.

Figure 44. Simulated Exposures for Typical Study Populations at Fasted State



AUC – area under the concentration time curve, mg – milligrams, ng – nanograms, hr – hours, mL – milliliters, Cmax – maximum concentration, Cmin – minimum concentration, HV – healthy volunteers (reference), T2DM – Type 2 diabetes mellitus.

Source: Applicant’s PopPK Report THR-1442-C-447, Figure 26, page 59
Covariates were set to mean baseline values in each population; median and 90% prediction intervals; red dotted lines are 80% and 125% reference values

FDA Reviewer Comment: As the final popPK model has acceptable precision of parameter estimates and low to moderate shrinkages, the simulation approach to generate exposure metrics for typical populations is reasonable to demonstrate similarity of bexagliflozin exposures across patient populations of interest.

Table 124. Analysis Datasets

File Name	Description	Location in \\cdsnas\pharmacometrics\
NONMEM dataset for the base and final model	thernmv6.csv	...\NDA_214373_bexagliflozin_JIAJUNLIU\PPK_Analysis\runs
NONMEM code for the base model	ctl1.mod	...\NDA_214373_bexagliflozin_JIAJUNLIU\PPK_Analysis\runs
NONMEM code for the final model	ctl2.mod	...\NDA_214373_bexagliflozin_JIAJUNLIU\PPK_Analysis\runs

Source: Reviewer generated.

14.3.5. Reviewer’s Independent Analysis

14.3.5.1. Introduction

Trial C-449 was a phase 2b, randomized, double-blind, placebo-controlled, parallel group dose-ranging study in subjects with type 2 diabetes mellitus. The primary endpoint was to: 1) compare HbA1c reduction from baseline in treatment groups receiving 5 mg, 10 mg, or 20 mg

bexagliflozin to placebo group over 12 weeks, and 2) identify dose(s) for late-stage clinical trials. This analysis aims to describe the dose-response efficacy relationship (and the associated parameter variability) in T2DM subjects in Trial C-449.

14.3.5.2. Objectives

Analysis objectives are:

- To identify the dose-response relationship of bexagliflozin
- To quantify the percent of pharmacological effect achieved with proposed dosage

14.3.5.3. Methods

Analysis was conducted in R (version 3.6.3; R Core Team) and *DoseFinding*, an R package (Bjoern). After excluding the missing efficacy endpoints, a nonlinear model (dose-response $E_{\max}$ model) was fitted to the observed change in HbA1c (n=256) at Week 12 for the full analysis population using the *fitMod* function. Standard errors of the parameter estimates were used to generate the 95% confidence interval.

To obtain the placebo-adjusted percent of maximal pharmacological effect achieved at bexagliflozin 20 mg, a sensitivity analysis was conducted with placebo mean change set to zero. The analysis dataset is summarized in [Table 125](#).

Table 125. Analysis Dataset

Trial Number	Name	Link to EDR
C-449	adeff.xpt	\\CDSESUB1\EVSPROD\nda214373\0001\m5\datasets\thr-1442-c-449\analysis\adam\datasets\adeff.xpt

Source: Submitted by Sponsor in NDA in Module 5.

14.3.5.4. Results

After excluding missing data, 265 subjects were included in the analysis. [Table 126](#) provides a summary of the sample size and efficacy endpoint for the analysis. [Figure 45](#) illustrates the $E_{\max}$ model fit and the associated 95% CI based on parameter standard errors. The estimated half maximal effective dose was 2.96 mg (SE, 2.2) and $E_{\max}$ was -0.82% (SE, 0.16).

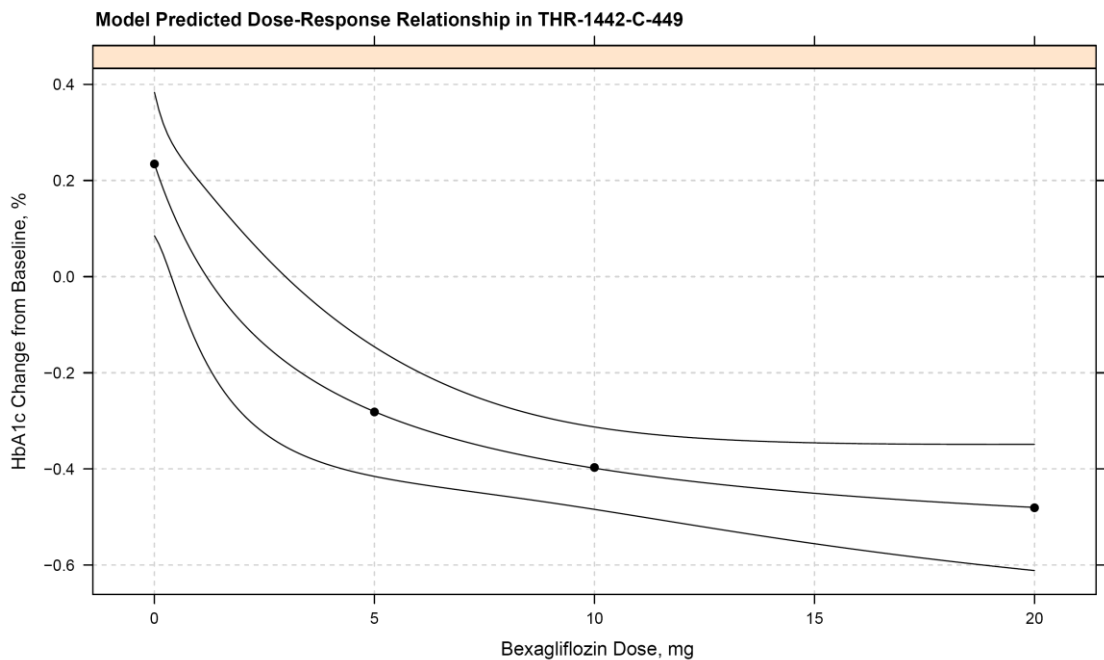
Table 126. Summary of Sample Size and Efficacy Endpoint by Treatment Groups

Treatment Groups	Sample Size	Mean HbA1c % Change From Baseline
		(25 th , 75 th Percentiles)
Placebo	64	0.23 (-0.2, 0.63)
5 mg	65	-0.28 (-0.6, 0)
10 mg	68	-0.40 (-0.7, 0)
20 mg	68	-0.48 (-0.7, -0.28)

Source: Reviewer's analysis from dataset adeff.xpt from Table 126

Abbreviations: HbA1c, hemoglobin A1c.

Figure 45. Mean Change in HbA1c From Baseline at Week 12



Source: Reviewer generated.
Black dots, mean change from baseline of each subgroup by dosage shown; middle black line, model predictions based on parameter estimates; top and bottom black lines, upper and lower bounds of 95% confidence interval based on the parameter standard errors, respectively.
Abbreviations: HbA1c, hemoglobin A1c.

After adjusting for placebo in a sensitivity analysis (plot not shown), $E_{\max}$ was estimated to be -0.63% and 20 mg of bexagliflozin is predicted to achieve 76.8% (95% CI: 60.0%, 94.0%) of the maximum pharmacological effect (RCoreTeam 2020; Bornkamp et al. 2021).

Table 127. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
R Script	Bexa_plots.R	...\NDA 214373 bexagliflozin JIAJUNLIU\PPK Analysis

Source: Reviewer generated.

14.4. Summary of Bioanalytical Method Validation and Performance

Bioanalytical Methods for the Measurement of Plasma Bexagliflozin

LC-MS/MS methods were developed and validated to determine concentrations of bexagliflozin and its metabolites in human plasma collected in the completed clinical studies. Detailed methods and validation parameters are described below ([Table 128](#) to [Table 132](#)). The linearity of standard curve, selectivity/specificity, assay accuracy and precision, extraction efficiency, and dilution fulfilled the standard acceptance criteria. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period. The reviewers deemed that these method validations and sample analyses are acceptable.

Table 128. Bioanalytical Method for Bexagliflozin ((b) (4))

Method Validation Report	No. 8201366
Studies	Trials THR-1474-C-328, THR-1474-C-396, THR-1442-C-402, THR-1442-C-410, THR-1442-C-428, THR-1442-C-429, THR-1442-C-453, THR-1442-C-454, THR-1442-C-455, THR-1442-C-458, THR100-CLR-002, THR-1442-C-481
Methodology	The analyte (Bexa) and the internal standard (EGT0001479) were extracted from human plasma by liquid-liquid extraction. After evaporation under nitrogen, the residue was reconstituted and analyzed using LC-MS/MS.
Calibration curve range	2.00-8000 ng/mL
Accuracy (% bias)	±15.0% bias (±20.0% bias at the LLOQ)
Within-run	±15.0% bias (±20.0% bias at the LLOQ)
Between run	
Precision (CV%)	≤15.0% (≤20.0% at LLOQ)
Within-run	≤15.0% (≤20.0% at LLOQ)
Between run	
Long-term stability	78 days at -10°C to -30°C
Processed Extract stability	79 hours at 2°C to 8°C
Freeze-thaw stability	Demonstrated for 5 cycles
Analyte Recovery	97.2 -106.8% for Bexa and 108.1- 109.4% for EGT0001479

Source: Generated by Clinical Pharmacology reviewers based on data from Method Validation Report No. 8201366
Abbreviations: Bexa, bexagliflozin; CV%, coefficient of variation; LC-MS/MS, liquid chromatography mass spectrometry; LLOQ, lower limit of quantification.

Table 129. Bioanalytical Method for Bexagliflozin, EGT0001494 and EGT0001301 ((b) (4))

Method Validation Report	No. 8273043
Studies	Study THR-1442-C-424
Methodology	Bexa, EGT0001494, EGT0001301 and the internal standard (ISTD), EGT0001479, were extracted from K2EDTA Human Plasma by protein precipitation. The wet extracts were then analyzed using LC-MS/MS detection.
Calibration curve range	2.00-1000 ng/mL
Accuracy (% bias)	±15.0% bias (±20.0% bias at the LLOQ)
Within-run	±15.0% bias (±20.0% bias at the LLOQ)
Between run	
Precision (CV%)	≤15.0% (≤20.0% at LLOQ)
Within-run	≤15.0% (≤20.0% at LLOQ)
Between run	
Long-term stability	185 days at -10°C to -30°C
Processed Extract stability	120 hours at 2°C to 8°C
Freeze-thaw stability	Demonstrated for 5 cycles at -10°C to -30°C
Analyte Recovery	101.5%, 81.2%, 100.8%, and 109.3% for Bexa, EGT0001494, EGT0001301, and the internal standard, respectively

Source: Generated by Clinical Pharmacology reviewers based on data from Method Validation Report No. 8273043
Abbreviations: Bexa, bexagliflozin; CV%, coefficient of variation; LC-MS/MS, liquid chromatography mass spectrometry; LLOQ, lower limit of quantification.

Table 130. Bioanalytical Method for EGT00021491 ((b) (4))

Method Validation Report	No. 8276908
Studies	Studies THR-1442-C-424 and THR-1442-C-454
Methodology	EGT0002149 and the internal standard (ISTD), EGT0001479, were extracted from K2EDTA Human Plasma by protein precipitation. The wet extracts were then analyzed using LC-MS/MS detection.
Calibration curve range	2.00-1000 ng/mL
Accuracy (% bias)	±15.0% bias (±20.0% bias at the LLOQ)
Within-run	±15.0% bias (±20.0% bias at the LLOQ)
Between run	
Precision (CV%)	≤15.0% (≤20.0% at LLOQ)
Within-run	≤15.0% (≤20.0% at LLOQ)
Between run	
Long-term stability	69 days at -10°C to -30°C
Processed Extract stability	99 hours at 2°C to 8°C
Freeze-thaw stability	Demonstrated for 5 cycles at -10°C to -30°C
Analyte Recovery	96.8%, and 98.5% for EGT0002149 and the internal standard, respectively

Source: Generated by Clinical Pharmacology reviewers based on data from Method Validation Report No. 8276908
Abbreviations: CV%, coefficient of variation; LC-MS/MS, liquid chromatography mass spectrometry; LLOQ, lower limit of quantification

Table 131. Bioanalytical Method for Bexagliflozin ((b) (4))

Method Validation Report	No. T431-1301
Studies	Study THR-1442-C-445
Methodology	Plasma samples (Bexa) were spiked with internal standard (EGT0001479), processed by protein precipitation extraction, and analyzed using reversed-phase HPLC with Turbo Ion Spray® MS/MS detection
Calibration curve range	1.00-1000 ng/mL
Accuracy (% bias)	±15.0% bias (±20.0% bias at the LLOQ)
Within-run	±15.0% bias (±20.0% bias at the LLOQ)
Between run	
Precision (CV%)	≤15.0% (≤20.0% at LLOQ)
Within-run	≤15.0% (≤20.0% at LLOQ)
Between run	
Long-term stability	152-153 days at -20°C to -70°C
Processed Extract stability	162 hours at 10°C
Freeze-thaw stability	Demonstrated for 5 cycles at -20°C to -70°C
Analyte Recovery	81% and 80% for Bexa and the internal standard, respectively

Source: Generated by Clinical Pharmacology reviewers based on data from Method Validation Report No. T431-1301
Abbreviations: Bexa, bexagliflozin; CV%, coefficient of variation; HPLC, high performance liquid chromatography; LLOQ, lower limit of quantification.

Table 132. Bioanalytical Method for EGT0002149 (b) (4)

Method Validation Report	No. T431-1303
Studies	Study THR-1442-C-445
Methodology	Plasma samples (EGT0002149) were spiked with internal standard (EGT0001479), processed by protein precipitation extraction, and analyzed using reversed-phase HPLC with Turbo Ion Spray® MS/MS detection.
Calibration curve range	2.00-1000.00 ng/mL
Accuracy (% bias)	±15.0% bias (±20.0% bias at the LLOQ)
Within-run	±15.0% bias (±20.0% bias at the LLOQ)
Between run	
Precision (CV%)	≤15.0% (≤20.0% at LLOQ)
Within-run	≤15.0% (≤20.0% at LLOQ)
Between run	
Long-term stability	124-125 days at -20°C to -70°C
Processed Extract stability	112 hours at 10°C
Freeze-thaw stability	Demonstrated for 5 cycles at -20°C to -70°C
Analyte Recovery	78% and 84% for Bexa and the internal standard, respectively

Source: Generated by Clinical Pharmacology reviewers based on data from Method Validation Report No. T431-1303
Abbreviations: Bexa, bexagliflozin; CV%, coefficient of variation; HPLC, high performance liquid chromatography; LLOQ, lower limit of quantification; MS/MS, mass spectrometry.

15. Trial Design: Additional Information and Assessment

15.1. Phase 3 Protocol Synopses

15.1.1. Clinical Protocol Synopsis for C-419 (Version 1.0, Date: July 26, 2017)

Sponsor: TheracosBio, LLC

Name of Finished Product: Bexagliflozin Tablet

Name of Active Ingredient: Bexagliflozin

Study Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Bexagliflozin in Subjects with Type 2 Diabetes Mellitus Who Are not Adequately Controlled by Metformin Alone

Study Number: THR-1442-C-419

Study Phase: 3

Primary Objective: The primary objective of this study is to determine the effect of bexagliflozin on the placebo-corrected change in HbA1c from baseline to Week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

Secondary Objectives:

- To assess the effect of bexagliflozin on the change in FPG as a function of time
- To assess the effect of bexagliflozin on the change in SBP as a function of time

- To assess the effect of bexagliflozin on the proportion of subjects achieving HbA1c of $\leq 7\%$ as a function of time
- To assess the change in total body weight as a function of time in subjects with baseline body mass index (BMI) $\geq 25 \text{ kg/m}^2$
- To assess the change in HbA1c as a function of time
- To assess the change in HbA1c as a function of time among subjects who have baseline HbA1c of $>10.5\%$ and $\leq 12.0\%$

Study Design: Trial C-419 is designed to evaluate the safety and effectiveness of bexagliflozin tablets, 20 mg, for the treatment of T2DM in adult diabetics whose disease is inadequately controlled by metformin alone. The study will recruit 300 subjects with HbA1c between 7.5% and 10.5%, inclusive, to be randomized 1:1 to receive bexagliflozin tablets, 20 mg, or placebo in a double-blind treatment assignment. The primary endpoint of the study will be the placebo-corrected change from baseline to Week 24 of the HbA1c percentage. This is the main study and these subjects are in the double-blind treatment group. The study will also recruit 50 subjects with HbA1c $>10.5\%$ and $\leq 12.0\%$ into an open-label arm, to receive bexagliflozin tablets, 20 mg, for 24 weeks. The endpoint for the open-label arm will be the change from baseline to Week 24 of the HbA1c percentage. These subjects are in the high glycemic group.

All subjects are to have taken metformin at an optimal or near optimal stable dose for ≥ 8 weeks prior to screening and are to have received diet and exercise counseling. Subjects who meet all the inclusion criteria, none of the exclusion criteria, and who have consented to participate in the study, are eligible for study enrollment. Subjects who successfully complete a 1-week run-in and who remain eligible will be randomized.

Approximately 300 subjects with HbA1c values ≥ 7.5 and $\leq 10.5\%$ at screening will be randomized 1:1 to receive bexagliflozin tablets, 20 mg, or placebo, in addition to their customary metformin dosage for 24 weeks in an outpatient setting. Study subjects will not change their metformin dosage unless adjustment is medically necessary to manage hypoglycemia. The treatment period will last 24 weeks. Subjects will visit their study sites at Weeks 6, 12, 18, and 24 for safety and efficacy evaluations, and at Week 26 for a follow-up evaluation.

Up to 50 subjects who have HbA1c $>10.5\%$ and $\leq 12.0\%$ at screening will be assigned to the open-label treatment group to receive bexagliflozin tablets, 20 mg, in addition to their existing metformin regimen. There will be no placebo arm for the high glycemic group. Subjects enrolled in the open label treatment group will be asked to follow the same procedures as subjects enrolled in the blinded arms of the study.

Subjects with persistent hyperglycemia based on blood glucose levels may receive approved antidiabetic rescue medications. A sparse sampling assessment of bexagliflozin PK in the study population will also be performed. A net enrollment of approximately 200 subjects is planned for this aspect of the study. Samples will be taken between Weeks 6 and 12. The population PK study design and analysis plan will be described in a designated study protocol and the analysis will be reported separately.

Study Population: Approximately 350 subjects with T2DM will be enrolled in the study. The subjects must:

- (1) have an age of ≥ 20 years at screening. Women of childbearing potential must test negative for pregnancy and agree to abstinence or contraception for the duration of the

study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months) are eligible if they test negative for pregnancy at screening.

- (2) have a history of T2DM with an HbA1c level of $\geq 7.5\%$ and $\leq 10.5\%$ at screening, or have a history of T2DM with an HbA1c level of $>10.5\%$ and $\leq 12.0\%$ at screening
- (3) have been prescribed a stable dose of metformin (≥ 1500 mg per day in the US or ≥ 1000 mg per day in Japan) as their sole anti-diabetic medication
- (4) have a body mass index (BMI) ≤ 45 kg/m²
- (5) be able to comprehend and willing to provide written informed consent in accordance with institutional and regulatory guidelines
- (6) not have recently changed their medications for hypertension or hyperlipidemia (if applicable)
- (7) be able to regularly self-administer medication, as evidenced by consumption of all, or at worst one less than all, doses of run-in medication prior to randomization (at Visit 3)

Test Product, Dose, and Mode of Administration: Bexagliflozin tablets, 20 mg or placebo, once daily oral administration in 300 subjects Bexagliflozin tablets, 20 mg once daily oral administration in 50 subjects

Duration of Treatment: One week of run-in placebo treatment and 24 weeks of investigational product treatment

Efficacy Assessments:

The primary efficacy assessment is:

- The effect of bexagliflozin on the placebo-corrected change in HbA1c from baseline to Week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

The key secondary efficacy assessments are:

- To assess the effect of bexagliflozin on the change in FPG as a function of time
- To assess the effect of bexagliflozin on the change in SBP as a function of time
- To assess the effect of bexagliflozin on the change in HbA1c as a function of time
- To assess the effect of bexagliflozin on the change in total body weight as a function of time in subjects with baseline BMI ≥ 25 kg/m²
- To assess the effect of bexagliflozin on the proportion of subjects achieving an HbA1c $\leq 7.0\%$ over time
- To assess the change in HbA1c as a function of time among subjects who have baseline HbA1c level of $\geq 7.5\%$ and $\leq 10.5\%$
- To measure the change from baseline to Week 24 in subjects with baseline HbA1c level of $>10.5\%$ and $\leq 12.0\%$

Other assessment: Evaluation of bexagliflozin pharmacokinetics

Safety Assessments: Adverse events record, laboratory data including hematology, serum chemistry, urinalysis, electrocardiogram (ECG), vital signs, physical examinations, and concomitant medication use.

Statistical Methods: Summaries will be presented for double-blinded portion of the study, separately from the 50-subject open-label substudy. No formal hypothesis testing will be

performed for the substudy. Data summaries will report descriptive statistics (number of subjects [n], mean, SD, Q1, median, Q3, minimum, and maximum) for continuous variables, and frequency and percentage for categorical and ordinal variables.

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo. The analysis of the change in HbA1c at Week 24 will be based on the intent-to-treat (ITT) analysis set using all observed data and an MMRM approach that will include terms for treatment, visit, treatment-by-visit interaction, baseline HbA1c value, and country (United States or Japan) as fixed effect covariates. Least squares mean treatment differences between the bexagliflozin group and the placebo group at Week 24 will be estimated from the model with the corresponding p-values and their two-sided 95% CIs presented. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the analysis.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following analysis steps will be performed on the ITT analysis set:

- Missing HbA1c data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will not be excluded from the analysis.
- HbA1c values collected after the start of rescue medication will be excluded (considered missing), and the MMRM analyses will be reperformed.
- A last observation carried forward (LOCF) method will be used to impute the missing observations prior to carrying out the MMRM model.

The effect of bexagliflozin on fasting plasma glucose, the change in SBP, the proportion of subjects reaching $\leq 7.0\%$ HbA1c, the change in HbA1c over time, and the change in total body weight will be analyzed as secondary efficacy endpoints and will not be adjusted for multiplicity. Safety data will include adverse event (AE) descriptions, physical exam results, vital sign measurements, ECG results, and clinical lab results from analyses of serum chemistry, hematology, serum lipids, glycemic control parameters, and urinalysis. The general safety of bexagliflozin in subjects with type 2 diabetes mellitus will be analyzed as well as the contribution of bexagliflozin to AEs of special interest.

The sample size calculation for this study is based on two group t-test with a two-sided significance of 0.05 level. The assumptions that led to the estimated required sample size of 150 per group with 1:1 ratio for a power of 90% are as follows:

- A treatment effect of 0.4%.
- A population HbA1c standard deviation of 1%.
- A two-sided significance level of 0.05.
- A drop-out rate of 12%.

FDA Reviewer Comment: *Metformin is the most commonly prescribed oral antihyperglycemic agent for T2DM and is often recommended as a first-line therapy for the treatment of T2DM. The study was conducted in the United States and Japan, and stratification by country (United*

States versus Japan) and baseline HbA1c status ($\leq 8.5\%$ versus $> 8.5\%$) was performed. The protocol was similar to other protocols reviewed in the Division; however, it is noteworthy that subjects were eligible for enrollment at Japanese sites if on stable metformin doses $\geq 1,000$ mg metformin per day (as opposed to ≥ 1500 mg per day, which is a commonly used threshold in other programs and was used at US-based sites in this trial). However, this would not be expected to change the overall conclusions from the study.

With regards to trial conduct, there were no amendments to Version 1 and the only modifications to the protocol were regarding planned analyses. Investigators were trained on the study protocol and procedures during site initiation meetings. Each center was visited at regular intervals by a monitor to ensure compliance with the study protocol, good clinical practice (GCP) guidelines, and the law. This included on-site checking of the CRFs for completeness and clarity, verification with source documents, and clarification of administrative matters. Seven site audits were conducted during the trial. One critical finding, regarding lack of review of laboratory results by the investigator within 3 days of receipt, was found at a US clinical site. The investigator was retrained on review of laboratory reports, GCP, and site SOPs. This finding is unlikely to impact trial outcomes.

There were 14 (8.9%) and 11 (6.9%) subjects with at least one major protocol violation/deviation in the bexagliflozin and placebo groups, respectively. The majority of protocol deviations in both treatment groups were “IP not taken as per protocol” and “noncompliance with visit schedule.” The number of protocol deviations/violations was low and was generally consistent between treatment groups.

Overall, the protocol is generally similar to other protocols reviewed in the Division to evaluate the impact of SGLT2 inhibitor treatment on glycemic control in subjects on metformin monotherapy, and the trial appears to have been conducted adequately.

15.1.2. Clinical Protocol Synopsis for C-423 (Version 2.0, Date: April 06, 2017)

Sponsor: TheracosBio, LLC

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

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

Study Number: THR-1442-C-423

Study Phase: 3

Primary Objective: The primary efficacy objective is to demonstrate that bexagliflozin is noninferior to sitagliptin by evaluating the treatment effect on hemoglobin A1c (HbA1c) reduction at Week 24 in subjects whose T2DM is inadequately controlled by metformin.

Secondary Objectives: The key secondary objectives are:

- To evaluate the treatment effect of bexagliflozin versus sitagliptin on the change in FPG at Week 24
- To evaluate the treatment effect of bexagliflozin versus sitagliptin on the change in body weight in subjects with baseline BMI ≥ 25 kg/m² at Week 24
- To evaluate the treatment effect of bexagliflozin versus sitagliptin on the change in SBP in subjects at Week 24

Exploratory Objectives:

- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in the proportion of subjects achieving HbA1c <7.0% over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in FPG over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in body weight over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in SBP over time

Safety Objectives: To compare the effects of bexagliflozin with sitagliptin on the incidence of AEs of interest. AEs of interest are urinary tract infections (UTIs), urosepsis and pyelonephritis, genital mycotic infections (GMI), diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, major adverse cardiovascular events (MACE), falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders including DKA, pancreatitis, amputations, and renal failure events. To compare the effects of bexagliflozin with sitagliptin on general safety assessments including treatment-emergent AEs, clinical laboratory findings, 12-lead ECG parameters, physical examinations, vital signs including orthostatic blood pressure (BP), and use of concomitant medications.

Study Design: C-423 is a phase 3, multicenter, randomized, double-blind, active controlled study to evaluate the efficacy and safety of bexagliflozin versus sitagliptin in subjects whose T2DM is not well controlled by metformin alone. A total of 374 subjects are planned to be randomized in a ratio of 1:1 to receive once daily treatment of bexagliflozin tablets, 20 mg, with sitagliptin tablets, placebo (Group 1) or bexagliflozin tablets, placebo, with sitagliptin tablets, 100 mg (Group 2) for 24 weeks in an outpatient setting.

The main eligibility criteria include 1) male or female subjects with T2DM and 2) screening HbA1c between 7.0% and 11% (inclusive). Qualified subjects must have taken metformin at a stable dose of ≥ 1500 mg/day in addition to diet and exercise counseling for at least 8 weeks prior to screening. Study subjects will continue taking open-labeled metformin during the entire study. All eligible subjects will start a single-blind run-in period by taking placebo bexagliflozin and placebo sitagliptin once daily for one week. Subjects who meet all inclusion criteria and no exclusion criteria after completion of the run-in period will be eligible for randomization and receive investigational products.

During the treatment period, subjects will receive once daily sitagliptin tablets, 100 mg, and bexagliflozin tablets, placebo, or bexagliflozin tablets, 20 mg, and sitagliptin tablets, placebo, for

24 weeks. Each subject will be instructed to return to the clinic at Weeks 6, 12, 18, and 24 for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up exit visit at Week 26 or 2 weeks after last dose of study drug if subjects early terminate prior to Week 24. During the study, a data and safety monitoring board (DSMB) will review the unblinded data periodically and may recommend an early termination of the trial for safety reasons. In the event of administrative changes or other related reasons, the Sponsor reserves the right to terminate the study early. There will be no interim analysis; final statistical analysis will be performed after all subjects complete the study.

Study Population and Main Eligibility Criteria: A total of 374 eligible subjects are planned for this study. The study population will comprise:

- (1) Male or female adult subjects ≥ 18 years of age
- (2) If subjects are female of childbearing potential, subjects must be negative on the urine pregnancy test and agree to abstain from coitus or use contraception during the entire study to avoid any possible pregnancy
- (3) Subjects with a diagnosis of T2DM with HbA1c levels between 7.0% and 11% (inclusive) at screening
- (4) Subjects whose T2DM is treated with a stable dose of ≥ 1500 mg/day metformin only along with diet and exercise counseling for at least 8 weeks prior to screening
- (5) Subjects with a BMI ≤ 45 kg/m² at screening
- (6) If applicable, taking stable doses of treatment for dyslipidemia and/or hypertension for 30 days prior to screening. Subjects do not need to be treated for dyslipidemia or hypertension to be eligible for the study
- (7) Subjects who are willing and able to return for all clinic visits and to complete all study-required procedures, including self-monitoring blood glucose (SMBG) measurements

Prior to randomization, all subjects must:

- (8) Adhere to the investigational product administration requirements as evidenced by missing no more than 1 day of placebo run-in medication

Test Products, Dose, and Mode of Administration:

Once daily oral administration of bexagliflozin and sitagliptin with or without food taken together in the morning

- Group 1: bexagliflozin tablets, 20 mg, and sitagliptin tablets, placebo
- Group 2: bexagliflozin tablets, placebo, and sitagliptin tablets, 100 mg

Duration of Treatment: Eligible subjects will receive a total treatment duration of 25 weeks including 1 week of run-in medications and 24 weeks of investigational products.

Efficacy Assessments:

Primary efficacy assessment:

- Change in HbA1c from baseline at Week 24

Secondary efficacy assessments:

- Change in FPG from baseline at Week 24
- Change in body weight in subjects with baseline BMI ≥ 25 kg/m² at Week 24
- Change in SBP in subjects from baseline at Week 24

Other efficacy endpoints:

- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in the proportion of subjects achieving HbA1c <7.0% over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in HbA1c over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in FPG over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in body weight over time
- To assess the treatment effect of bexagliflozin versus sitagliptin on the change in SBP over time

Safety endpoints:

- Treatment-emergent AEs, including AESIs (genital and urinary tract infections, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fractures, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, pancreatitis, amputations, and renal failure events)
- Laboratory testing, including hematology, serum chemistry, and urinalysis
- Physical examination
- 12-lead ECG
- Vital signs
- Concomitant medication use

Statistical Methods: The primary hypothesis is that bexagliflozin is noninferior to sitagliptin by evaluating the treatment effect on HbA1c reduction at Week 24 in combination with metformin. The noninferiority margin for mean change from baseline at Week 24 in HbA1c comparing bexagliflozin group with sitagliptin group will be 0.35%. Superiority will be declared without additional statistical testing when the upper bound of the 95% CI for difference in change from baseline at Week 24 in HbA1c comparing bexagliflozin group with sitagliptin group is less than 0. The treatment difference will be examined by using an MMRM analysis of covariance model (ANCOVA). The model will include treatment, visit, treatment-by-visit interaction, region, and the baseline HbA1c value as fixed effect covariates. Least squares mean treatment differences between the bexagliflozin group and the comparator group at Week 24 in change from baseline will be estimated from the model. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive (1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from this primary analysis. Primary endpoints will be analyzed on both ITT and per protocol (PP) analysis sets.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed on both ITT and PP analysis sets:

- (1) Missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will be excluded.
- (2) Missing data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
- (3) HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be reperformed.

The effects of bexagliflozin on the changes from baseline at Week 24 in FPG, body weight, and SBP will be tested as key secondary endpoints and will be analyzed in a hierarchical testing strategy and only if the primary objective is met. Similar to the primary endpoint, MMRM ANCOVA models will be used. A hierarchical testing strategy will be followed to preserve experiment-wide alpha at 0.05:

- (1) Superiority test of the change in FPG in the bexagliflozin group versus the sitagliptin group at Week 24
- (2) Superiority test of the change in body weight in subjects with baseline BMI ≥ 25 kg/m² in the bexagliflozin group versus the sitagliptin group at Week 24
- (3) Superiority test of the change in SBP in the bexagliflozin group versus the sitagliptin group at Week 24

Additional effects of bexagliflozin versus sitagliptin on the changes in HbA1c, FPG, SBP, body weight, and the proportion of subjects who reach an HbA1c <7%, as well as the general safety in subjects with T2DM, will be analyzed as exploratory efficacy endpoints. These endpoints are considered exploratory and will not be adjusted for multiplicity.

For the primary efficacy endpoint, a minimum of 172 subjects are needed in each treatment arm to detect noninferiority of bexagliflozin to sitagliptin with respect to the change in HbA1c from baseline at Week 24 by a margin of 0.35%, assuming an estimated pooled SD of 1.0%. This estimation is based on a one-sided t-test with 90% power at a 0.025 level of significance. To allow for an estimated 8.0% dropout rate, 187 patients will be randomized in each treatment arm, and the total sample size will be 374 subjects for this study.

Statistical analyses and summaries will be performed using SAS® software (SAS Institute, Cary, NC).

Date of Protocol V2.0: April 6, 2017

Date of Protocol V1.0: February 1, 2017

FDA Reviewer Comment: This study was intended to evaluate whether bexagliflozin is noninferior compared to another antihyperglycemic agent (sitagliptin) commonly prescribed as add-on for patients failing to achieve glycemic goals on metformin. Sitagliptin was used at the recommended dosage strength for patients without renal impairment (i.e., 100 mg), which is appropriate for this study design to ensure that that NI is not resultant from suboptimal dosing in the active comparator arm. The protocol is similar to other protocols reviewed in the Division,

although the NI margin was larger than what has been used in other SGLT2 inhibitor development programs (i.e., 0.35% as opposed to 0.3%). At the IND stage, FDA agreed with the margin selection and accepted the Applicant's justification for the proposed margin.

Protocol version 2.0 was the only protocol used in the study. Each center was visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP, and legal aspects. A clinical site audit was conducted at investigational site 1271 on December 11, 2017. Major findings in GCP conduct included performing prescreening activities prior to subjects providing written informed consent for the study, lack of appropriate participation and oversight by the investigator, and failure of the investigator to provide adequate and accurate case histories for subjects treated in the study. Based on these findings, the Applicant decided to discontinue the investigator's participation of the study on March 22, 2018. Seven subjects had completed screening procedures and two subjects, one assigned to the bexagliflozin group and one assigned to the active-comparator group, were enrolled and received double blind investigational products for 6 to 12 weeks. Data of the two enrolled subjects were excluded from the ITT and safety analysis sets. Exclusion of these two subjects from the ITT would not be expected to change efficacy conclusions from the trial.

Protocol deviations were reported for 9 (4.7%) and 8 (4.1%) of subjects in the bexagliflozin and placebo groups, respectively. The number of protocol deviations was low and consistent between treatment groups.

Overall, the study appears adequately designed and conducted.

15.1.3. Clinical Protocol Synopsis for C-448 (Version 4.0, Date: October 25, 2016)

Sponsor: TheracosBio, LLC

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 A1c in Patients With Type 2 Diabetes Mellitus and Moderate Renal Impairment

Study Number: THR-1442-C-448

Study Phase: 3

Primary Objective: The primary objective of this study is to determine the efficacy of bexagliflozin on lowering HbA1c in patients with type 2 diabetes mellitus and moderate renal impairment.

Secondary Objectives: The key secondary efficacy objectives are:

- To assess the effect of bexagliflozin on the change in body weight at Week 24 in subjects with baseline BMI ≥ 25 kg/m²
- To assess the effect of bexagliflozin on the change in SBP at Week 24 in subjects with baseline SBP ≥ 130 mm Hg

- Change in HbA1c in subjects with estimated glomerular filtration rate (eGFR) 45 to 59 mL/min/1.73 m² at Week 24
- Change in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m² at Week 24

Study Design: C-448 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral administration of bexagliflozin tablets, 20 mg compared to placebo in subjects with T2DM, moderate renal impairment, and inadequate glycemic control. Main eligibility criteria include: 1) male or female subjects with T2DM, 2) screening HbA1c of 7.0 to 10.5% (inclusive), and 3) eGFR based on serum creatinine at 2 different assessments ≥ 30 to < 60 mL/min/1.73 m². The eGFR will be calculated by the modification of diet in renal disease study equation (MDRD). At the time of screening, the doses and frequency of all antidiabetic medications must have been stable for 8 weeks.

All eligible subjects will continue their prescreening antidiabetic medications and start a 1-week placebo run-in period. Subjects who are compliant in taking run-in medication (missing no more than one dose) will be eligible for randomization and receive study drug. Approximately 300 subjects (150 per arm) will be randomly assigned to receive bexagliflozin tablets, 20 mg or placebo, in equal ratio once daily for 24 weeks in an outpatient setting. Randomization will be stratified by screening HbA1c level (7.0 to 8.5% or 8.6 to 10.5%), screening antidiabetic treatment regimen (insulin treated or other) and screening eGFR (30 to 44 mL/min/1.73 m² or 45 to 59 mL/min/1.73 m²). A minimum of 135 subjects must be in the eGFR 30 to 44 mL/min/1.73 m² stratum.

Subjects with hyperglycemia based on blood glucose levels may receive approved antidiabetic medication. In addition, adjustment by the investigator to the prescreening antidiabetic therapies will be recommended if hypoglycemia occurs. Study subjects will have scheduled visits at Weeks 2, 6, 12, 18, and 24 for safety and efficacy evaluation. At Weeks 2 and 18, the visit will be conducted by a phone interview unless clinically necessary. A final follow-up visit will be conducted at Week 26. Measurement of bexagliflozin plasma concentration over time (sparsely sampled) will also be conducted from approximately 144 study subjects as part of a bexagliflozin popPK study.

Study Population: The study population will consist of 300 subjects who have been diagnosed with suboptimally controlled T2DM with moderate renal impairment. The study population will comprise:

- (1) Men or nonpregnant women ≥ 20 years of age. Women of childbearing potential must agree to use contraception during the entire study to avoid any possible pregnancy. Females who are surgically sterile (hysterectomy, oophorectomy) or postmenopausal (absence of menses greater than 12 months and age > 45 years) are eligible if they test negative on the urine pregnancy test.
- (2) Subjects with a diagnosis of T2DM with an HbA1c between 7.0 and 10.5% (inclusive) at the time of screening.
- (3) Subjects who are treatment naïve or are treated with a stable regimen of anti-diabetic medications that do not provide adequate glycemic control when combined with diet and exercise. At the time of screening, the doses and frequency of all anti-diabetic medications must have been stable for 8 weeks.
- (4) Subjects who have an eGFR ≥ 30 and < 60 mL/min/1.73 m² at 2 time points: screening (V1), and 1 additional time point between 1 and 12 months of screening (the most recent

historical value may be obtained from available medical records). The eGFR will be calculated by the MDRD equation.

- (5) Subjects who have a BMI ≤ 45 kg/m² (inclusive)
- (6) Subjects who taking stable doses of medications for hypertension or hyperlipidemia for at least 30 days prior to randomization
- (7) Subjects who have stable eGFR between the most recent historic value and day of screening (no more than 20% change in eGFR).

Test Product, Dose, and Mode of Administration: Bexagliflozin tablets, 20 mg or placebo, once daily by mouth

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

Efficacy Assessments:

Primary efficacy assessment:

- Change of HbA1c from baseline to Week 24

Secondary efficacy assessments:

- Change in body weight in subjects with baseline BMI ≥ 25 kg/m
- Changes in SBP over time in subjects with baseline SBP ≥ 130 mm Hg
- Change in HbA1c over time in subjects with eGFR 45 to 59 mL/min/1.73 m²
- Change in HbA1c over time in subjects with eGFR 30 to 44 mL/min/1.73 m²
- Samples for population PK analysis will be collected and the required plasma concentrations determined. The PK parameters will be assessed separately as part of the population PK analysis.

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

Statistical Methods: In general, descriptive statistics will be presented for continuous variables, and frequency and percentage for categorical variables.

For the primary objectives, efficacy is defined as lowering of HbA1c at Week 24 from baseline for bexagliflozin when compared to placebo. For the primary endpoint analysis, the primary analysis will utilize an MMRM ANCOVA approach, with treatment, visit, treatment-by-visit interaction, and randomization stratification factors as the fixed effects terms and baseline HbA1c as a covariate on all available data, incorporating all visits from each patient at which HbA1c was measured in the ITT analysis set. All observed data will be analyzed and data obtained after rescue will not be excluded. In addition, same analyses will be conducted in PP analysis set (if it is deemed different from the ITT analysis set).

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed for the ITT analysis set:

- (1) Missing HbA1c data will be imputed via multiple imputation, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will not be excluded.

- (2) Missing HbA1c data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
- (3) HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be reperformed.

If the PP analysis set is different from the ITT analysis set, the same analyses as described above will be conducted in PP analysis set as well.

The effects of bexagliflozin on the secondary endpoints will be tested in a hierarchical testing strategy to preserve experiment-wide type I error at 0.05:

- (1) Superiority test of the change in body weight in subjects with baseline BMI ≥ 25 kg/m² in the bexagliflozin group compared to the placebo group
- (2) Superiority test of the change in SBP over time in subjects with SBP ≥ 130 mm Hg in the bexagliflozin group compared to the placebo group
- (3) Superiority test of the change in HbA1c over time in subjects with eGFR 45 to 59 mL/min/1.73m² in the bexagliflozin group compared to the placebo group
- (4) Superiority test of the change in HbA1c over time in subjects with eGFR 30 to 44 mL/min/1.73m² in the bexagliflozin group compared to the placebo group

Additional effects of bexagliflozin on FPG, changes in HbA1c over time, proportion of subjects who reach an HbA1c <7%, change in body weight over time, change in urine albumin-to-creatinine ratio (UACR) over time, and the general safety of bexagliflozin in subjects with T2DM will be analyzed. No hypothesis testing will be conducted and will not be adjusted for multiplicity.

For the primary efficacy endpoint, sample size calculation is based on a two-sided significance at the 5% level. Assuming 1.0% as the standard deviation for difference in mean changes from baseline in HbA1c between bexagliflozin and placebo, an estimated sample size of 133 in each arm will have 90% power to detect a difference in mean HbA1c changes of 0.40% between bexagliflozin and placebo. To account for an estimated dropout rate of 12%, we propose randomizing 150 subjects in each study arm.

Statistical analyses and summaries will be performed using SAS software (SAS Institute, Cary, NC).

FDA Reviewer Comment: *This trial evaluated the use of bexagliflozin as add-on to standard of care (i.e., not as monotherapy or add-on to metformin) in subjects with T2DM and moderate renal impairment failing standard of care antihyperglycemic therapy, which is a patient population for whom an SGLT2 inhibitor would be added in clinical practice. Considering the variability of eGFR measurements, randomization of subjects based on a single laboratory assessment could result in inclusion of participants with an eGFR less than or greater than the desired eGFR criteria. To identify subjects with moderate renal impairment, the protocol specified that subject must have screening eGFR ≥ 30 and < 60 mL/min/1.73 m² and stable GFR (no more than 20% change in eGFR between a historical value and the value determined at the screening visit). Randomization was stratified by HbA1c level (≥ 7.0 to $< 8.5\%$ versus ≥ 8.5 to $< 10.5\%$), antidiabetic treatment regimen (with insulin or without), and eGFR (30 to 44 mL/min/1.73 m² versus 45 to 59 mL/min/1.73 m²). In general, the protocol is similar to others reviewed in the Division to assess efficacy and safety of SGLT2 inhibitor treatment in subjects*

with renal impairment, although it is noteworthy that studies differ with regards to the specific populations being enrolled (e.g., evaluation only in subjects with stage 3a chronic kidney disease (CKD) versus stage 3a and 3b CKD). The degree of renal impairment and other comorbidities may be expected to impact study results, and thus, cross-study comparisons are inadvisable.

Updates to the protocol from Version 3, which was the first version under which subjects were enrolled, to Version 4 were generally minor (e.g., addition of amputation as an AESI, clarification of selected inclusion criteria). There were 13 (8.3%) and 12 (7.7%) subjects in the bexagliflozin group and placebo groups that had at least one major protocol deviation, respectively. The number of protocol deviations were low and generally balanced between treatment arms. Overall, the trial design, enrolled population, and treatment duration were adequate and generally consistent with trials submitted to the Division to inform labeling in this patient population.

15.1.4. Clinical Protocol Synopsis for C-450 (Version 4.0, Date: April 04, 2017)

Sponsor: TheracosBio, LLC

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Compare the Efficacy and Safety of Bexagliflozin to Placebo in Subjects With Type 2 Diabetes Mellitus and Inadequate Glycemic Control

Study Number: THR-1442-C-450

Study Phase: 3

Primary Objective: To determine the placebo-adjusted treatment effect of bexagliflozin tablets, 20 mg on the change in HbA1c from baseline to Week 24 in subjects with type 2 diabetes mellitus and inadequate glycemic control.

Key Secondary Objectives:

- To assess the effect of bexagliflozin on systolic blood pressure compared to placebo
- To assess the effect of bexagliflozin on body weight in subjects with a baseline BMI ≥ 25 kg/m² compared to placebo

Exploratory Secondary Objectives

- To compare the effect of bexagliflozin to the effect of placebo on the proportion of subjects with HbA1c of <7%
- To compare the effect of bexagliflozin to the effect of placebo on change in HbA1c over time
- To compare the effect of bexagliflozin to the effect of placebo on FPG over time

Safety Objectives:

- To assess the safety of bexagliflozin in subjects with T2DM
- To assess the effect of bexagliflozin on the incidence of AESIs

- To contribute MACE+ events to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo or comparator treatment

Study Design: C-450 is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of once daily oral administration of bexagliflozin tablets, 20 mg, versus placebo in subjects with T2DM who are treatment-naïve or previously treated with one oral hypoglycemic agent (OHA).

The study will enroll male or female subjects with T2DM. If treatment-naïve, they must have an HbA1c at the screening visit of between 7% and 10.5%. Alternatively, prospective subjects may be eligible if at the time of the screening visit, they are being treated with one OHA, have an HbA1c of between 6.5% and 10.0%, and are willing to complete a 6-week washout. Individuals taking thiazolidinediones are not eligible for the study. A candidate will be considered treatment-naïve if they have received no more than 14 days of prescription medication for diabetes in the 12 weeks prior to screening. All eligible subjects will start a 2-week placebo run-in period. Subjects who miss no more than one dose of the run-in medication, have fasting blood glucose values ≥ 250 mg/dL on no more than two consecutive days, and who, at the baseline visit (Visit V5), have an HbA1c level between 7 and 10.5% and a fasting glucose level < 250 mg/dL will be eligible for randomization.

Approximately 210 subjects will be randomly assigned to receive oral bexagliflozin tablets, 20 mg, or placebo in a 2:1 ratio once daily for 24 weeks in an out-patient setting. Subjects with uncontrolled hyperglycemia based on blood glucose levels may receive additional approved antidiabetic medications. Treatment group assignment at the start of the treatment period will be stratified by baseline (Visit V5) HbA1c level (7.0 to 8.5% or 8.6 to 10.5%) and background antidiabetic treatment status (treatment-naïve or not). Each subject will be contacted by telephone at Week 2 (Visit V7) for safety monitoring and will be instructed to return to the clinic at Weeks 6, 12, 18, and 24 (Visits V8, V9, V10, and V11, respectively) for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up visit at Week 26 or two weeks after the last dose of investigational product if the subject terminates prior to Week 24 (Visit V12).

Study Population and Main Eligibility Criteria: Approximately 210 subjects are planned for this study. The study will enroll:

- (1) Male or female adult subjects ≥ 18 years of age at screening.
- (2) Subjects with T2DM who are treatment-naïve or receiving one OHA in combination with diet and exercise. Subjects taking thiazolidinediones are not eligible.
- (3) Subjects with HbA1c levels at screening (Visit V1) between 7.0% and 10.5% (inclusive) if treatment-naïve or with HbA1c levels between 6.5 and 10.0% (inclusive) if on one OHA
- (4) Subjects with a BMI ≤ 45 kg/m²
- (5) Subjects with a fasting plasma glucose < 250 mg/dL (13.9 mmol/L) at baseline (Visit V5)

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

Duration of Treatment: 24 weeks

Efficacy Assessments: The primary efficacy measure will be the change in HbA1c from baseline to Week 24. The key secondary measures will be the changes from baseline to Week 24 of systolic blood pressure and body weight. The exploratory secondary measures will be the change from baseline of the fasting plasma glucose concentration over time, the change from baseline of HbA1c over time, and the proportion of subjects who achieve an HbA1c <7% over time.

Safety Assessments: The safety of bexagliflozin will be assessed over the 24-week treatment phase. AEs of special interest include genital and urinary tract infections, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fractures, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, renal failure events, and amputations.

Statistical Methods: Data summaries will report descriptive statistics (number of subjects [n], mean, SD, Q1, median, Q3, minimum, and maximum for continuous variables, and frequency and percentage for categorical and ordinal variables). If there are missing values, the number missing will be presented, but without a percentage. All data collected will be included in by-subject data listings.

The primary efficacy hypothesis is that bexagliflozin reduces HbA1c after 24 weeks of treatment when compared to placebo. The analysis of the change in HbA1c at Week 24 will be based on ITT analysis set using all observed data and an MMRM approach that will include terms for treatment, visit, treatment-by-visit interaction, and randomization stratification factors as fixed effects and the baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the placebo group at Week 24 will be estimated from the model with the corresponding p-values and their two-sided 95% CI presented. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive (1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from the analysis.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed on the ITT analysis set:

- (1) Missing HbA1c data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will not be excluded from the analysis.
- (2) HbA1c values collected after the start of rescue medication will be excluded (considered missing), and the MMRM analyses will be reperformed.
- (3) An LOCF method will then be used to impute the missing observations prior to carrying out the MMRM model.

The effect of bexagliflozin on body weight and systolic blood pressure will be tested as key secondary efficacy endpoints and will be analyzed in a hierarchical testing strategy only if the primary objective is met. ANCOVA models will also be used for the continuous secondary endpoints analyses. Longitudinal data will be evaluated through repeated measures tests. A

hierarchical testing in the following order will be applied to preserve experiment-wide alpha at 0.05 in the case each successive determination meets significance:

- (1) To test the hypothesis that bexagliflozin reduces systolic blood pressure from baseline to Week 24 compared with placebo
- (2) To test the hypothesis that bexagliflozin reduces body weight from baseline to Week 24 compared with placebo in subjects with a BMI ≥ 25 kg/m²

The effect of bexagliflozin on fasting plasma glucose, on the proportion of subjects reaching <7.0% HbA1c, and on the change in HbA1c over time will be analyzed as exploratory efficacy endpoints and will not be adjusted for multiplicity.

Safety data will include AEs, physical exam results, vital signs, ECG results, and clinical lab results including serum chemistry, hematology, serum lipids, glycemic control parameters and urinalysis. The general safety of bexagliflozin in subjects with type 2 diabetes mellitus will be analyzed as well as the contribution of bexagliflozin to AEs of special interest.

For the primary efficacy endpoint, a power calculation was performed for significance calculated by a two-group t-test with a two-sided α of 0.05. Taking the standard deviation for the change in HbA1c to be 1%, a sample size of 128 in the bexagliflozin group and 64 in the placebo group is predicted to have 90% power to detect a difference between groups of 0.5% in mean HbA1c change. To account for an estimated drop-out rate of approximately 10%, a study design was adopted in which 140 subjects are planned to be randomized to the bexagliflozin group and 70 subjects to the placebo group. Statistical analyses and summaries will be performed using SAS software (SAS Institute, Cary, NC).

FDA Reviewer Comment: *This trial evaluated the effect of bexagliflozin on HbA1c in treatment-naïve subjects with T2DM or who were on one OHA and had inadequate glycemic control. Subjects were considered treatment-naïve if they had received no more than 14 days of prescription medication for diabetes in the 12 weeks prior to screening. In addition, subjects were considered treatment-naïve if taking one oral antihyperglycemic agent and willing to undergo a 6-week washout period prior to randomization. All subjects were required to undergo a 2-week placebo run-in period. Therefore, subjects on one oral antihyperglycemic agent would have been without diabetes management therapy for a minimum of 8 weeks prior to administration of the investigational product. Randomization was stratified by HbA1c (7.0 to 8.5% or 8.6 to 10.5%) and background antidiabetic treatment status (treatment-naïve or not). These procedures appear reasonable to include subjects previously taking one oral antihyperglycemic agent in the trial.*

The original protocol (Version 2.1) was dated February 10, 2016. Minor changes were made to the protocol in Version 3 (change of medical monitor/study statistician, addition of amputation as an AESI) and Version 4 (subsequent change of study statistician and updates to analysis plan). There were 36 (26.1%) and 12 (17.4%) of subjects with at least one major protocol deviation in the bexagliflozin and placebo groups, respectively. In both groups, the majority of protocol deviations were “noncompliance with visit schedule.” Three randomized subjects, two in the bexagliflozin group and one in the placebo group, were excluded from the ITT population due to protocol violations. Subject 450 (b) (6) and Subject 450 (b) (6) were the same person who enrolled in two clinical sites ((b) (6) and (b) (6)). Subject 450 (b) (6) enrolled in another bexagliflozin trial (C-480) while they were also enrolled in Trial C-450. It is unlikely that these violations significantly impact the results of the study.

15.1.5. Clinical Protocol Synopsis for C-476 (Version 8.0, Date: October 28, 2016)

Sponsor: TheracosBio, LLC.

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

Study Title: A Double-Blind Placebo-Controlled Study to Evaluate the Effects of Bexagliflozin on Hemoglobin A1c in Patients With Type 2 Diabetes and Increased Risk of Cardiovascular Adverse Events

Study Number: THR-1442-C-476

Study Phase: 3

Primary Efficacy Objective: The primary efficacy objective of this trial is to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects at high risk of cardiovascular adverse events.

Secondary Efficacy Objectives:

The key secondary efficacy objectives are:

- To evaluate the effect of bexagliflozin compared to placebo on the change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- To evaluate the effect of bexagliflozin on the change in body weight from baseline to Week 48 in randomized subjects with a BMI ≥ 25 kg/m² compared to placebo
- To evaluate the effect of bexagliflozin on the change in SBP from baseline to Week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg compared to placebo

Additional exploratory efficacy objectives are:

- To assess the effect of bexagliflozin treatment on the change in HbA1c versus placebo over time
- To evaluate the effect of bexagliflozin treatment on the change in FPG versus placebo over time
- To measure the proportion of subjects requiring an intensification of antidiabetic regimen versus placebo over time
- To measure the proportion of subjects requiring a relaxation of their antidiabetic regimen versus placebo over time
- To measure the incidence of hospitalization for heart failure among all subjects and among subjects with a history of heart failure at baseline.

Safety Objectives: The primary safety objective of this study is the contribution of at least 134 MACE+ to an eventual meta-analysis that is intended to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to placebo. MACE+ is defined as cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina. An additional objective is the evaluation of the safety of exposure to bexagliflozin for a minimum of 52 weeks in a treatment population that is at elevated risk for major adverse cardiovascular events.

Other Objectives:

- Measurement of bexagliflozin plasma concentration as a function of time from dosing (sparsely sampled) will be conducted at 30 sites and will include approximately 240 subjects
- Measurement of cardiovascular biomarkers at baseline and Week 12 in an exploratory study to increase the understanding of bexagliflozin treatment effect on the biomarkers that are relevant in the CV disease diagnosis and prognosis

Study Design: C-476 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Approximately 1650 subjects with poorly controlled T2DM and at high risk of CV adverse events will be randomized to bexagliflozin tablets, 20 mg, or placebo in a ratio of 2:1 in addition to the background antidiabetic medications.

Potential participants with suboptimal glycemic control (HbA1c between 7.0% and 11%) despite treatment as recommended in local guidelines and at high risk of cardiovascular adverse events will enter a screening period of up to three weeks. Qualified participants will enter a single-blind, placebo run-in period to allow for diabetes education and optimization of compliance with diet and exercise recommendations. Qualified subjects will continue their prescreening regimen for glycemic control and will be instructed to take the run-in medication once daily for 13±2 days. Adjustment of treatment for hypertension or dyslipidemia will not be permitted during the screening and run-in periods although initiation of anticoagulant therapy (if clinically indicated) will be permitted. If a change in treatment is required to improve management of hypertension or dyslipidemia, the subject may re-enter the screening after the clinical condition and treatment regimen have not changed for at least four weeks. Subjects who continue to qualify for the study and who have demonstrated compliance by missing no more than one dose of the run-in doses as instructed will be randomized to receive the investigational product.

Assignment to treatment groups will be stratified by baseline HbA1c ($>$ or $\leq 9.5\%$), baseline eGFR ($\text{eGFR} \geq$ or $< 60 \text{ mL/min/1.73 m}^2$), baseline BMI ($\geq$ or $< 25 \text{ kg/m}^2$), and history of heart failure. The study subjects will visit the clinic or complete phone interviews for evaluation at 2, 6, 12, 18, 24, 36, and 48 weeks postrandomization with subsequent visits scheduled every 24 weeks and a phone interview at 12 weeks after each clinic visit. The study duration will be determined by event accumulation. The treatment period will end when all randomized subjects have completed at least 52 weeks of treatment and a total of 134 subjects have experienced a MACE+. A follow-up visit will take place four weeks after the conclusion of treatment.

During the first 24 weeks of the efficacy assessment period, hyperglycemia should be managed with diet and exercise counseling. Changes in the medical therapy are allowed if the investigator feels it is necessary for the well-being of the subject. After 24 weeks, changes to the medical therapy for hyperglycemia should occur at the discretion of the investigator based on SMBG, FPG, and HbA1c information using local standards of care for subjects with T2DM. During the course of the study investigators will adjust other medications to affect changes in blood pressure and serum lipid values according to national or local guidelines. At every visit participants will be queried regarding adverse events and information on all events that potentially represent a MACE endpoint will be forwarded to a cardiovascular endpoint committee (CEC) for blinded adjudication. An investigator should also query the subject about symptoms that may be associated with possible DKA at every visit. A DKA adjudication committee will review and adjudicate all suspected DKA cases.

In this study, the incidence of MACE+ will be recorded for subsequent meta-analysis. MACE+ is defined as CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina. It is estimated that the required total of 134 patients with a MACE+ will accrue over a treatment period of 2 to 3 years. During the trial, a DSMB will review the unblinded data periodically and may recommend an early termination of the trial for safety reasons. No interim analysis will be performed for efficacy assessment and the study will not be stopped for futility or benefit of bexagliflozin treatment.

Measurement of bexagliflozin plasma concentration as a function of time (sparsely sampled) will also be conducted at 30 centers and will include approximately 240 study subjects as part of a bexagliflozin population PK study. Samples will be drawn at Weeks 6 or 12. Cardiovascular biomarkers will be measured at baseline before treatment is administered and after 12 weeks of treatment in an exploratory study to evaluate the effect of bexagliflozin treatment on biomarkers that are relevant in cardiovascular disease diagnosis and prognosis.

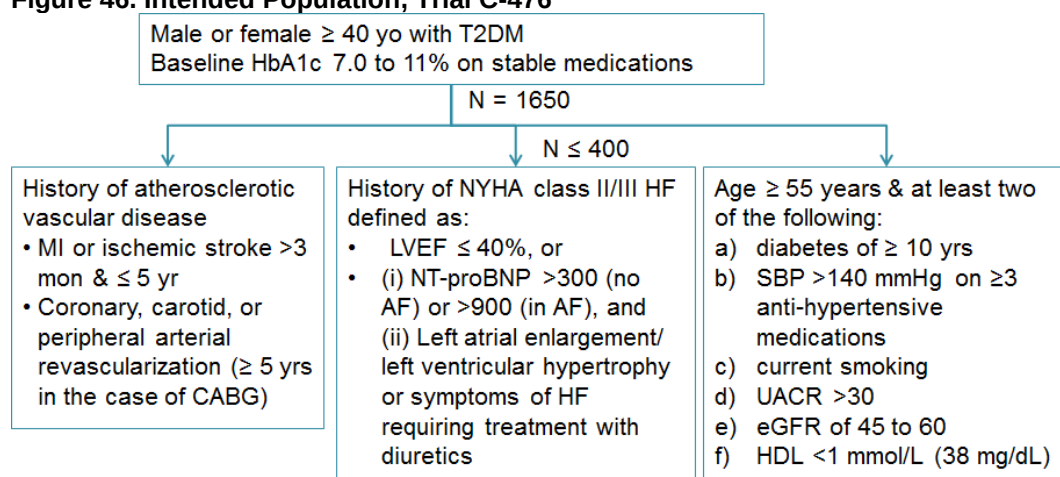
Study Population: The study population will consist of approximately 1650 subjects who have been diagnosed with suboptimally controlled T2DM and who exhibit an elevated risk of cardiovascular events. The study population will comprise:

- (1) Male or female adult subjects (age ≥ 40 years)
- (2) Subjects with a diagnosis of T2DM
- (3) Subjects with HbA1c values of 7.0 to 11%, inclusive
- (4) Subjects with FPG ≤ 300 mg/dL at screening
- (5) Subjects who have a regimen for treatment of T2DM that has been stable for the past 3 months. A stable regimen is defined as: no changes in dose or frequency of oral hypoglycemic agents or GLP-1 agonists, or $<20\%$ variability in total daily insulin dose.
- (6) Subjects with either established cardiovascular disease or with multiple cardiovascular risk factors (if no documented cardiovascular disease) having the following attributes:
 - a. **Group 1:** A history of atherosclerotic vascular disease as defined by one or more of the following: a) MI or ischemic (nonhemorrhagic) stroke >3 months but ≤ 5 years prior to screening or b) documented history of coronary, carotid, or peripheral arterial revascularization (coronary artery bypass grafting must have occurred ≥ 5 years prior to screening)
 - b. **Group 2:** A history of New York Heart Association (NYHA) class II or class III heart failure (Appendix 4) at the time of screening. A history of heart failure is defined as:
 - i. documented left ventricular ejection fraction (LVEF) $\leq 40\%$ and no subsequent LVEF $>40\%$ within 6 months of screening, or
 - ii. an N-terminal probrain natriuretic peptide (NT-proBNP) >300 pg/mL and no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP >900 pg/mL and evidence of AF at the time of the screening ECG and (ii) either (a) structural heart disease documented by report of left atrial enlargement or left ventricular hypertrophy, or (b) exhibiting symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening

- c. **Group 3:** Age ≥ 55 years with 2 or more of the following:
- diabetes duration of ≥ 10 years,
 - uncontrolled hypertension defined as SBP >140 mm Hg despite 3 or more antihypertensive medications,
 - current smoking,
 - UACR >30 mg/g,
 - eGFR of 45 to 60 mL/min/1.73 m², or
 - high-density lipoprotein <1 mmol/L (38 mg/dL)

To ensure that subjects with various cardiovascular risks are adequately represented, a minimum of 352 subjects (21%) from each of the three groups will be recruited and ≤ 400 subjects who have a history of heart failure will be randomized in the study. The intended population is presented in [Figure 46](#) below.

Figure 46. Intended Population, Trial C-476



Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass graft; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal probrain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UACR, urine albumin-to-creatinine ratio.

If a subject has a history of class II or III heart failure, the subject will be allocated to Group 2, regardless of any history of atherosclerotic vascular disease or cardiovascular risk factors. If a subject does not have a heart failure history and has a history of atherosclerotic vascular disease, the subject will be allocated to Group 1 regardless of having other cardiovascular risks.

Test Product, Dose, and Mode of Administration: Bexagliflozin tablets, 20 mg, or placebo administered orally once per day

Duration of Treatment: The study is an event-driven trial. The treatment period will end when the last randomized subject has completed at least 52 weeks of treatment and at least 134 subjects have experienced a MACE+.

Efficacy Assessments:

Primary efficacy endpoint:

- Change in HbA1c from baseline to Week 24, compared to placebo

Secondary efficacy endpoints:

- Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- Change in body weight from baseline to Week 48 in subjects with a BMI ≥ 25 kg/m²
- Change in SBP from baseline to Week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg

Exploratory efficacy endpoints:

- Change in HbA1c from baseline over time
- Change in FPG from baseline over time
- Change in body weight from baseline over time
- Change in SBP over time
- Requirement of additional antidiabetic medications, including insulin, over time
- Requirement of reduced antidiabetic medications, including insulin, over time
- Incidence of hospitalization for heart failure among all subjects and among subjects who have a history of heart failure

Other endpoints:

Samples for population PK analysis will be collected and the plasma concentration of bexagliflozin determined. The PK parameters will be assessed separately as part of the population PK analysis. Biomarker samples will be collected. The biomarker analysis will be performed separately.

Safety Assessments:

The safety endpoints will include:

- A 5-point composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or coronary revascularization
- A 6-point composite endpoint of CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, coronary revascularization, or hospitalization for heart failure
- Individual events including all-cause mortality, CV death, fatal and nonfatal MI, fatal and nonfatal stroke, hospitalization for unstable angina, hospitalization for coronary heart failure, or coronary revascularization. Both first events and total events, taking account of repeat events will be examined
- Change in eGFR from baseline
- Change in UACR from baseline
- Incidence of adverse events of interest. Adverse events of interest including urinary tract infections including urosepsis and pyelonephritis, genital mycotic infections, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders, renal failure events, and amputations

Other safety assessments:

- Adverse events
- Clinical laboratory events
- Physical examinations

- Vital signs including orthostatic blood pressure
- Use of concomitant medications

Statistical Methods: The primary endpoint is the difference in the change in HbA1c from Week 0 (randomization visit) to Week 24 among subjects exposed to bexagliflozin, 20 mg, compared to subjects exposed to placebo. Statistical significance will be declared at a two-sided 0.05 level of significance. The ITT population that includes all randomized subjects regardless of treatment adherence or availability of follow-up data will be analyzed. An MMRM ANCOVA with baseline HbA1c as a covariate will be performed on the available data, incorporating all visits from each patient at which HbA1c was measured.

Three key secondary endpoints are:

- (1) Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes
- (2) Change in body weight from baseline to Week 48 in subjects with a BMI ≥ 25 kg/m²
- (3) Change in SBP from baseline to Week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg

A hierarchical testing strategy in the following order will be undertaken, if the null hypothesis is excluded for the primary efficacy endpoint:

- (1) Effect of bexagliflozin on the change in HbA1c from baseline to Week 24 in subjects who have been prescribed insulin to control diabetes at baseline, using MMRM ANCOVA adjusting for baseline HbA1c at a two-sided 0.05 level of significance; if a significant bexagliflozin effect is found, then:
- (2) Comparison of treatments on the change in body weight at Week 48 in subjects with baseline BMI ≥ 25 kg/m², using MMRM ANCOVA adjusting for baseline body weight. at a two-sided 0.05 level of significance; if a significant bexagliflozin effect is found, then:
- (3) Comparison of treatments on the change in SBP at Week 24 in subjects with baseline systolic blood pressure ≥ 140 mm Hg, using MMRM ANCOVA, adjusting for baseline SBP, at a two-sided 0.05 level of significance.

Additional effects of bexagliflozin on FPG, changes in HbA1c over time, changes in body weight over time, frequency of hospitalization for heart failure (in all subjects and in subjects with a history of heart failure), and general safety of bexagliflozin in subjects with T2DM will be analyzed as exploratory endpoint and will not be adjusted for multiplicity.

The sample size of 1650 patients is estimated based on the required number of events of MACE+ for the program-wide meta-analysis to assess bexagliflozin effect on cardiovascular safety and provides adequate power to compare treatments on the primary endpoint of change in HbA1c from baseline to 24 weeks.

Statistical analyses and summaries will be performed using SAS software (SAS Institute, Cary, NC).

Date of Revised Protocol Version 8.0: October 28, 2016

Table 133. Protocol History, Trial C-476

Protocol History	Date
Version 1.0:	May 06, 2015
Version 2.0:	June 22, 2015
Version 3.0:	July 07, 2015
Version 4.0:	August 25, 2015
Version 5.0:	September 08, 2015
Version 5.1 (Canada only)	October 26, 2015
Version 6.0:	February 02, 2016
Version 7.0:	October 12, 2016
Version 8.0:	October 28, 2016

FDA Reviewer Comment: *This trial was designed to assess the safety and effectiveness of bexagliflozin for improved glycemic control in subjects with increased risk for MACE as identified by the following three groups: 1) subjects with documented atherosclerotic CV disease, 2) subjects with congestive heart failure, or 3) subjects exhibiting multiple CV risks for atherosclerotic vascular disease. In addition, this trial was designed to accrue MACE events for the planned MACE meta-analysis.*

The protocol for this study was submitted to the Agency and feedback on the study design and analysis plan was issued on July 30, 2015, and January 8, 2016 (see communications under IND 103822 in DARRTS). The Applicant appears to have incorporated FDA feedback into their study protocol and analysis plan. Protocol Version 5, dated September 8, 2015, was the first version under which subjects were consented. The protocol was amended to implement the following changes:

- *Protocol Version 6, dated February 2, 2016, implemented DKA surveillance and documentation procedures as a result of FDA communications regarding rare but potentially serious ketoacidosis events occurring in the setting of SGLT2 inhibitor treatment.*
- *Protocol Version 7, dated October 12, 2016, contained several changes to enrollment criteria and study design (discussed further in the next bullet point). However, no subjects were consented under this protocol version as additional revisions were needed to communicate emerging findings related to potential increased risk of SGLT2 inhibitor treatment with lower limb amputation.*
- *Protocol Version 8, dated October 28, 2016, was the final version for the study. It contained the following modifications from Version 6:*
 - *Based on preliminary data indicating that approximately half of the subjects enrolled in the study were prescribed insulin at baseline, the Applicant proposed to analyze the effects of bexagliflozin on HbA1c and other endpoints in the corresponding subpopulations instead of conducting dedicated clinical studies evaluating cohorts recruited for these characteristics. This proposal was submitted to FDA. The Division issued feedback on September 21, 2016, noting that this approach is reasonable provided that the design and conduct of the glycemic efficacy portion of the trial is consistent with what would be expected if the trial was conducted as a separate study. The protocol was amended to include these analyses in the subpopulations.*

- *As over 50% of the consented subjects exhibited HbA1c values lower than the threshold of $\geq 7.5\%$ at screening, the HbA1c inclusion criterion was widened to be between 7.0% and 11%. The eligibility criteria were similarly relaxed to allow entry of subjects with fasting plasma glucose concentrations ≤ 300 mg/dL as opposed to ≤ 250 mg/dL. The Division issued feedback on September 21, 2016, stating that this protocol update was acceptable.*
- *The initial study design anticipated that approximately 25% of the participants would exhibit heart failure with reduced LVEF ($< 40\%$). The recruitment of subjects with existing NYHA class II or III heart failure who had an LVEF $< 40\%$ was substantially slower than the recruitment of subjects without these characteristics.*
 - *Group 2 Criteria (Version 6): A history of NYHA class II or III HF with a LVEF $\leq 40\%$ and no subsequent LVEF $> 40\%$ documented within 6 months of screening.*
 - *Group 2 Criteria (Version 7 and 8): A history of heart failure is defined as:*
 - *documented LVEF $\leq 40\%$ and no subsequent LVEF $> 40\%$ within 6 months of screening, or*
 - *an NT-proBNP > 300 pg/mL and no evidence of atrial fibrillation/flutter (AF) at the time of the screening ECG or an NT-proBNP > 900 pg/mL and evidence of AF at the time of the screening ECG and (ii) either (a) structural heart disease documented by report of left atrial enlargement or left ventricular hypertrophy, or (b) exhibiting symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening.*

The Division issued feedback on September 21, 2016, stating that this protocol update was acceptable as the assessment of heart failure is an exploratory endpoint.

- *Due to emerging data on the potential association with SGLT2 inhibitor treatment and increased risk of lower limb amputation, additional processes for identifying amputation and revascularization procedures were added to the protocol.*

The number of subjects who consented to each protocol version are as follows:

- *Version 5: 348 subjects*
- *Version 6: 567 subjects*
- *Version 8: 765 subjects*

Eighty-two percent of total study follow-up time occurred under a consent or reconsent to protocol Version 8.

Overall, the protocol and subsequent amendments incorporated key FDA recommendations, and changes to the protocol were generally agreed upon by FDA.

NDA 214373
Brenzavvy (bexagliflozin)

Regarding study conduct, each center was visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP guidelines, and applicable laws and regulations. This included inspections of the CRFs for completeness and clarity, verification with source documents, and clarification of administrative matters. Fourteen investigational sites, located in Canada, Czech Republic, Republic of Korea, Mexico, the Netherlands, Poland, Russian Federation, Taiwan, and the United States were audited during the trial. One critical finding regarding missing documentation was observed at a site located in Russia enrolling a small number of subjects (11 randomized subjects). This finding is unlikely to impact study results. Audit certificates were submitted with the NDA. Protocol deviations were identified and documented, and a list of all protocol deviations was provided. Review of the major protocol deviations did not reveal any obvious trends or treatment differences across treatment groups.

Overall, the trial appears appropriately designed and conducted to meaningfully inform glycemic efficacy in the studied subject population.

15.1.6. Clinical Protocol Synopsis for C-480 (Version 3.0, Date: October 27, 2016)

Sponsor: TheracosBio, LLC

Name of Finished Product: Bexagliflozin Tablets

Name of Active Ingredient: Bexagliflozin

Study Title: A Phase 3, Randomized, Double-Blind, Active-Controlled Study to Evaluate the Effects of Bexagliflozin versus Glimepiride in Subjects with Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control by Metformin

Study Number: THR-1442-C-480

Study Phase: 3

Primary Objective: The primary efficacy objective is to demonstrate that bexagliflozin is noninferior to glimepiride by evaluating the treatment effect on HbA1c reduction at Week 60 in subjects whose T2DM is inadequately controlled by metformin.

Secondary Objectives: The key secondary objectives are:

- To evaluate the treatment effect of bexagliflozin versus glimepiride on the change in body weight in subjects with baseline BMI ≥ 25 kg/m² at Week 60
- To evaluate the treatment effect of bexagliflozin versus glimepiride on the change in SBP in subjects with baseline SBP ≥ 140 mm Hg at Week 60
- To evaluate the treatment effect of bexagliflozin versus glimepiride on the difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks
- To evaluate if bexagliflozin is superior to glimepiride on HbA1c reduction at Week 60

Exploratory Objectives:

- To assess the treatment effect of bexagliflozin versus glimepiride on the change in the proportion of subjects achieving HbA1c $< 7.0\%$ over time

- To assess the treatment effect of bexagliflozin versus glimepiride on the change in HbA1c over time
- To evaluate the treatment effect of bexagliflozin versus glimepiride on the change in FPG over time
- To assess the treatment effect of bexagliflozin versus glimepiride on the change in SBP over time
- To assess the treatment effect of bexagliflozin versus glimepiride on the change in body weight over time
- To assess the treatment effect of bexagliflozin versus glimepiride on the difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time

Safety Objectives:

- To compare the effects of bexagliflozin versus glimepiride on the incidence of adverse events of interest. Adverse events of interest are urinary tract infections including urosepsis and pyelonephritis, genital mycotic infections, diuretic effects including hypovolemia, hypotension episodes, hypoglycemia, hepatotoxicity, MACE, falls and fractures, malignancies, hypersensitivity reactions, acid-base disorders including diabetic ketoacidosis, and renal failure events.
- To compare the effects of bexagliflozin versus glimepiride on general safety assessments including treatment emergent adverse events, clinical laboratory events, 12-lead ECG) parameters, physical examinations, vital signs including orthostatic blood pressure, and use of concomitant medications

Other Objectives:

- To compare the effects of bexagliflozin versus glimepiride on health-related quality of life using a validated instrument EQ-5D-3L.

Study Design: C-480 is a phase 3, multicenter, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of bexagliflozin versus glimepiride in subjects with T2DM is inadequately controlled by metformin. A total of 420 subjects are planned to be randomized in a ratio of 1:1 to receive once daily treatment of active bexagliflozin with placebo glimepiride (Group 1) or placebo bexagliflozin with active glimepiride (Group 2) for 96 weeks in an outpatient setting. Active treatment in Group 1 will be bexagliflozin tablets, 20 mg. Active treatment in Group 2 will be glimepiride capsules, 2, 4, or 6 mg. At the time of screening, subjects will be taking metformin only (metformin-only) or metformin in addition to no more than one additional oral hypoglycemic agent (metformin-and-OHA). Study subjects will continue receiving open-labeled metformin background medication during the entire study.

The main eligibility criteria include 1) male or female subjects with T2DM and 2) screening HbA1c between 7.0% and 10.5% (inclusive) for subjects who are metformin-only treated, or screening HbA1c between 6.5% and 10.0% (inclusive) for subjects who are metformin-and-OHA treated. All eligible subjects must have taken metformin at a stable dose of ≥ 1500 mg/day for at least 8 weeks prior to screening. Subjects who are metformin-and-OHA treated must be willing to undergo a 6-week wash-out of the non-metformin OHA prior to the start of a 2-week run-in period. During the wash-out, subjects will discontinue non-metformin OHA and continue taking metformin at the dose and frequency taken at screening.

All eligible subjects who are metformin-only treated or have completed the 6-week wash-out period will start a 2-week single-blind run-in period. During the run-in, subjects will receive placebo bexagliflozin and placebo glimepiride. Subjects who meet all inclusion criteria and no exclusion criteria prior to randomization will be eligible for randomization and receive investigational products.

During the treatment period, glimepiride will be provided in three dose levels: 2 mg, 4 mg, and 6 mg. Placebo glimepiride will also be provided in three dose levels: placebo for 2 mg, placebo for 4 mg, and placebo for 6 mg. Subjects will receive the starting dose of glimepiride, 2 mg or placebo. Subjects who meet protocol-specified glycemic criteria will undergo up-titration of the glimepiride dose at Weeks 2, 4, and 6. The dose will be increased to the next dosing level if during the preceding 2 weeks: (1) $\geq 50\%$ of fasting SMBG measurements >110 mg/dL and (2) no severe or documented symptomatic hypoglycemia events. Subjects assigned to receive placebo glimepiride, will receive mock titrations of glimepiride at Weeks 2, 4, and 6 based on the same glycemic criteria. No dose changes of glimepiride will occur after 6 weeks of treatment.

Each subject will be instructed to return to the clinic at Weeks 0, 2, 4, 6, 12, 24, 36, 48, 60, 72, 84 (off-site phone visit), and 96 for efficacy assessment and safety monitoring. Subjects will return to the clinic for a follow-up exit visit at Week 98 or 2 weeks after last dose of study drug if subjects early terminate prior to Week 96.

During the study, a DSMB will review the unblinded data periodically and may recommend early termination of the trial for safety reasons. In the event of administrative changes or other related reasons, the Sponsor reserves the rights to terminate the study early. There will be no interim analysis; final statistical analysis will be performed after all subjects complete the study.

Study Population and Main Eligibility Criteria: A total of 420 eligible subjects are planned for this study. The study population will comprise:

- (1) Male or female adult subjects ≥ 18 years of age
- (2) If subjects are female of childbearing potential, subjects must be negative on the urine pregnancy test and agree to abstain from coitus or use contraception during the entire study to avoid any possible pregnancy
- (3) Subjects who are in one of the two categories:
 - a. Metformin-only treated: receive ≥ 1500 mg/day metformin only for at least 8 weeks prior to screening or
 - b. Metformin-and-OHA treated: receive ≥ 1500 mg/day metformin for at least 8 weeks prior to screening and ≥ 14 days of 1 additional OHA in the 8 weeks prior to screening.
- (4) Subjects with a diagnosis of T2DM with HbA1c levels between 7.0% and 10.5% (inclusive) at screening if metformin-only treated or with HbA1c levels between 6.5% and 10.0% (inclusive) at screening if metformin- and-OHA treated
- (5) Subjects with a BMI ≤ 45 kg/m² at screening
- (6) If applicable, taking stable doses of treatment for dyslipidemia and/or hypertension for 30 days prior to screening. Subjects do not need to be treated for dyslipidemia or hypertension to be eligible for the study
- (7) Subjects who are willing and able to return for all clinic visits and to complete all study-required procedures, including SMBG measurements

Prior to randomization, all subjects must:

- (8) Maintain adequate glycemic control during the washout and run-in periods (fasting plasma glucose values are not ≥ 250 mg/dL on consecutive days)
- (9) Have an HbA1c between 7.0% and 10.5% (inclusive) at Visit V5
- (10) Adhere to the investigational product administration requirements as evidenced by missing no more than two placebo run-in medication doses of any kind

Test Products, Dose, and Mode of Administration:

Once daily oral administration of bexagliflozin and glimepiride

- Group 1: bexagliflozin tablets, 20 mg, and glimepiride capsules, placebo
- Group 2: bexagliflozin tablets, placebo, and glimepiride capsules, 2 mg, 4 mg, or 6 mg

Duration of Treatment: Eligible subjects will receive a total treatment duration of 98 weeks including 2 weeks of run-in medications and 96 weeks of investigational products.

Efficacy Assessments:

Primary efficacy assessment:

- Change in HbA1c from baseline at Week 60

Secondary efficacy assessments:

- Change in body weight in subjects with baseline BMI ≥ 25 kg/m² at Week 60
- Change in SBP in subjects with baseline SBP ≥ 140 mm Hg from baseline at Week 60
- Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks
- Change in HbA1c from baseline at Week 60

Other efficacy endpoints:

- Change in proportion of subjects achieving HbA1c $< 7.0\%$ over time
- Change in body weight over time
- Change in FPG over time
- Change in SBP over time
- Change in HbA1c over time
- Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time

Safety endpoints:

- Adverse events, including adverse events of special interest (genital and urinary tract infections, diuretic effects, hepatotoxicity, MACE, hypoglycemia, fractures, malignancy, hypersensitivity reactions, hypotensive episodes, acid-base disorders, and renal failure events)
- Laboratory testing, including hematology, serum chemistry, and urinalysis
- Physical examination
- 12-lead ECG
- Vital signs
- Concomitant medication use

Other assessments:

- Health-related quality of life instrument EQ-5D-3L

Statistical Methods: The primary hypothesis is that bexagliflozin is noninferior to glimepiride by evaluating the treatment effect on HbA1c reduction at Week 60 in combination with metformin. The noninferiority margin for mean change from baseline at Week 60 in HbA1c comparing bexagliflozin group with glimepiride group will be 0.35%. Superiority will be declared without additional statistical testing when the upper bound of the 95% CI for difference in change from baseline at Week 60 in HbA1c comparing bexagliflozin group with glimepiride group is less than 0. The treatment difference will be examined by using an MMRM ANCOVA. The model will include treatment, visit, treatment-by-visit interaction, and randomization stratification factors as the fixed effects terms and the baseline HbA1c value as a fixed effect covariate. Least squares mean treatment differences between the bexagliflozin group and the comparator group at Week 60 in change from baseline will be estimated from the model. An unstructured covariance will be used to model the within-subject correlation. If the model with the unstructured covariance structure does not converge, an autoregressive (1) covariance structure will be used. HbA1c values obtained after the start of rescue medication will not be excluded from this primary analysis. Primary endpoint will be analyzed on both ITT and PP analysis sets.

The MMRM model is one approach to obtain treatment effect estimates in the presence of missing data. As sensitivity analyses for missing data, the following will be performed on both ITT and PP analysis sets:

- (1) Missing data will be imputed via multiple imputations, following which the MMRM will be repeated on the complete datasets with results combined across complete datasets using standard multiple imputation techniques; HbA1c values collected after the start of rescue medication will not be excluded.
- (2) Missing data will be imputed via LOCF, following which the MMRM will be repeated; HbA1c values collected after the start of rescue medication will be considered missing.
- (3) HbA1c values collected after the start of rescue medication will be considered missing, and the MMRM analyses will be reperformed.

The effects of bexagliflozin on the changes from baseline at Week 60 in body weight and systolic blood pressure, the difference in the proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks and the change in HbA1c from baseline at Week 60 will be tested as key secondary endpoints and will be analyzed in a hierarchical testing strategy and only if the primary objective is met. Similar to the primary endpoint, ANCOVA models will be used for the continuous secondary endpoints and logistic regression model will be used for the binary endpoint. A hierarchical testing strategy will be followed to preserve experiment-wide alpha at 0.05:

- (1) Superiority test of the change in body weight in subjects with baseline BMI ≥ 25 kg/m² in the bexagliflozin group versus the glimepiride group at Week 60
- (2) Superiority test of the change in SBP in subjects with baseline SBP ≥ 140 mm Hg in the bexagliflozin group versus the glimepiride group at Week 60
- (3) Superiority test of the difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia event in the bexagliflozin group versus the glimepiride group over 96 weeks

Additional effects of bexagliflozin versus glimepiride on the changes in HbA1c, FPG, SBP, body weight, the proportion of subjects who reach an HbA1c <7%, and the proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over time, as well as the general safety in subjects with T2DM, will be analyzed as exploratory efficacy endpoints. These endpoints are considered exploratory and will not be adjusted for multiplicity.

For the primary efficacy endpoint, a minimum of 172 subjects are needed in each treatment arm to detect noninferiority of bexagliflozin to glimepiride with respect to the change in HbA1c from baseline at Week 60 by a margin of 0.35%, assuming an estimated pooled standard deviation of 1.0%. This estimation is based on a one-sided t-test with 90% power at a 0.025 level of significance. To allow for an estimated 18.0% dropout rate, 210 patients will be randomized in each treatment arm, and the total sample size will be 420 subjects for this study.

Statistical analyses and summaries will be performed using SAS software (SAS Institute, Cary, NC).

FDA Reviewer Comment: *This trial aimed to demonstrate that bexagliflozin is noninferior to the sulfonylurea glimepiride as add-on therapy in subjects with T2DM not adequately controlled by metformin treatment. Sulfonylureas may be prescribed with metformin as a combination therapy for treating T2DM. As such, clinical programs for other SGLT2 inhibitors have evaluated noninferiority of the candidate drug to glimepiride. Glimepiride is an appropriate comparator for the evaluation of noninferiority of bexagliflozin to another oral agent prescribed for the treatment of T2DM.*

The trial enrolled subjects with T2DM taking stable doses of metformin monotherapy, or subjects taking metformin and one other antihyperglycemic agent willing to undergo a 6-week washout period. The trial also included a two-week run-in period, such that subjects requiring washout were on metformin monotherapy for a minimum of 8 weeks prior to randomization. In addition, randomization was stratified by background treatment status (metformin only versus metformin plus an additional oral agent), HbA1c ($\leq 8.5\%$ versus $> 8.5\%$), and eGFR (≥ 90 mL/min/1.73 m² versus < 90 mL/min/1.73 m²). These procedures appear reasonable to mitigate the possibility that oral antihyperglycemic agents other than metformin taken prior to study enrollment impacted study outcomes.

Sulfonylureas are known to increase the risk of hypoglycemia. To control hyperglycemia and minimize hypoglycemia, subjects were initiated on glimepiride (or placebo glimepiride) at 2 mg and underwent dose up-titration based on protocol-specified criteria during the first 6 weeks of the study. Although the maximum approved dose in the US is 8 mg, titration of glimepiride only occurred up to 6 mg, potentially due to differences among countries in maximum approved doses in this global trial. The procedures for glimepiride titration in this trial appear generally reasonable. Similar to active controlled Trial C-423, the NI margin was larger than what has been used in other SGLT2 inhibitor development programs (i.e., 0.35% as opposed to 0.3%). At the IND stage, FDA reviewed agreed with the margin selection and accepted the Applicant's justification for the proposed margin.

Minor changes occurred from Protocol Version 1 to Version 3, including the addition of amputation and revascularization procedures as AESIs. Protocol deviations were captured during clinical monitoring visits and recorded in the CRF. Review of the above major protocol deviations did not reveal any obvious/important trends or treatment differences across treatment groups.

16. Efficacy: Additional Information and Assessment

16.1. Bexagliflozin for T2DM Clinical Program

The Applicant, Theracos, submitted eight efficacy studies for supporting the efficacy of bexagliflozin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The bexagliflozin clinical program was designed in accordance with the recommendations set forth in FDA's draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (March 2008). The guidance states, "Efficacy and safety of new products for the treatment of type 2 diabetes can be evaluated in placebo-controlled monotherapy trials, placebo-controlled add-on therapy trials, and active-controlled trials."

Based on consultation with the medical team, the statistical efficacy review will be focused on the six phase 3 HbA1c studies: Trial C-450, a placebo-controlled monotherapy study in T2DM patients who are treatment-naïve or previously treated with one OHA; Trial C-419, a placebo-controlled add-on to metformin study in T2DM patients who are not adequately controlled by metformin alone; Trials C-423 and C-480, two active-controlled add-on to metformin studies in T2DM patients who have inadequate glycemic control by metformin with sitagliptin (C-423) or glimepiride (C-480) as an active control; Trial C-448, a placebo-controlled study in T2DM patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73 m²); and Trial C-476, a placebo-controlled study in T2DM patients with increased risk of cardiovascular adverse events.

Based on consultation with the medical team, results from Trials C-450 and C-419 serve as the key basis of the benefit evaluation.

16.2. Trial Design Overview

See Trial Design Overview in Section [6.2.1](#).

16.3. Statistical Analysis Plan Overview

16.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint in all the six studies was change from baseline in HbA1c. Except for the glimepiride-controlled study, which used a 60-week endpoint, the primary endpoint was evaluated at 24 weeks. The primary endpoint point selection was also in accordance with the above-mentioned FDA 2008 Draft Guidance. The draft guidance states "For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control"(March 2008).

16.3.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints (mainly, change from baseline in weight, FPG, and SBP) varied little across the six trials. However, in each trial the endpoints were ranked in different orders (see [Table 136](#)), as each order was reflected in the corresponding study specific prespecified sequential testing procedures for multiplicity control. The study designs were similar, but the study populations varied across trials; neither the individual study protocols nor the NDA Clinical Overview offers reasons why the secondary endpoints should differ across trials and be prioritized in different orders. Hence, in this review, the same set of secondary efficacy endpoints were evaluated across trials when data were available.

Of note, in C-419, no formal hypothesis testing was planned for the secondary efficacy endpoints.

In addition, the Applicant's statistical analysis plan (SAP) prespecified that efficacy in terms of weight and SBP were to be evaluated in subgroups of subjects:

- In all six studies, efficacy on change from baseline in weight was to be evaluated in the subgroup of subjects with baseline BMI ≥ 25 kg/m²
- In C-448, efficacy on change from baseline in SBP was to be evaluated in the subgroup of subjects with baseline SBP ≥ 130 mm Hg; and, in Trials C-476 and C-480, in the subgroup of subjects with baseline SBP ≥ 140 mm Hg.

Of note, in C-476, the Applicant added HbA1c changes from baseline to Week 24 in subjects who have been prescribed sulfonylurea as an exploratory endpoint in the late stage of the trial, one day before the database lock (see [Section 12](#)). The Applicant proposed to include the results for this exploratory endpoint in labeling.

16.3.2.1. Labeling Considerations on the Key Secondary Efficacy Endpoints

From an individual study perspective, at the judgement of the review team, when the results for a specific key secondary endpoint are statistically significant based on the prespecified sequential testing procedure and also deemed clinically meaningful, these data could be included in the labeling Clinical Studies section as it could be used to support distinct claims of effectiveness.

Since multiple studies are included in the bexagliflozin for T2DM development program, some key secondary endpoints did not meet the criteria for statistical significance in all studies. In such cases, the review team should determine whether the totality of evidence supports inclusion of the endpoint in labeling. For body weight and SBP endpoints that were prespecified in the subset, the results should be indicated clearly with the number of subjects used in the analysis and described in the text instead of a table format in the Clinical Studies section of the labeling.

16.3.2.2. Other Secondary Efficacy Endpoint: Proportion of Subject Reaching HbA1c <7% at Week 24/60

The primary efficacy endpoint of change from baseline in HbA1c (%) was established by rigorous statistical methods. However, the binary measure of HbA1c (%) levels, *proportion of subjects reaching <7%*, is an important endpoint for understanding the treatment effects in

HbA1c (%) and a measure useful to prescribers and patients. Since the binary version HbA1c endpoint was not included in any of study-specific sequential multiplicity testing procedures for multiplicity protection, a descriptive statistic, the responder proportional information, was considered for inclusion in the labeling. The statistical reviewer has also verified the Applicant's analysis results for this endpoint.

16.3.3. Analysis Set

The screened analysis set included all subjects screened for eligibility prior to randomization. The screened population will include screen failures. This population was used for subject listings and for summaries of subject disposition.

All subjects who were randomized and had taken at least one dose of double-blind study medication were included in the safety analysis set. Safety analyses were based on the first medication kit that was dispensed to a subject. The safety analysis set is the primary analysis set for safety evaluation.

All subjects who were randomized were included in the ITT analysis set. All analyses of the ITT analysis set were based on the randomization schedule. The ITT analysis set was preplanned to serve as the primary set for the efficacy analyses.

16.3.4. Analysis Method

16.3.4.1. Primary Analysis Method – Regulatory Interaction History

During the IND stage, the Applicant first proposed an LOCF analysis, and then an MMRM method for the primary analysis of the primary or secondary endpoints with missing data. We advised against the LOCF first, and then advised that the MMRM approach likely does not appropriately address missing data, as it treats the behavior of missing data for those subjects who are off-treatment to be the same as that of observed data for those subjects who are on-treatment in the same treatment group. We clarified that the preferred estimand is the treatment policy (de facto) estimand. To estimate the treatment policy estimand, efficacy data should be collected and utilized in analyses on all randomized treated subjects regardless of treatment adherence, rescue status, or other post baseline status (e.g., post bariatric surgery status). Missing data should be imputed in a fashion consistent with what the measurement would have been, had it been measured.

Disagreeing with the proposed MMRM approach in the Applicant's preNDA meeting package (meeting date December 5, 2019), we recommended that where there are a sufficient number of retrieved dropouts (subjects who discontinued treatment before the final assessment window but still had an efficacy measurement in the final assessment window), we prefer a multiple imputation approach that models the missing final assessment of nonretrieved dropouts (subjects who discontinued treatment before the final assessment window and did not have a measurement in this assessment window) based on known measurements from the retrieved dropouts. We suggested that, for the nonretrieved dropouts, the Sponsor should multiply impute the change from the last measurement before treatment discontinuation to the final assessment, using this

information from the retrieved dropouts. Where there are not enough retrieved dropouts to do a retrieved dropout analysis, we recommended a return-to-baseline analysis. In this analysis a subject's final assessment is multiply imputed based on the subject's baseline value. Variance for the multiple imputation can be based on residual variance from an ANCOVA model, using the nonmissing final assessments as the response variable. Henceforth, we refer to this approach as the return-to-baseline coupled ANCOVA.

In the Applicant's final SAP, the primary efficacy endpoint was to be tested based on the ITT analysis set using all observed data and the MMRM approach. The MMRM model included terms for stratification factors as a fixed effect covariate. HbA1c values obtained after the start of rescue medication were not excluded from the analysis.

Table 134. Pivotal Study Milestones

Trial	First Subject Enrolled	Last Subject Completed	Report Date
C-450	March 29, 2016	April 28, 2017	April 05, 2018
C-419	November 28, 2017	January 23, 2019	August 29, 2019
C-423	October 12, 2017	October 31, 2018	March 26, 2019
C-480	August 15, 2016	June 19, 2019	January 06, 2021
C-448	September 23, 2016	January 11, 2018	September 10, 2018
C-476	November 05, 2015	November 06, 2019*	March 24, 2021

Source: FDA statistical reviewer, summarized from the title page of the pivotal clinical study reports.

*Database lock date was November 22, 2019, according to discussion of Question 9 in the PreNDA meeting.

The Applicant's pivotal trials were all completed and unblinded (see Section [6.2.1](#) for C-476: database locked on November 22, 2019, treatment unblinding date unknown) at the time of the preNDA meeting (Meeting Date: December 05, 2019). Aside from C-476, all clinical study reports (CSRs) had been finalized before we provided our specific recommendation of the retrieved drop-out approach or return-to-baseline approach. Accepting our advice, since there were not enough retrieved dropouts to do a retrieved dropout analysis, the Applicant incorporated the return-to-baseline coupled ANCOVA method into a revised Integrated Summary of Effectiveness (ISE) SAP and submitted the document under NDA 214373 Supporting Document Number (SDN) 1 submission.

In the Applicant's initial NDA submission (SDN 1), the return-to-baseline coupled ANCOVA analysis method was only applied to the primary endpoint and the corresponding results were included in the ISE. This analysis was not carried out for any of the key secondary endpoints or the preplanned subgroup analyses of the primary endpoint. FDA requested these analyses via information requests during the NDA review. These results have been validated and are presented in this review.

A more detailed summary of the IND phase statistical interactions between FDA and Theracos can be located in Section [12 Table 54](#).

16.3.4.2. Primary Analysis Method – A Return-to-Baseline Coupled ANCOVA

As lack of enough retrieved dropouts rendered the pattern mixture multiple imputation approach analysis not feasible, we used the three-step return-to-baseline coupled ANCOVA in this NDA review.

Missing Data Handling Approach

Across the six pivotal studies, there were not enough retrieved dropouts to do a retrieved dropout analysis. The Applicant's return-to-baseline multiple imputation method is based on the baseline data of an endpoint for the subject, with variance adjustment for the baseline data estimated from an ANCOVA model of nonmissing Week 24 (Week 60 for Trial C-480) HbA1c for the treatment arms. The ANCOVA model will include the same variables. The variance, σ^2 , for the Week 24 (Week 60 for Trial C-480) data for each treatment arm will be used as the variance in an imputation model $X_{\text{Week 24 or 60}} \sim N(X_{\text{baseline}}, \sigma^2)$ to impute the missing Week 24 (Week 60 for Trial C-480) data.

FDA Reviewer Comment: The predictor/covariate variables used in the imputation variance estimation ANCOVA model were the same treatment and stratification factors and the corresponding baseline variable as prespecified in the MMRM model (shown in [Table 135](#)).

Table 135. ANCOVA Model Covariates in Return-to-Baseline Variance Estimation by Study

Trial Number	Predictor/Covariate Variables
C-419	Treatment, baseline HbA1c value and country (United States or Japan)
C-423	Treatment, baseline HbA1c value and region
C-448	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
C-450	Treatment, country, background anti-diabetes treatment status (treatment naïve or not), and baseline HbA1c value
C-476	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
C-480	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

Source: Applicant's ISE Version 1, NDA 214373, SDN 1.

Abbreviations: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; OHA, oral hypoglycemic agent

ANCOVA Model Analysis

Then, for continuous endpoints, for each iteration of the multiply imputed full dataset, the primary and secondary endpoints were analyzed using an ANCOVA model with treatment and stratification factors as fixed effects and the corresponding baseline value as a covariate. Based on this model, the least squares (LS) mean differences between bexagliflozin 20 mg and control, and the associated two-sided 95% CIs were estimated.

For the categorical secondary efficacy endpoint (proportion of subjects reaching HbA1c <7.0%), the imputation results from the corresponding HbA1c (%) values were used to derive the responder status. For descriptive analysis, the Applicant chose to present the crude by arm proportion of subjects reaching HbA1c <7.0%. We also carried out a logistic model analysis with treatment and stratification factors as fixed effects and baseline HbA1c as a covariate to estimate the by arm responder rates.

Rubin's Rule to Combine the Results

Lastly, Rubin's rule was applied to combine the analysis results from the multiply imputed datasets for both the continuous endpoints and the binary HbA1c responder proportion endpoint.

16.3.4.3. Primary Endpoint – Subgroup Analysis Methods

16.3.4.3.1. Sample Estimates of Subgroup Treatment Effects

Following the primary analysis method change that was finalized during our NDA review, the analysis method for the SAP preplanned subgroup analyses of the primary endpoint was also updated. For each subgrouping factor level, an LS mean difference versus placebo at Week 24/60 was assessed using the same return-to-baseline coupled ANCOVA model as described for the primary endpoint. When carrying out subgroup analyses, the corresponding subgroup factor was removed from the primary analysis model. Forest plots were used to display subgroup level LS mean differences together with the associated 95% CI.

When a subgroup analysis interaction test was necessary, we took a three-step approach in deriving the interaction test p-value. First, for each imputation, the difference (double-delta) between the two subgroup-level placebo-adjusted treatment effects was derived by running a full analysis model including the interaction term; second, we used Rubin's Rule to summarize the double-deltas across iterations; lastly, we output the t-test p-value associated with the iteration mean double-delta as the treatment by subgroup interaction test p-value.

16.3.4.3.2. "Shrinkage" Estimates of Subgroup Treatment Effects

There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater the ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior to derive shrinkage estimates for all subgroups. The

Bayesian hierarchical model assumptions for change in HbA1c (%) from baseline at Week 24/60 are:

For $i=1, 2, \dots$ Y_i represents the observed sample estimate of treatment effect in a subgroup level i , assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 9)$, $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$

A flat prior with mean 0 and variance of 9 was chosen. The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups, are presented in Forest plots respectively. Some of the sample subgroup analyses are indicative of certain subgroups having no treatment benefit. However, after shrinkage, the subgroup treatment effects are, in general, consistent across subgroups and with the overall treatment effect.

16.3.4.4. Exploration of Potential Modulation Effect of Baseline HbA1c Levels

To investigate the potential modulation effect of baseline HbA1c levels, aside from the Applicant's preplanned subgroup analysis on the dichotomized baseline HbA1c levels ($\leq 8.5\%$, or $> 8.5\%$), an additional "subgroup" analysis was carried out for the four placebo-controlled studies by treating baseline HbA1c as a continuous variable. For each of the four studies, a simple linear regression model based on the completers data was used for this exploratory analysis. The response variable was still change from baseline in HbA1c at Week 24, the predictor variables include treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction. The size and significance level of the interaction term (difference in by-arm baseline HbA1c slopes) from this model fitting is an indicator of the potential modulation effect.

16.3.4.5. Primary Endpoint – Tipping Point Sensitivity Analysis Method

16.3.4.5.1. Placebo-Controlled Studies

To conduct analyses that systematically and comprehensively explore the space of plausible missing data assumptions, at the IND stage, we recommended the inclusion of tipping point analyses that vary assumptions about the missing outcomes on the two treatment arms. The tipping point analyses should target the de facto estimand and therefore include all observed data regardless of treatment adherence. The analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on bexagliflozin have worse outcomes than dropouts on control. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect.

The Applicant's preplanned tipping point sensitivity analysis method consists of three steps:

- (1) Nonmonotone (intermediate visits) missing data were to be imputed first using the Monte Carlo Markov Chain (MCMC) method under the missing at random (MAR) assumption

in all treatment arms (using the MCMC statement in PROC MI). Multiple chains option (CHAIN = MULTIPLE option in the MCMC statement of PROC MI) was to be used. For the nonmonotone imputation of the HbA1c missing data, a multivariate normal model was to be used including variables for the HbA1c at baseline and all postbaseline visits within each treatment group. The Applicant preplanned to generate five hundred imputed datasets.

- (2) After the nonmonotone missing data have been imputed, the remaining monotone missing data were to be imputed within each treatment arm and subgroup, using a regression approach. The predictors for the regression imputation model at any time point were the stratification factors, and HbA1c at all previous time points, including baseline. Imputations were performed using a sequence of regression-based imputations (using PROC MI statement MONOTONE REG) at each postbaseline time point.
- (3) The first imputed values were to be penalized or rewarded based on the treatment the subject received:
 - a. Subjects in the bexagliflozin group: missing value will be analyzed assuming the treatment effect is worsened by δ_1 (where $\delta = 0.1$ to 0.5 , in step of 0.1) compared to the subjects who have no missing value in the reduction of HbA1c;
 - b. Subjects in the placebo group: missing value was to be analyzed assuming the treatment effect is better by δ_2 (where the range and step of change δ_2 also depends on the observed study effect size) compared to the subjects who have no missing value in the reduction of HbA1c.

FDA Reviewer Comment: *The Applicant's preplanning only included a range of δ_1 and by δ_2 from 0.1 to 0.5 with a fixed step. In this review, depending on the observed study effect sizes, we adjusted the range of the deltas by increasing the size of the steps (size tailored for each study) to reach the tipping points.*

16.3.4.5.2. Active-Controlled Studies

For each of the two active-controlled studies, we performed a one-dimensional tipping point analysis: based on the return-to-baseline multiple imputation, we penalized the missing outcomes on the bexagliflozin arm by the null hypothesis of the noninferiority test (i.e., the margin) while multiply imputing the active-control arm missing outcomes with the return-to-baseline method. The goal was to determine if the null margin penalty applied to the bexagliflozin changes the primary analysis conclusion, and if not, under what level of penalty there is no longer evidence of a treatment effect.

16.3.4.6. Secondary Endpoint – Primary Analysis Method

All the key secondary efficacy endpoints were continuous change from baseline endpoints. The above-described return-to-baseline coupled ANCOVA approach was also used for the key secondary endpoint analyses.

16.3.4.7. Multiple Testing Procedures

In each of the six pivotal studies, the study SAP prespecified a hierarchical testing sequence to control for overall type I error due to multiplicity. For each endpoint in the sequence, a two-sided

statistical test was to be conducted at the 5.0% significance level. [Table 136](#) summarizes, for each study, the ranks of the primary and key secondary endpoints within the study specific testing sequence.

Table 136. Primary and Key Secondary Efficacy Endpoints and Ranks in Orders

Category	Trial	Primary Endpoint	Key Secondary Endpoints			
		HbA1c (%)	Weight ^b	Fasting Plasma Glucose	Systolic Blood Pressure ^c	Additional Key Secondary Efficacy Endpoint(s)
Monotherapy	450	#1	#3		#2	
Adjunct to metformin	419 ^a	#1	Wk 24	Time Profile	Time Profile	
	423	#1 NI	#3	#2	#4	
	480	#1 NI	#2, Wk60		#3, Wk60	#4, % of subjects with hypo-glycemic event Over 96 wks
Special population	448	#1	#2		#3	#4, HbA1c in eGFR 45-59 #5, HbA1c in eGFR 30-45
	476	#1	#3, Wk48		#4	#2, HbA1c in subjects prescribed insulin at BL

Source: Summarized by FDA statistical reviewer.

Notes: 1. Each study has its own prespecified sequential testing procedure for the primary and key secondary efficacy endpoints for multiplicity control, an endpoint's rank in the testing order is listed within its corresponding cell.

2. Grey background was given to endpoints either not preplanned as key secondary endpoint (when the corresponding cell is empty) or when though the endpoint was designated as key secondary but was not included in the study multiplicity control procedure.

3. The four placebo-controlled trials were designed as superiority trials, each primary and key secondary endpoint being tested for superiority over control. Although the primary endpoint in the two active-controlled trials were tested for noninferiority of study drug over control, the key secondary endpoints were all preplanned for superiority testing.

^a In C-419, no formal hypothesis testing was planned for the secondary efficacy endpoints

^b In all the 6 studies, efficacy on change from baseline in weight is prespecified to be evaluated in the subgroup of subjects with baseline BMI ≥ 25 kg/m² in all 6 studies

^c In C-448, efficacy on change from baseline in systolic blood pressure (SBP) is prespecified to be evaluated in the subgroup of subjects with baseline SBP ≥ 130 mm Hg; in C-476 and C-480, in the subgroup of subjects with baseline SBP ≥ 140 mm Hg.

Abbreviations: BL, baseline; eGFR, estimated glomerular filtration rate (unit: mL/min/1.73 m², milliliters per minute per square meters of body surface area); HbA1c, hemoglobin A1C; NI, noninferiority.

16.4. Primary and Key Secondary Efficacy Results

For each study, a brief description of study specific trial design and study analysis plan are provided first before presenting the efficacy analysis results.

16.4.1. Trial C-450

16.4.1.1. Design, Trial C-450

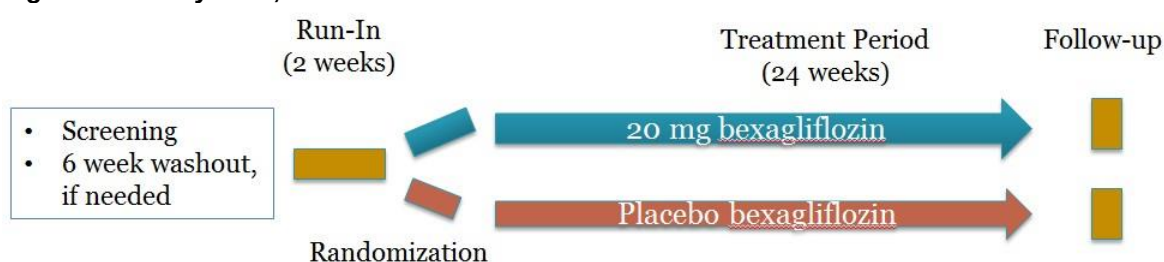
Trial C-450 was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. C-450 was designed to compare the efficacy and safety of once daily oral administration of bexagliflozin tablets, 20 mg, to placebo in treatment-naïve T2DM subjects or subjects previously treated with no more than one OHA.

Run-In Procedures for OHA Treatment Naïve or Not

Potential subjects were screened within three weeks of the start of the wash-out or run-in period. The study included both treatment-naïve T2DM subjects with inadequate control on diet and exercise and subjects on an OHA, who underwent a washout of the OHA. Subjects not on an OHA directly entered a 2-week, single-blind, placebo run-in period, while subjects on an OHA underwent a 6-week OHA washout period followed by a 2-week single-blind placebo run-in period. After the placebo run-in period, all subjects were randomized into a 24-week, double-blind, placebo-controlled period, followed by a 2-week follow-up period.

Treatment assignment randomization was stratified by HbA1c level at the start of the run-in period (≤ 8.5 or $> 8.5\%$), country (Canada or United States), and background antidiabetic treatment status (treatment-naïve or not). The study design is depicted in [Figure 47](#).

Figure 47. Study Plan, Trial C-450



Source: Study 450 Clinical Study Report, Figure 1.

16.4.1.2. Statistical Analysis Plan, Trial C-450

16.4.1.2.1. Efficacy Endpoints

The primary and key secondary endpoints listed in this subsection are shown in the study prespecified hierarchical testing sequence.

Primary Endpoint

- Change from baseline in HbA1c at Week 24

Key Secondary Endpoints

- Change from baseline in SBP at Week 24
- Change from baseline in body weight at Week 24 in subjects with a BMI ≥ 25 kg/m²

16.4.1.2.2. Analysis Methods

See Section [6.2.2](#) for description of the analysis methods.

16.4.1.3. Results of Analyses, Trial C-450

16.4.1.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics were generally balanced between these two groups, as summarized in [Table 137](#). There was a slightly higher proportion of male subjects (52%) than female subjects (48%) in C-450. The median age was 56 years ranging from 26 to 81 years of age (18% of all subjects were 65 years or older at trial enrollment). Slightly above 50% of all subjects identified as Hispanic or Latino. The trial was conducted in North America, with 84% of the subjects from the United States and the rest from Canada. The bexagliflozin 20 mg arm had slightly higher mean and median baseline BMI (mean 32.8, [SD 5.7] kg/m²; median 31.8) than the placebo arm (mean 30.5 [SD 4.6] kg/m²; median 29.8). Overall, 92% of the subjects were either overweight or obese at baseline (BMI ≥25 kg/m²); median duration of diabetes was 8 years.

Table 137. Baseline Demographic and Clinical Characteristics, ITT, Trial C-450

Characteristic	Bexagliflozin 20 mg N=138	Placebo N=69	Total N=207
Sex			
F	72 (52%)	35 (51%)	107 (52%)
M	66 (48%)	34 (49%)	100 (48%)
Age (years)			
Mean (SD)	56 (10)	55 (11)	55 (10)
Median (min, max)	56 (26, 79)	55 (33, 81)	56 (26, 81)
Age group			
Age <65 years	112 (81%)	58 (84%)	170 (82%)
Age ≥65	26 (19%)	11 (16%)	37 (18%)
Age ≥75 years	4 (3%)	4 (6%)	8 (4%)
Race			
American Indian or Alaska native			
Asian	15 (11%)	5 (7%)	20 (10%)
Black or African American	25 (18%)	6 (9%)	31 (15%)
Multiple			
Native Hawaiian or other Pacific Islander	1 (<1%)	0	1 (<1%)
Other	1 (<1%)	0	1 (<1%)
White	96 (70%)	58 (84%)	154 (74%)
Ethnicity			
Hispanic or Latino	67 (49%)	40 (58%)	107 (52%)
Not Hispanic or Latino	71 (51%)	29 (42%)	100 (48%)
Country			
Canada	21 (15%)	12 (17%)	33 (16%)
United States	117 (85%)	57 (83%)	174 (84%)
BMI at baseline (kg/m ²)			
Mean (SD)*	32.8 (5.7)	30.5 (4.6)	32.0 (5.4)
Median (min, max)*	31.8 (20.4, 46.0)	29.8 (23.4, 44.1)	31.0 (20.4, 46.0)
BMI at baseline (kg/m ²) group			
Missing*	1 (<1%)	0	1 (<1%)
<25 kg/m ²	9 (7%)	7 (10%)	16 (8%)
≥25 kg/m ²	128 (93%)	62 (90%)	190 (92%)

Characteristic	Bexagliflozin 20 mg N=138	Placebo N=69	Total N=207
Duration of diabetes (years)			
Mean (SD)	9.3 (6.6)	8.9 (5.9)	9.1 (6.2)
Median (min, max)	8.0 (0.2, 33.1)	8.0 (0.2, 31.1)	8.0 (0.2, 33.1)
Baseline insulin, n (%)			
Insulin treated	NA	NA	NA
Not insulin treated	NA	NA	NA
Baseline HbA1c (%) mean			
Mean (SD)	8.7 (0.9)	8.6 (0.8)	8.6 (0.8)
Median (min, max)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)
Baseline HbA1c (%) group			
7.0 - 8.5%	107 (78%)	55 (80%)	162 (78%)
8.6 - 10.5%	31 (22%)	14 (20%)	45 (22%)
Baseline eGFR, mL/min/1.73 m ²			
Mean (SD)	93.4 (19.0)	97.3 (24.2)	94.7 (20.9)
Median (min, max)	93 (57, 164)	93 (58, 181)	93 (57, 181)
Baseline eGFR group, mL/min/1.73 m ²			
<30			
≥30 to <45			
≥45 to <60	3 (2%)	2 (3%)	5 (2%)
≥60 to <90	59 (43%)	29 (42%)	88 (43%)
≥90	76 (55%)	38 (55%)	114 (55%)
Baseline SBP, mm Hg			
Mean (SD)	131.0 (14.4)	125.6 (13.8)	129.2 (14.4)
Median (min, max)	131 (93, 188)	126 (98, 158)	130 (93, 188)
SBP group, mm Hg			
<130 mm Hg	62 (45%)	41 (59%)	103 (50%)
≥130 mm Hg	76 (55%)	28 (41%)	104 (50%)
Baseline FPG, mg/dL			
Mean (SD)	169 (36)	169(38)	169 (36)
Median (min, max)	169 (92, 284)	164 (99, 268)	166 (92, 284)

Source: FDA statistical reviewer

*Subject C-450 (b) (6) had baseline BMI information missing.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intention-to-treat; Min: minimum; Max: maximum; mm Hg: millimeter of mercury, N, number of subjects in treatment group; n, number of subjects with given characteristic; kg, kilogram; m, meter; SBP, systolic blood pressure; SD: standard deviation.

Disposition

Subject disposition information for Trial C-450 is summarized in [Table 138](#); 272 (58%) of the subjects screened for participation entered the run-in period in the trial. Among subjects who entered the run-in period, 210 (77%) passed the run-in period and were randomized into the double-blind phase of the trial.

Table 138. Subject Screening and Randomization, Trial C-450

Disposition	Screened (%)	Entered Run-In (%)
No. subjects consented to participate and completed the screening procedures	466 (100%)	
No. screening failures before run-in	194 (42%)	
No. subjects entered run-in period	272 (58%)	272 (100%)
No. screening failures after run-in	62 (13%)	62 (23%)
No. subjects randomized	210 (45%)	210 (77%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis population and subject disposition information for Trial C-450 are summarized in [Table 139](#). Overall, about 90% of the subjects completed study treatment, the bexagliflozin group had a numerically lower treatment completion rate (88%) than the placebo arm (93%). The most frequent reasons for treatment discontinuation were “subjects withdrew consent” and “subjects lost to follow-up” for the bexagliflozin arm.

This disposition table reveals two issues with trial disposition data collection and consolidation. First, a “withdrawal of consent” is a broad umbrella term that covers potentially multiple specific reasons why subjects opt to withdraw consent and participation in the trial. Withdrawal of consent is the result of these potential reasons, the term itself gives no deliberate reason as to which caused the subject to opt out (e.g., efficacy, safety, or administrative reasons). More specific reasons such as adverse drug effects and tolerability issues, lack of efficacy, subject relocation, and others could be handled differently in a missing data imputation algorithm. Second, in analysis dataset derivation, the more than one entry in the form of “adverse event: specific reason” should be consolidated under one category “adverse event” so unnecessary details could be omitted from crowding a summary level table. The overall study completion rate (90.3%) is very close to the treatment completion rate (89.4%).

Table 139. Subject Disposition, ITT, Trial C-450

	Bexagliflozin 20 mg N=138 n (%)	Placebo N=69 n (%)	Total N=207 n (%)
Disposition			
Analysis population*			
Subjects randomized**	140 (100%)	70 (100%)	210 (100%)
ITT population	138 (99%)	69 (99%)	207 (99%)
Per protocol population	131 (94%)	67 (96%)	198 (94%)
Safety population	138 (99%)	69 (99%)	207 (99%)
Treatment completion status			
Completed	121 (87.7%)	64 (92.8%)	185 (89.4%)
Discontinued	17 (12.3%)	5 (7.2%)	22 (10.6%)
Reason for discontinuation of treatment			
Adverse event: body cramps	1 (<1%)	0	1 (<1%)
Adverse event: elevated liver function tests	1 (<1%)	0	1 (<1%)
Other: missed last 2 visits	1 (<1%)	0	1 (<1%)
Other: subject noncompliant	0	1 (1.4%)	1 (<1%)
Study terminated by Sponsor: subject leaving for Florida	0	1 (1.4%)	1 (<1%)
Subject died	0	1 (1.4%)	1 (<1%)
Subject lost to follow-up	8 (5.8%)	1 (1.4%)	9 (4.3%)
Subject withdrew consent	6 (4.3%)	1 (1.4%)	7 (3.4%)
Adverse event: body cramps	1 (<1%)	0	1 (<1%)

	Bexagliflozin 20 mg N=138 n (%)	Placebo N=69 n (%)	Total N=207 n (%)
Disposition			
Study completion status			
Completed the study	123 (89.1%)	64 (92.8%)	187 (90.3%)
Discontinued from the study	15 (10.9%)	5 (7.2%)	20 (9.7%)
Reason for discontinuation from study			
Other	2 (1.4%)	1 (1.4%)	3 (1.4%)
Study terminated by Sponsor	0	1 (1.4%)	1 (<1%)
Subject died	0	1 (1.4%)	1 (<1%)
Subject lost to follow-up	7 (5.1%)	1 (1.4%)	8 (3.9%)
Subject withdrew consent	6 (4.3%)	1 (1.4%)	7 (3.4%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

** Note: Three randomized subjects were excluded in the ITT and the safety populations due to GCP violation. Subject 450 (b) (6) and subject 450 (b) (6) were the same person who enrolled in two clinical sites (b) (6) and (b) (6). Subject 450 (b) (6) enrolled in another bexagliflozin clinical Trial C-480 while he was also enrolled in C-450 study. These incidents were documented as protocol violations.

Abbreviation: GCP, good clinical practice; ITT, intention-to-treat; N, number of subjects; n, number of subjects with given characteristic

16.4.1.3.2. Primary Endpoint, and Key Secondary Efficacy Results

Primary Endpoint – Primary Analysis

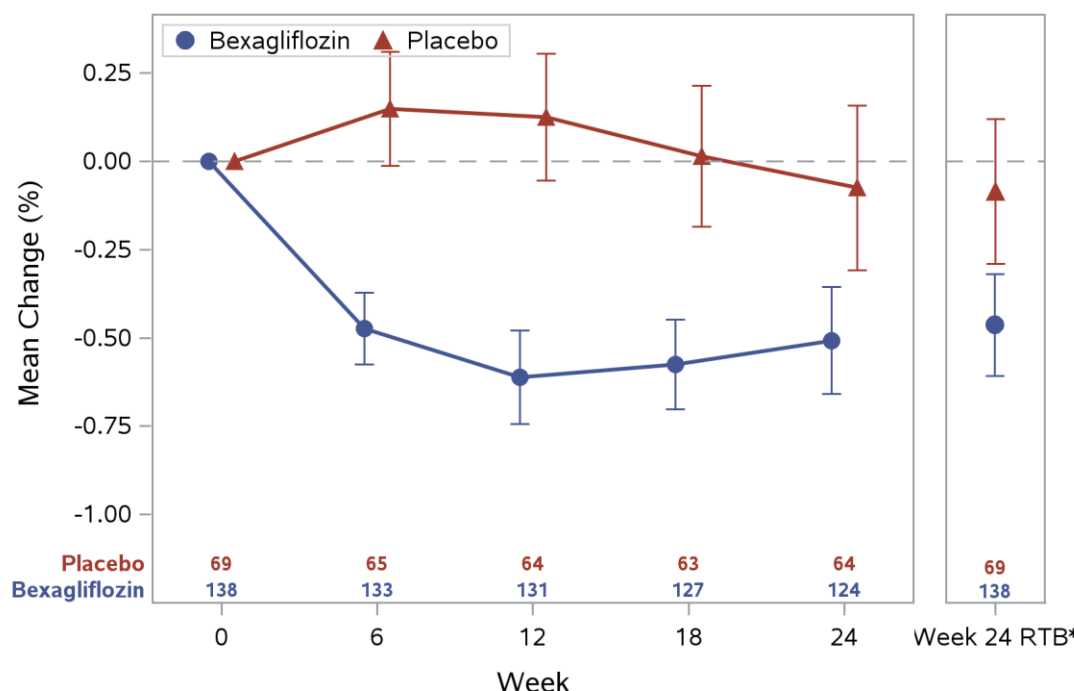
[Table 140](#) summarizes the primary analysis results for C-450. Twelve (8.7%) and 5 (7.2%) subjects in the Bexagliflozin 20 mg group and the placebo group, respectively, had missing HbA1c data at Week 24.

In the primary analysis based on the ITT analysis set, using the return-to-baseline coupled ANCOVA analysis, at Week 24, bexagliflozin statistically significantly reduced HbA1c from baseline compared with placebo. The adjusted mean difference was -0.38 (95%CI: -0.63, -0.13; one-sided p-value, 0.0016).

[Figure 48](#) displays the mean change from baseline in HbA1c (%) over 24 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 24 is plotted separately.

Figure 48. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-450

C-450 Mean Change from Baseline in HbA1c (%) by Time and Treatment



Note: Vertical lines represent 95% confidence intervals. *Data was analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat; RTB, return to baseline.

In addition, tipping point sensitivity analysis results ([Table 184](#)) show that only under implausible situations will the treatment effect demonstrated by the primary analysis lose significance: after imputing both the two treatment arm missing data assuming MAR for the nonmonotone missing data, then awarding the placebo arm and penalizing the bexagliflozin arm for the first missing data point within each subject with a delta method, the analysis results for the regression-based imputation of HbA1c value at Week 24 show that only when penalizing the bexagliflozin arm by adding 1.6 (%) or more to the imputed data will the estimated treatment effect lose significance.

Also based on the return-to-baseline multiply imputed HbA1c (%) values at Week 24, a responder defined as subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%) was derived. The logistic regression model adjusted proportions are 26.8% and 14.4% for the bexagliflozin 20 mg group and the placebo group, respectively.

Table 140. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-450

Characteristic	Bexagliflozin 20 mg (N=138)	Placebo (N=69)
Number of subjects	138	69
Number (%) of values imputed for Week 24	12 (8.7)	5 (7.2)
Baseline		
Mean (SD)	8.05 (0.824)	7.97 (0.757)
Median	8.00	7.80
Q1, Q3	7.40, 8.50	7.40, 8.30
Minimum, Maximum	7.0, 10.5	7.0, 10.2
Model-adjusted change from baseline		
LS mean (SE)	-0.46 (0.074)	-0.09 (0.104)
95% confidence interval	(-0.61, -0.32)	(-0.29, 0.12)
Difference from placebo		
Difference of LS means	-0.38	
95% confidence interval	(-0.63, -0.13)	
One-sided p-value	0.0016	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count: subjects [N (%)] ^a	43 (31.2)	14 (20.3)
Model based proportion ^b	26.8	14.4

Source: FDA statistical reviewer

^a Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

^b Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Key Secondary Endpoint – Primary Analysis

Change from baseline in systolic blood pressure at Week 24 and change from baseline in body mass at Week 24 are two prespecified key secondary endpoints. [Table 141](#) summarizes changes from baseline in these prespecified key secondary efficacy endpoints at Week 24. At Week 24, bexagliflozin use was associated with numerical reductions in systolic blood pressure and body mass compared with placebo, but these differences did not reach statistical significance. More detailed analysis results for these two endpoints and fasting plasma glucose can be located in Section [16.5.1 Table 166](#), [Table 167](#), and [Table 168](#).

Table 141. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-450

Characteristic	Bexagliflozin 20 mg	Placebo
Change from baseline in SBP at Week 24		
Number of subjects	138	69
Number (%) of values imputed for Week 24	12 (8.7)	5 (7.2)
Baseline		
Mean (SD)	131.02 (14.351)	125.64 (13.836)
Model-adjusted change from baseline		
LS mean (SE)	-0.72 (1.019)	1.03 (1.467)
95% confidence interval	(-2.72, 1.28)	(-1.85, 3.90)

Characteristic	Bexagliflozin 20 mg	Placebo
Difference from placebo		
Difference of LS means	-1.75	
95% confidence interval	(-5.26, 1.77)	
One-sided p-value	0.1649	
Change from baseline in body mass at Week 24 (baseline BMI ≥ 25 kg/m² subgroup)		
Number of subjects	128	62
Number (%) of values imputed for Week 24	11 (8.6)	5 (8.1)
Baseline		
Mean (SD)	92.51 (19.553)	86.94 (19.358)
Model-adjusted change from baseline		
LS mean (SE)	-1.46 (0.291)	-0.76 (0.414)
95% confidence interval	(-2.03, -0.89)	(-1.58, 0.05)
Difference from placebo		
Difference of LS means	-0.70	
95% confidence interval	(-1.69, 0.30)	
One-sided p-value	0.0848	

Source: FDA statistical reviewer

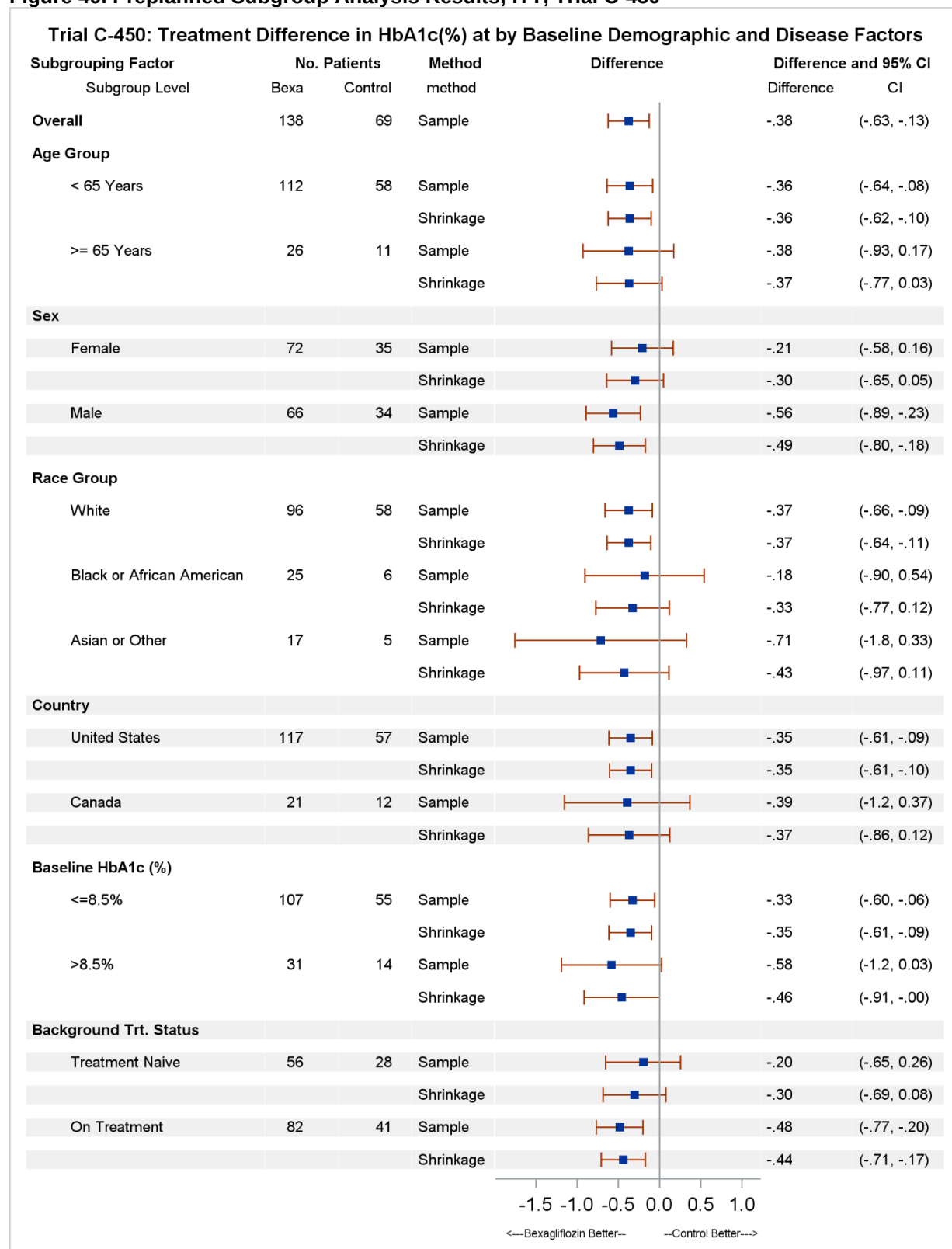
Abbreviation: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure.

16.4.1.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses showed that the HbA1c lowering effect was consistent across subgroup levels ([Figure 49](#)). There are trends that HbA1c reductions with bexagliflozin were greater in males, in the subgroup of subjects who had higher baseline HbA1c ($>8.5\%$), and in the subgroup of subjects who were on an OHA at screening.

To further investigate the potential modulation effect of baseline HbA1c level, a linear regression “subgroup” analysis using the continuous baseline HbA1c level based on the completers data was carried out. [Figure 50](#) shows a scatter plot of change from baseline in HbA1c at Week 24 versus baseline HbA1c data, overlayed with the estimated by-arm group regression lines. In general, in both bexagliflozin-treated subjects and in placebo subjects, higher baseline HbA1c level is associated with a bigger change from baseline HbA1c levels at Week 24. The two by-arm regression lines are nearly parallel, the difference in slope (slope in bexagliflozin arm - slope in placebo arm) is -0.042 (standard error [SE]=0.167, p-value=0.80). The small size of the difference and the p-value of 0.80 suggest that baseline HbA1c level is less likely to have any modulating effect on the action of this SGLT2 inhibitor drug in this study population.

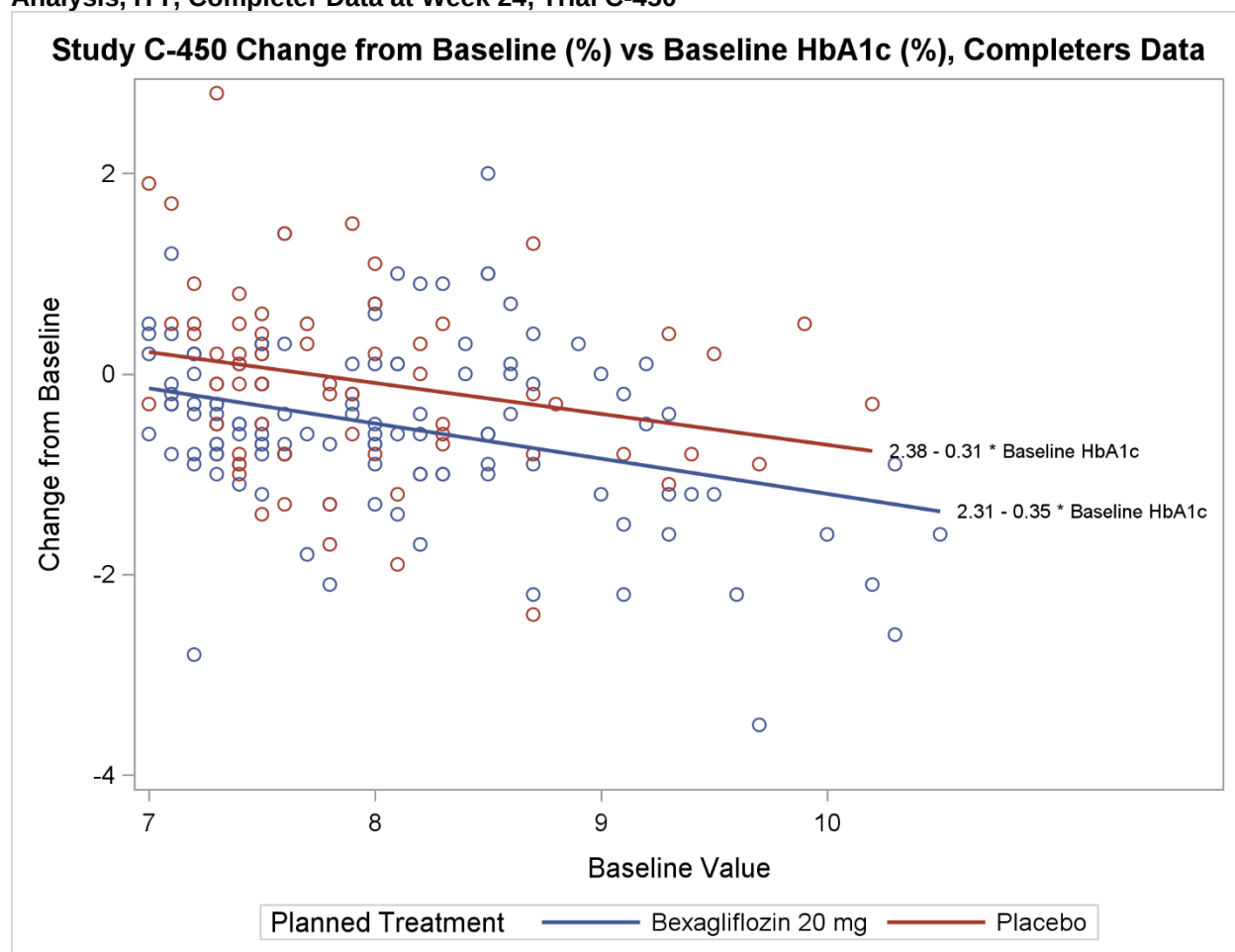
Figure 49. Preplanned Subgroup Analysis Results, ITT, Trial C-450



Source: FDA statistical reviewer

Abbreviation: Bexa, bexagliflozin; CI, confidence interval; HbA1c, hemoglobin A1c; ITT, intention-to-treat; No, number of.

Figure 50. Trial C-450 Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-450



Source: FDA statistical reviewer

Note: The estimated difference in slope between the bexagliflozin arm and the placebo arm is -0.04 (standard error [SE]=0.167, p-value=0.80). These results are derived from a simple linear regression model based on the completers data with change from baseline in HbA1c at Week 24 as the response variable, and treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction as the predictor variables.

Abbreviations: HbA1c, hemoglobin A1c; ITT, intention-to-treat

16.4.2. Trial C-419

16.4.2.1. Design, Trial C-419

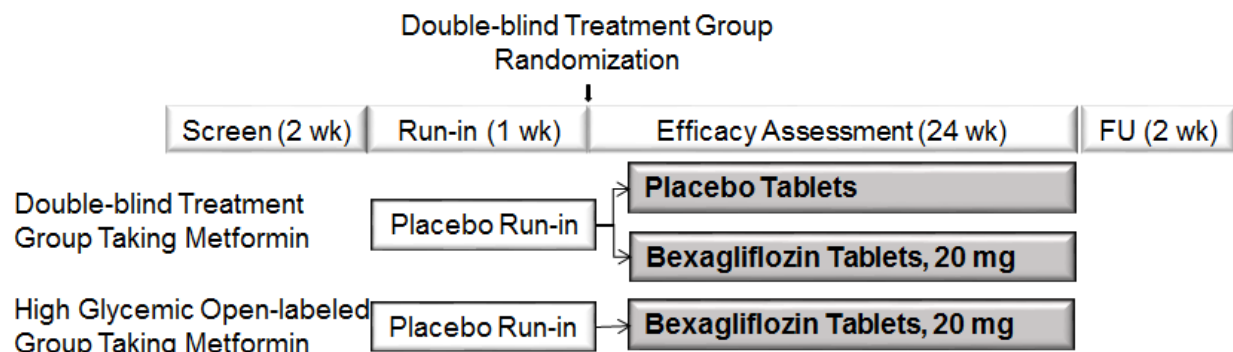
Trial C-419 was a phase 3, randomized, double-blind, placebo-controlled study conducted to determine the effect of bexagliflozin as add-on to metformin on the placebo-corrected change in HbA1c from baseline to Week 24 in adults with T2DM whose disease is inadequately controlled by metformin alone.

The trial consisted of a double-blinded main part of the study and an open-label single-arm high glycemic arm of the study. [Figure 51](#) illustrates the schematic of the overall study plan. The high glycemic arm recruited 37 subjects with HbA1c >10.5% and ≤12.0% into an open-label arm, to receive bexagliflozin tablets, 20 mg, for 24 weeks. The endpoint for the open-label arm was the

change from baseline to Week 24 of the HbA1c (%). For this efficacy review, we focus on the main part (placebo-controlled) of the study.

In the placebo-controlled part of the study, subjects who successfully completed a 1-week run-in and who remained eligible were randomized 1:1 to receive bexagliflozin 20 mg or placebo, in addition to their customary metformin dosage for 24 weeks in an outpatient setting. The randomization was stratified by HbA1c ($\leq 8.5\%$ or $> 8.5\%$) and country (United States or Japan). Study subjects were not to change their metformin dosage unless adjustment was medically necessary to manage hypoglycemia.

Figure 51. Study Plan, Trial C-419



Source: Study 419 Clinical Study Report, Figure 1.
Abbreviations: FU, follow-up

16.4.2.2. Statistical Analysis Plan, Trial C-419

16.4.2.2.1. Efficacy Endpoints

Primary Endpoint

- Change from baseline in HbA1c at Week 24

Trial C-419 study protocol and SAP prespecified that no formal hypothesis testing will be performed for the secondary efficacy endpoints. For the secondary efficacy endpoint, nominal p-values will be presented for exploratory purposes.

16.4.2.2.2. Analysis Methods

See Section [6.2.2](#) for description of the analysis methods.

16.4.2.3. Results of Analyses, Trial C-419

16.4.2.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics were generally balanced between these two groups, as summarized in [Table 142](#).

There was a higher proportion of male (61%) than female subjects (39%) in C-419. The median age was 56 years ranging from 28 to 81 years of age (21% of all subjects were 65 years or older at trial enrollment). The trial was conducted in Japan and the United States, with 52% of the subjects from the United States and the rest from Japan. Overall, 77% of the subjects were either overweight or obese at baseline ($\text{BMI} \geq 25 \text{ kg/m}^2$); median duration of diabetes was 8.0 years.

Table 142. Baseline Demographic and Clinical Characteristics, ITT, Double-Blinded, Trial C-419

Characteristic	Bexagliflozin 20 mg N=158	Placebo N=159	Total N=317
Sex			
F	58 (37%)	65 (41%)	123 (39%)
M	100 (63%)	94 (59%)	194 (61%)
Age (years)			
Mean (SD)	56 (10)	56 (11)	56 (11)
Median (min, max)	56 (30, 79)	56 (28, 81)	56 (28, 81)
Age group			
Age <65 years	127 (80%)	124 (78%)	251 (79%)
Age ≥ 65 years	31 (20%)	35 (22%)	66 (21%)
Age ≥ 75 years	6 (4%)	7 (4%)	13 (4%)
Race			
American Indian or Alaska native	1 (<1%)	1 (<1%)	2 (<1%)
Asian	78 (49%)	79 (50%)	157 (50%)
Black or African American	26 (16%)	29 (18%)	55 (17%)
Multiple	1 (<1%)	2 (1%)	3 (<1%)
Native Hawaiian or other Pacific Islander	1 (<1%)	0	1 (<1%)
White	51 (32%)	48 (30%)	99 (31%)
Ethnicity			
Hispanic or Latino	35 (22%)	32 (20%)	67 (21%)
Not Hispanic or Latino	123 (78%)	127 (80%)	250 (79%)
Country			
Japan	75 (47%)	76 (48%)	151 (48%)
USA	83 (53%)	83 (52%)	166 (52%)
BMI at baseline (kg/m^2)			
Mean (SD)	29.7 (6.4)	30.0 (6.3)	29.8 (6.4)
Median (min, max)	28.9 (17.4, 45.4)	29.1 (19.1, 44.9)	29.0 (17.4, 45.4)
BMI at baseline (kg/m^2) group			
<25 kg/m^2	39 (25%)	35 (22%)	74 (23%)
$\geq 25 \text{ kg/m}^2$	119 (75%)	124 (78%)	243 (77%)
Duration of diabetes (years)			
Mean (SD)	9.3 (6.6)	8.9 (5.9)	9.1 (6.2)
Median (min, max)	8.0 (0.2, 33.1)	8.0 (0.2, 31.1)	8.0 (0.2, 33.1)
Baseline HbA1c (%) mean			
Mean (SD)	8.7 (0.9)	8.6 (0.8)	8.6 (0.8)
Median (min, max)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)	8.4 (7.5, 10.5)
Baseline HbA1c (%) group			
$\geq 7.5\%$ and <8.5%	83 (53%)	82 (52%)	165 (52%)
$\geq 8.5\%$ and $\leq 10.5\%$	75 (47%)	77 (48%)	152 (48%)
Baseline eGFR, mL/min/1.73 m^2			
Mean (SD)	89.0 (19.4)	91.5 (21.2)	90.2 (20.4)
Median (min, max)	85 (58, 143)	88 (60, 179)	87 (58, 179)

Characteristic	Bexagliflozin 20 mg N=158	Placebo N=159	Total N=317
Baseline eGFR group, mL/min/1.73 m ²			
<30	0	0	0
≥30 to <45	0	0	0
≥45 to <60	2 (1%)	0	2 (<1%)
≥60 to <90	87 (55%)	86 (54%)	173 (55%)
≥90	69 (44%)	73 (46%)	142 (45%)
Baseline SBP, mm Hg			
Mean (SD)	128.8 (14.4)	129.7 (15.1)	129.2 (14.7)
Median (min, max)	129 (99, 173)	129 (98, 173)	129 (98, 173)
SBP group, mm Hg			
<140 mm Hg	123 (78%)	119 (75%)	242 (76%)
≥140 mm Hg	35 (22%)	40 (25%)	75 (24%)

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD: standard deviation; Min: minimum; Max: maximum; SBP, systolic blood pressure.

Disposition

Subject disposition information for Trial C-419 is summarized in [Table 143](#). Among the 521 subjects enrolled and screened, there were 170 screen failures; 361 (66%) of the subjects screened for participation entered the run-in period of the trial. Among subjects who entered the run-in period, 351 (97%) passed the run-in period and were entered into the treatment period; among them, 317 eligible subjects were randomized into the double-blind treatment phase and 34 subjects who had HbA1c >10.5% and ≤12.0% at screening were assigned to the high glycemic group to receive open-label bexagliflozin.

Table 143. Subject Screening and Randomization, Trial C-419

Disposition	Screened (%)	Entered Run-in (%)
No. subjects consented to participate and completed the screening procedures	521 (100%)	
No. screening failures before run-in	160 (31%)	
No. subjects entered run-in period	361 (69%)	361 (100%)
No. screening failures after run-in	10 (2%)	10 (3%)
No. subjects randomized	351 (67%)	351 (97%)
No. subjects entered the double blind treatment substudy	317 (61%)	317 (88%)
No. subjects entered the high glycemic group open-label study	34 (7%)	34 (9%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis population and subject disposition information for Trial C-419 are summarized in [Table 144](#). Overall, 89% of the subjects completed study treatment, the treatment completion rates are balanced between the two treatment arms. The most frequent reasons for treatment discontinuation in the bexagliflozin group was “withdrawal by subject”; The most frequent reasons for treatment discontinuation in the placebo group was “lost to follow-up.” Study completion rates are the same as the corresponding treatment completion rates.

Table 144. Subject Disposition, ITT, Double-Blind Treatment Group, Trial C-419

Completion Status/ Discontinuation Reason	Bexagliflozin		Total N=317
	20 mg N=158	Placebo N=159	
Analysis populations*			
Subjects randomized	158 (100%)	159 (100%)	317 (100%)
ITT population	158 (100%)	159 (100%)	317 (100%)
Per protocol population	151 (96%)	156 (98%)	307 (97%)
Safety population	158 (100%)	159 (100%)	317 (100%)
Treatment completion			
Yes	141 (89%)	142 (89%)	283 (89%)
No	17 (11%)	17 (11%)	34 (11%)
Reason for discontinuation			
Adverse event	4 (3%)	2 (1%)	6 (2%)
Lost to follow-up	5 (3%)	9 (6%)	14 (4%)
Subject was withdrawn from participation by investigator	0	1 (<1%)	1 (<1%)
Withdrawal by subject	8 (5%)	5 (3%)	13 (4%)
Study completion			
Yes	141 (89%)	142 (89%)	283 (89%)
No	17 (11%)	17 (11%)	34 (11%)
Reason for discontinuation			
Adverse event	3 (2%)	2 (1%)	5 (2%)
Lost to follow-up	5 (3%)	9 (6%)	14 (4%)
Subject was withdrawn from participation by investigator	0	1 (<1%)	1 (<1%)
Withdrawal by subject	9 (6%)	5 (3%)	14 (4%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

Abbreviation: ITT, intention-to-treat; N, number of subjects; n, number of subjects with given characteristic

16.4.2.3.2. Primary Endpoint, and Key Secondary Efficacy Results

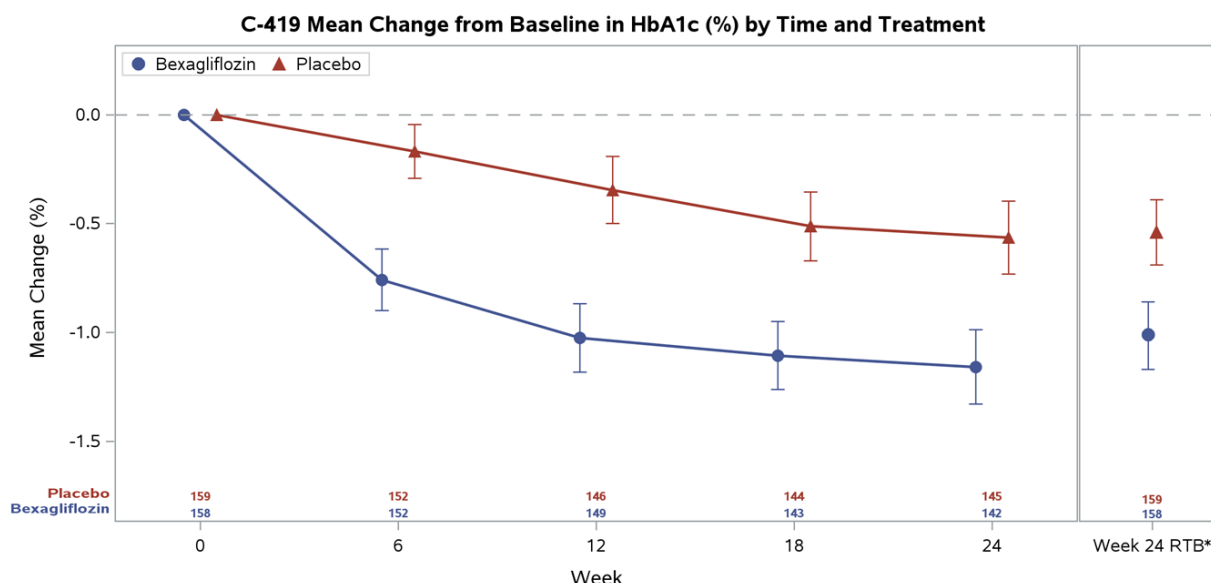
Primary Endpoint – Primary Analysis

[Table 145](#) summarizes the primary analysis results for C-419. Sixteen (10.1%) and 15 (9.4%) subjects in the bexagliflozin 20 mg group and placebo group, respectively, had missing HbA1c data at Week 24.

At Week 24, bexagliflozin 20 mg was statistically significant in lowering HbA1c compared with placebo in T2DM subjects who has inadequate glycemic control with metformin only with an adjusted mean difference of -0.48% (95% CI (-0.69 to -0.26); one-sided p-value<0.0001).

[Figure 52](#) displays the mean change from baseline in HbA1c (%) over 24 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 24 is plotted separately.

Figure 52. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419



Note: Vertical lines represent 95% confidence intervals. * Data was analyzed with ANCOVA using fixed categorical effects of treatment, region, screening, anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat; RTB, return to baseline.

In addition, tipping point sensitivity analysis results ([Table 185](#)) show that only under implausible situations will the treatment effect demonstrated by the primary analysis lack significance.

Table 145. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-419

Characteristic	Bexagliflozin 20 mg (N=158)	Placebo (N=159)
Number of subjects	158	159
Number (%) of values imputed for Week 24	16 (10.1)	15 (9.4)
Baseline		
Mean (SD)	8.66 (0.866)	8.57 (0.790)
Median	8.40	8.40
Q1, Q3	8.00, 9.40	7.90, 9.00
Minimum, maximum	7.5, 10.5	7.5, 10.5
Week 24 (Observed)		
Mean (SD)	7.48 (0.926)	7.95 (0.903)
Median	7.40	7.80
Q1, Q3	6.80, 8.00	7.40, 8.40
Minimum, maximum	5.5, 11.0	6.1, 11.9
Model-adjusted change from baseline		
LS mean (SE)	-1.01 (0.078)	-0.54 (0.078)
95% confidence interval	(-1.17, -0.86)	(-0.69, -0.39)

Characteristic	Bexagliflozin 20 mg (N=158)	Placebo (N=159)
Difference from placebo		
Difference of LS means	-0.48	
95% confidence interval	(-0.69, -0.26)	
One-sided p-value	<0.0001	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count and proportion [N (%)] ^[1]	41 (25.9)	16 (10.1)
Model based proportion ^[2]	25.3	9.0

Source: FDA statistical reviewer

^[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

^[2] Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Also based on the multiply imputed HbA1c (%) values at Week 24, a responder defined as reaching the treatment goal of glycemic control (HbA1c (%) <7%) was derived. A logistic regression model generated adjusted proportions for subjects reaching the goal at Week 24 of 25.3% and 9.0% for the bexagliflozin 20 mg group and the placebo group, respectively.

Key Secondary Efficacy Endpoints

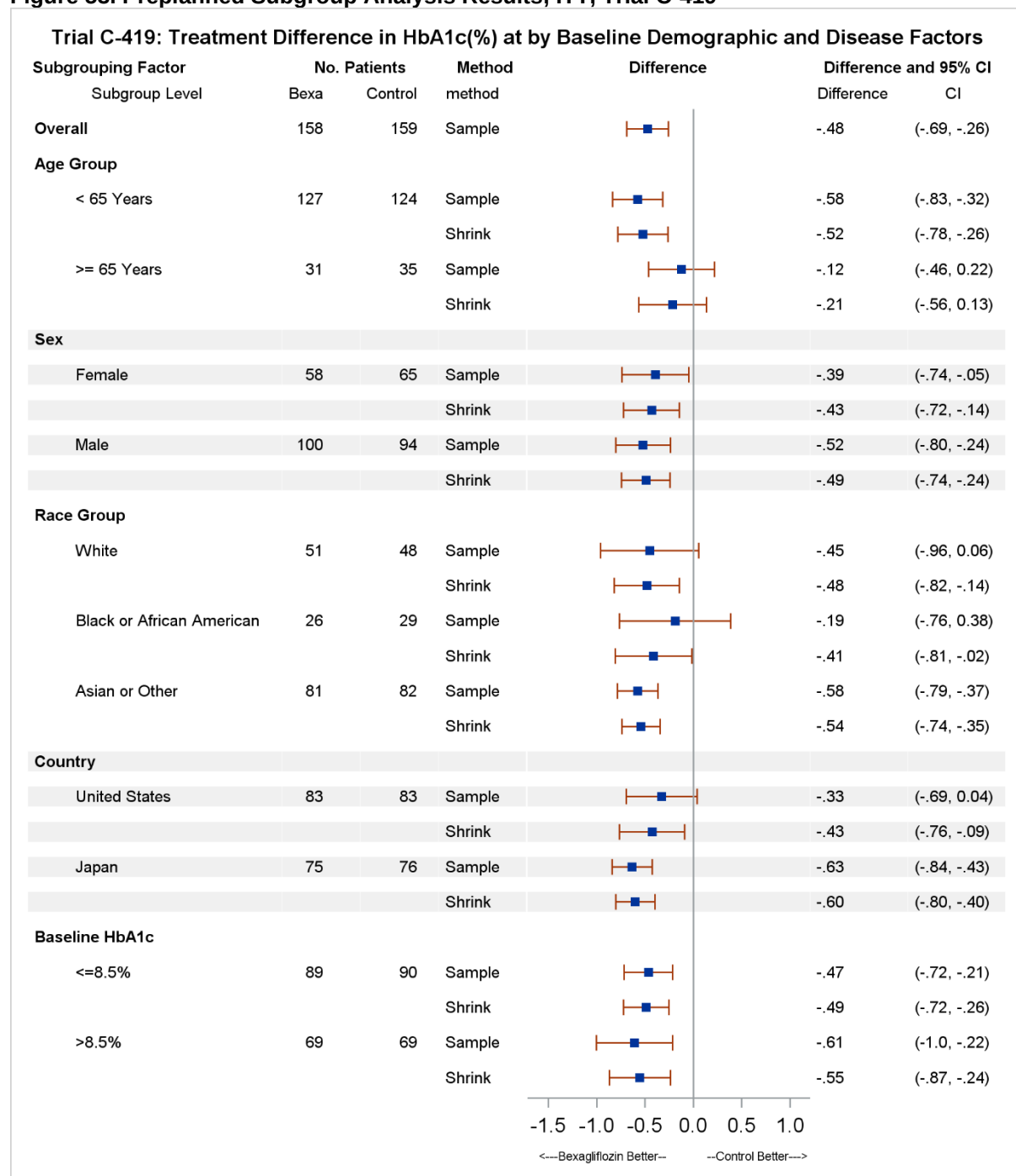
The study SAP prespecified that no formal hypothesis testing will be performed for the secondary efficacy endpoints. We validated the Applicant's analysis results of key secondary efficacy endpoints including changes from baseline in fasting plasma glucose, systolic blood pressure, and body mass (see Section 16.5.2). For the individual test results of the three endpoints, all nominal p-values (all <0.05) were presented for exploratory purposes.

16.4.2.3.3. Subgroup Analyses of the Primary Endpoint

Preplanned subgroup analyses showed that the HbA1c lowering effect was consistent across subgroup levels (Figure 53). There is a trend that HbA1c reductions with bexagliflozin were less effective in subjects 65 years of age and older in this study population.

Figure 54 shows a scatter plot of change from baseline in HbA1c at Week 24 versus baseline HbA1c data, overlaid with the estimated by-arm group regression lines. In general, in both bexagliflozin treated subjects and in placebo subjects, a higher baseline HbA1c level is associated with bigger change from baseline HbA1c levels at Week 24. Compared with placebo, bexagliflozin treatment is associated with a slightly flatter slope, the difference in slope (slope in bexagliflozin arm - slope in placebo arm) is 0.074 (standard error [SE]=0.127, p-value=0.56). The small size of the difference and the p-value of 0.56 suggest that baseline HbA1c level is less likely to have any modulating effect on the action of this SGLT2 inhibitor drug in this study population.

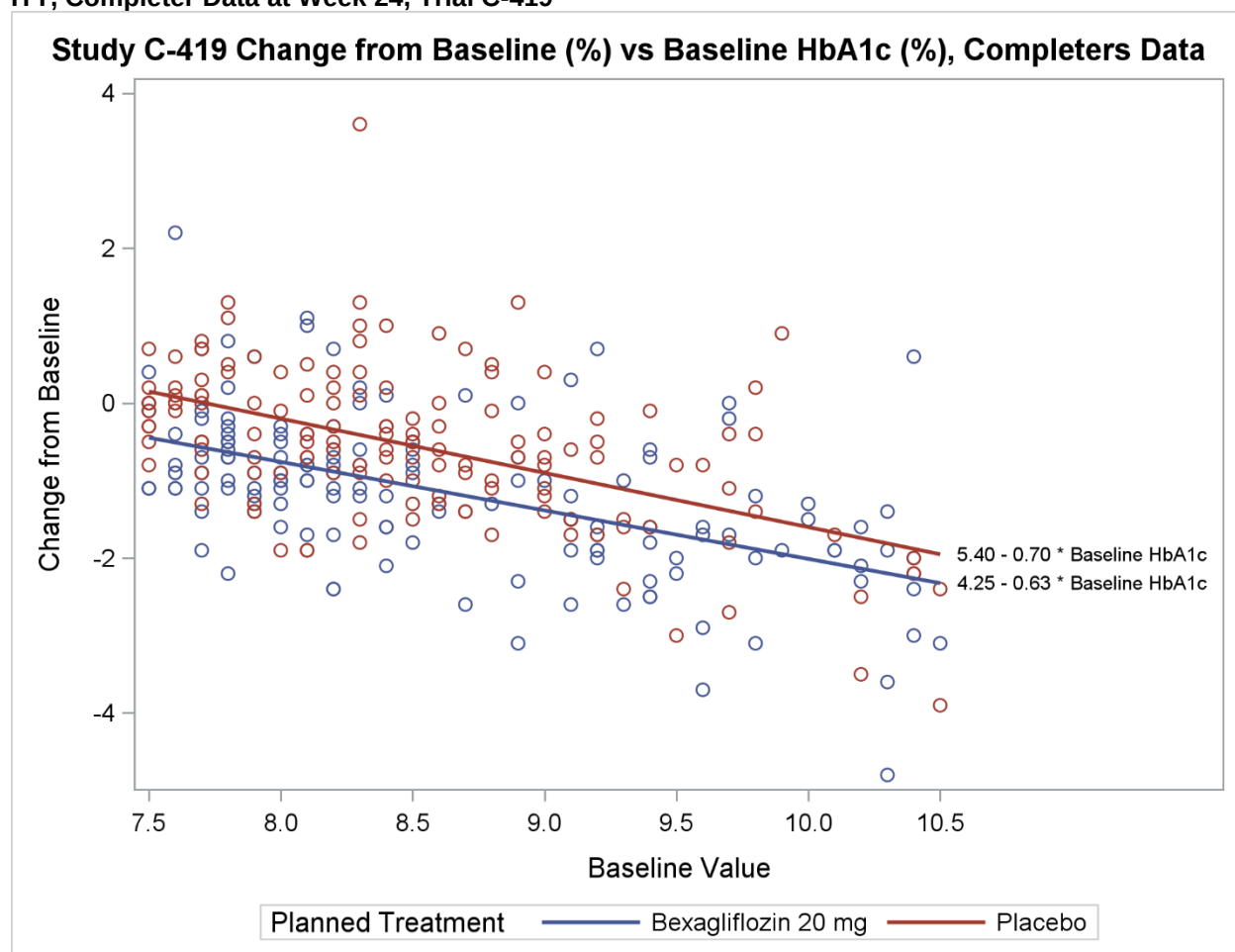
Figure 53. Preplanned Subgroup Analysis Results, ITT, Trial C-419



Source: FDA statistical reviewer

Abbreviation: Bexa, bexagliflozin; HbA1c, hemoglobin A1c; ITT, intention-to-treat; No, number of.

Figure 54. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-419



Source: FDA statistical reviewer

Note: The estimated difference in slope between the bexagliflozin arm and the placebo arm is 0.074 (standard error [SE]=0.127, p-value=0.56). These results are derived from a simple linear regression model based on the completers data with change from baseline in HbA1c at Week 24 as the response variable, and treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction as the predictor variables.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; No, number of.

16.4.3. Trial C-423

16.4.3.1. Design, Trial C-423

Study 423 is a phase 3, randomized, double-blind, active-controlled study to demonstrate that bexagliflozin is noninferior to sitagliptin by evaluating the treatment effect on HbA1c reduction in subjects with T2DM who have inadequate glycemic control by metformin.

Noninferiority Margin Selection and Justification

The Applicant's proposed noninferiority margin of 0.35% was based on a published clinical trial that demonstrated the effectiveness of sitagliptin, 100 mg, on HbA1c reduction in subjects with T2DM (Charbonnel et al. 2006). The Applicant further reasoned that: the sitagliptin study included male and female adult subjects with T2DM diagnosis and inadequate glycemic control

defined by an HbA1c $\geq 7.0\%$ and $\leq 10\%$ while taking metformin monotherapy at a stable dose of ≥ 1500 mg per day. Trial C-423 recruited the same patient population except that the HbA1c range was between 7.0% to 11%. Baseline HbA1c values in the sitagliptin study (Charbonnel et al. 2006) were $8.03 \pm 0.82\%$ in the placebo arm and $7.96 \pm 0.81\%$ in the active arm, respectively. This is close to the baseline mean HbA1c of $7.99 \pm 0.87\%$ in the C-423 subject population. In the published sitagliptin study, a placebo-adjusted least-squares mean (95% CI) treatment effect of reduction from baseline in HbA1c was -0.65% ($-0.77, -0.53$). The clinical meaningful margin is selected to be approximately half of sitagliptin effect, i.e., 0.35% reduction.

At the IND stage, FDA reviewed agreed with the margin selection and accepted the justification.

16.4.3.2. Statistical Analysis Plan, Trial C-423

16.4.3.2.1. Efficacy Endpoints

The primary and key secondary endpoints listed in this subsection are shown in the study prespecified hierarchical testing sequence.

Primary Endpoint

- Change from baseline in HbA1c at Week 24

Key Secondary Endpoints

- Change in FPG from baseline at Week 24
- Change in body weight in subjects with baseline BMI ≥ 25 kg/m² at Week 24
- Change in SBP from baseline at Week 24

16.4.3.2.2. Analysis Methods

See Section [6.2.2](#) for description of the analysis methods.

16.4.3.3. Results of Analyses, Trial C-423

16.4.3.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics for Trial C-423 are summarized in [Table 146](#).

Demographic factors were generally balanced between the bexagliflozin 20 mg and sitagliptin 100 mg groups. Overall, the majority of subjects in the trial were male (64%), white (82%), and overweight or obese (89%). The median age was 61 years ranging from 23 to 83 years of age.

Baseline clinical characteristics were generally balanced between the bexagliflozin 20 mg and sitagliptin 100 mg groups.

Table 146. Baseline Demographic and Clinical Characteristics, ITT, Trial C-423

Characteristics	Bexagliflozin 20 mg N=191	Sitagliptin 100 mg N=193	Total N=384
Sex			
F	71 (37%)	67 (35%)	138 (36%)
M	120 (63%)	126 (65%)	246 (64%)
Age (years)			
Mean (SD)	59 (10)	60 (10)	59 (10)
Median (min, max)	61 (36, 79)	61 (23, 83)	61 (23, 83)
Age group			
Age <65 years	130 (68%)	129 (67%)	259 (67%)
Age ≥65	61 (32%)	64 (33%)	125 (33%)
Age ≥75 years	6 (3%)	8 (4%)	14 (4%)
Race			
American Indian or Alaska native			
Asian	27 (14%)	35 (18%)	62 (16%)
Black or African American	6 (3%)	2 (1%)	8 (2%)
White	158 (83%)	156 (81%)	314 (82%)
Ethnicity			
Hispanic or Latino	3 (2%)	7 (4%)	10 (3%)
Not Hispanic or Latino	188 (98%)	186 (96%)	374 (97%)
Geographic region			
Asia	27 (14%)	35 (18%)	62 (16%)
Europe	149 (78%)	137 (71%)	286 (74%)
North America	15 (8%)	21 (11%)	36 (9%)
Country			
Canada			
Czech Republic	16 (8%)	25 (13%)	41 (11%)
Spain	30 (16%)	45 (23%)	75 (20%)
Hungary	33 (17%)	23 (12%)	56 (15%)
Japan	27 (14%)	35 (18%)	62 (16%)
Poland	70 (37%)	44 (23%)	114 (30%)
United States	15 (8%)	21 (11%)	36 (9%)
BMI at baseline (kg/m ²)			
Mean (SD)	32.1 (6.1)	31.4 (5.3)	31.7 (5.7)
Median (min, max)	31.3 (20.5, 46.7)	30.5 (18.6, 44.9)	31.1 (18.6, 46.7)
BMI at baseline (kg/m ²) group			
Missing	NA	NA	NA
<25 kg/m ²	22 (12%)	19 (10%)	41 (11%)
≥25 kg/m ²	169 (88%)	174 (90%)	343 (89%)
Duration of diabetes (years)			
Mean (SD)	8.2 (5.7)	9.4 (5.7)	8.8 (5.7)
Median (min, max)	7.4 (0.2, 33.9)	8.8 (0.2, 29.8)	7.8 (0.2, 33.9)
Baseline HbA1c (%) mean			
Mean (SD)	7.9 (0.8)	8.0 (0.9)	8.0 (0.9)
Median (min, max)	7.7 (6.7, 10.3)	7.8 (6.3, 10.8)	7.7 (6.3, 10.8)
Baseline HbA1c (%) group			
<8.5%	144 (75%)	145 (75%)	289 (75%)
≥8.5%	47 (25%)	48 (25%)	95 (25%)
Baseline eGFR, mL/min/1.73 m ²			
Mean (SD)	88.7 (17.3)	87.1 (18.3)	87.9 (17.8)
Median (min, max)	87.5 (54.6, 163.6)	85.0 (48.3, 148.6)	86.4 (48.3, 163.6)

Characteristics	Bexagliflozin 20 mg N=191	Sitagliptin 100 mg N=193	Total N=384
Baseline eGFR group, mL/min/1.73 m ²			
≥45 to <60	7 (4%)	6 (3%)	13 (3%)
≥60 to <90	100 (52%)	106 (55%)	206 (54%)
≥90	84 (44%)	81 (42%)	165 (43%)
Baseline SBP, mm Hg			
Mean (SD)	135.0 (12.2)	135.7 (14.3)	135.3 (13.3)
Median (min, max)	136 (100, 168)	138 (92, 172)	136 (92, 172)
SBP group, mm Hg			
<140	121 (63%)	105 (54%)	226 (59%)
≥140	70 (37%)	88 (46%)	158 (41%)
Baseline DBP, mm Hg			
Mean (SD)	81.0 (7.5)	81.0 (8.7)	81.0 (8.1)
Median (min, max)	80 (62, 97)	80 (59, 110)	80 (59, 110)
Baseline FPG, mg/dL			
Mean (SD)	176 (41)	180 (47)	178 (45)
Median (min, max)	169 (94, 358)	173 (94, 349)	171 (94, 358)

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intention-to-treat; N, number of subjects in treatment group; SD: standard deviation; Min: minimum; Max: maximum; mm Hg: millimeter of mercury; SBP, systolic blood pressure.

Disposition

Subject screening and randomization information for Trial C-423 are summarized in [Table 147](#). About 69% of the subjects screened for participation entered the run-in period in the trial; among subjects who entered the run-in period, 98% passed the run-in period and were randomized into the double-blind phase of the trial.

Table 147. Subject Screening and Randomization, Trial C-423

Disposition	Screened (%)	Entered Run-In (%)
No. subjects consented to participate and completed the screening procedures	563 (100%)	
No. screening failures before run-in	168 (30%)	
No. subjects entered run-in period	395 (70%)	395 (100%)
No. screening failures after run-in	9 (2%)	9 (2%)
No. subjects randomized	386 (69%)	386 (98%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis populations and subject disposition information for Trial C-423 are summarized in [Table 148](#). Of 386 randomized subjects, 384 received at least one dose of sitagliptin (n=193), or bexagliflozin 20 mg (n=191). The ITT analysis population and the safety population coincide. Trial C-423 had a higher treatment completion rate compared with the other bexagliflozin pivotal studies with 94% of subjects completing study treatment. The sitagliptin group had a numerically higher treatment completion rate (97%) than the bexagliflozin group (94%). The most frequent reason for treatment discontinuation for the two arms was “subjects withdrew consent.” Study completion subject number (N=369) was close to the treatment completion subject number (N=368).

Table 148. Subject Disposition, ITT, Trial C-423

Completion Status/ Discontinuation Reason	Bexagliflozin 20 mg N=191	Sitagliptin 100 mg N=193	Total N=384
Analysis populations*			
Subjects randomized**	192 (100%)	194 (100%)	386 (100%)
ITT population	191 (99%)	193 (99%)	384 (99%)
Per protocol population	188 (98%)	191 (98%)	379 (98%)
Safety population	191 (99%)	193 (99%)	384 (99%)
Treatment completion			
Yes	180 (94%)	188 (97%)	368 (96%)
No	11 (6%)	5 (3%)	16 (4%)
Reason for discontinuation			
Adverse event: 1 and 2	1 (<1%)	0	1 (<1%)
Adverse event: itching of the vagina	1 (<1%)	0	1 (<1%)
Adverse event: polyuria ae	1 (<1%)	0	1 (<1%)
Adverse event: sigmoid adenocarcinoma	1 (<1%)	0	1 (<1%)
Adverse event: thyroid ophthalmopathy	0	1 (<1%)	1 (<1%)
Adverse event: vomiting	1 (<1%)	0	1 (<1%)
Adverse event: worsening of nephropathy	1 (<1%)	0	1 (<1%)
Other: insulin prescribed	0	1 (<1%)	1 (<1%)
Other: pregnancy	1 (<1%)	0	1 (<1%)
Subject lost to follow-up	0	1 (<1%)	1 (<1%)
Subject withdrew consent	4 (2%)	2 (1%)	6 (2%)
Study completion			
Yes	180 (94%)	189 (98%)	369 (96%)
No	11 (6%)	4 (2%)	15 (4%)
Reason for discontinuation			
Adverse event: 1 and 2	1 (<1%)	0	1 (<1%)
Adverse event: 1,2	1 (<1%)	0	1 (<1%)
Adverse event: itching of the vagina	1 (<1%)	0	1 (<1%)
Adverse event: polyuria ae	1 (<1%)	0	1 (<1%)
Adverse event: thyroid ophthalmopathy	0	1 (<1%)	1 (<1%)
Adverse event: worsening of nephropathy	1 (<1%)	0	1 (<1%)
Other: pregnancy	1 (<1%)	0	1 (<1%)
Subject died	1 (<1%)	0	1 (<1%)
Subject lost to follow-up	0	1 (<1%)	1 (<1%)
Subject withdrew consent	4 (2%)	2 (1%)	6 (2%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

** Two subjects from site 1271 in the US, one assigned to each of the two study arms, were excluded from the ITT and the safety populations due to site closure.

Abbreviation: ITT, modified intention-to-treat; N, number of subjects; n, number of subjects with at least one event

16.4.3.3.2. Primary Endpoint, and Key Secondary Efficacy Results

Primary Endpoint – Primary Analysis

[Table 149](#) summarizes the primary analysis results for C-423. At Week 24, 11 (5.8%) and 3 (1.6%) subjects in bexagliflozin 20 mg group and sitagliptin 100 mg group, respectively, had missing data. A return-to-baseline approach multiple imputation analysis method was used for missing data handling. For lowering of HbA1c at 24 weeks, bexagliflozin 20 mg was noninferior to sitagliptin 100 mg (adjusted mean difference 0.08% [95% CI: -0.06, 0.22]).

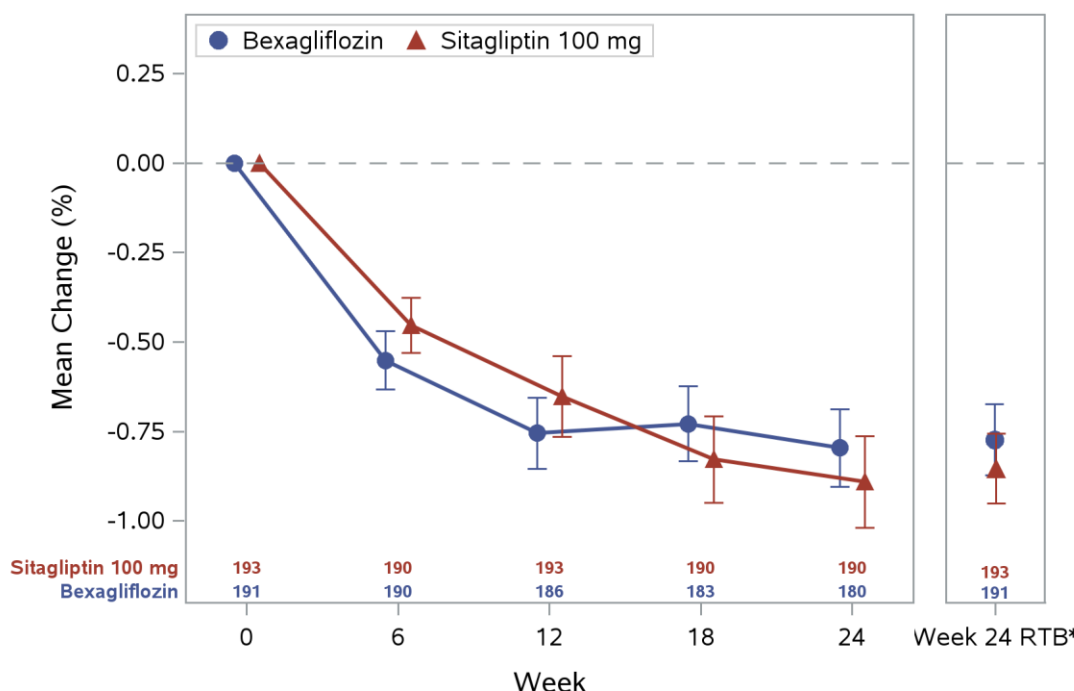
Also based on the multiply imputed HbA1c (%) values at Week 24, a responder defined as reaching the treatment goal of glycemic control (HbA1c (%) <7%) was derived. Seventy-seven (40.3%) subjects reached the treatment goal of glycemic control in the bexagliflozin 20 mg group versus 87 (45.1%) subjects in the sitagliptin 100 mg group. Logistic regression model adjusted proportions of responders were 36.4% and 44.5% for bexagliflozin 20 mg group and the sitagliptin 100 mg group, respectively.

[Figure 55](#) displays the mean change from baseline in HbA1c (%) over 24 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 24 is plotted separately.

In addition, the one-dimensional tipping point sensitivity analysis results ([Table 186](#)) show that at the null hypothesis imputation (i.e., a penalty of size 0.35% applied to the bexagliflozin arm missing data), the primary analysis conclusion is not changed; and only under the implausible situation, a penalty of size 1.75 applied to the bexagliflozin arm missing data, is the tipping point reached.

Figure 55. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423

C-423 Mean Change from Baseline in HbA1c (%) by Time and Treatment



Note: Vertical lines represent 95% confidence intervals. *The return-to-baseline multiply imputed data was analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c at Week 24 was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c ; ITT, intention-to-treat

Table 149. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-423

Characteristics	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Number of subjects	191	193
Number (%) of values imputed for Week 24	11 (5.8)	3 (1.6)
Baseline		
Mean (SD)	7.94 (0.808)	8.03 (0.921)
Median	7.70	7.80
Q1, Q3	7.30, 8.40	7.40, 8.40
Minimum, maximum	6.7, 10.3	6.3, 10.8
Week 24 (observed)		
Mean (SD)	7.13 (0.682)	7.15 (0.840)
Median	7.00	7.10
Q1, Q3	6.75, 7.50	6.60, 7.60
Minimum, maximum	5.1, 9.5	5.1, 9.8

Characteristics	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Model-adjusted change from baseline		
LS mean (SE)	-0.77 (0.051)	-0.85 (0.050)
95% confidence interval	(-0.87, -0.67)	(-0.95, -0.76)
Difference from sitagliptin 100 mg		
Difference of LS means	0.08	
95% confidence interval	(-0.06, 0.22)	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count and proportion [N (%)] ^[1]	77 (40.3)	87 (45.1)
Model based proportion ^[2]	36.4	44.5

Source: FDA statistical reviewer

^[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

^[2] Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Key Secondary Endpoints – Primary Analysis

[Table 150](#) summarizes changes from baseline in prespecified key secondary efficacy endpoints at Week 24. According to the preplanned hierarchical testing procedure, since bexagliflozin failed the significance test in change from baseline in FPG at Week 24 with a one-sided p-value greater than 0.025, the subsequent individual tests on body mass and SBP could only be described as summary statistics (thus, nominal p-values removed). More detailed analysis results for these three endpoints are located in Section [16.5.3](#).

Table 150. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-423

Endpoints	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Change from baseline in FPG at Week 24		
Number of subjects	191	193
Number (%) of values imputed for Week 24	11 (5.8)	3 (1.6)
Model-adjusted change from baseline		
LS mean (SE)	31 (2.2)	26 (2.2)
95% Confidence Interval	(-35, -26)	(-30, -21)
Difference from sitagliptin 100 mg		
Difference of LS means	-5	
95% confidence interval	(-11, 1)	
One-sided p-value	0.0494	
Change from baseline in body mass at Week 24		
Number of subjects	169	174
Number (%) of values imputed for Week 24	11 (6.5)	3 (1.7)
Difference from sitagliptin 100 mg		
Difference of LS means	-2.25	
95% confidence interval	(-2.88, -1.62)	
Change from baseline in SBP at Week 24		
Number of subjects	191	193
Number (%) of values imputed for Week 24	11 (5.8)	3 (1.6)
Model-adjusted change from baseline		
LS mean (SE)	-3.82 (0.864)	-1.55 (0.846)
95% confidence interval	(-5.52, -2.13)	(-3.21, 0.11)

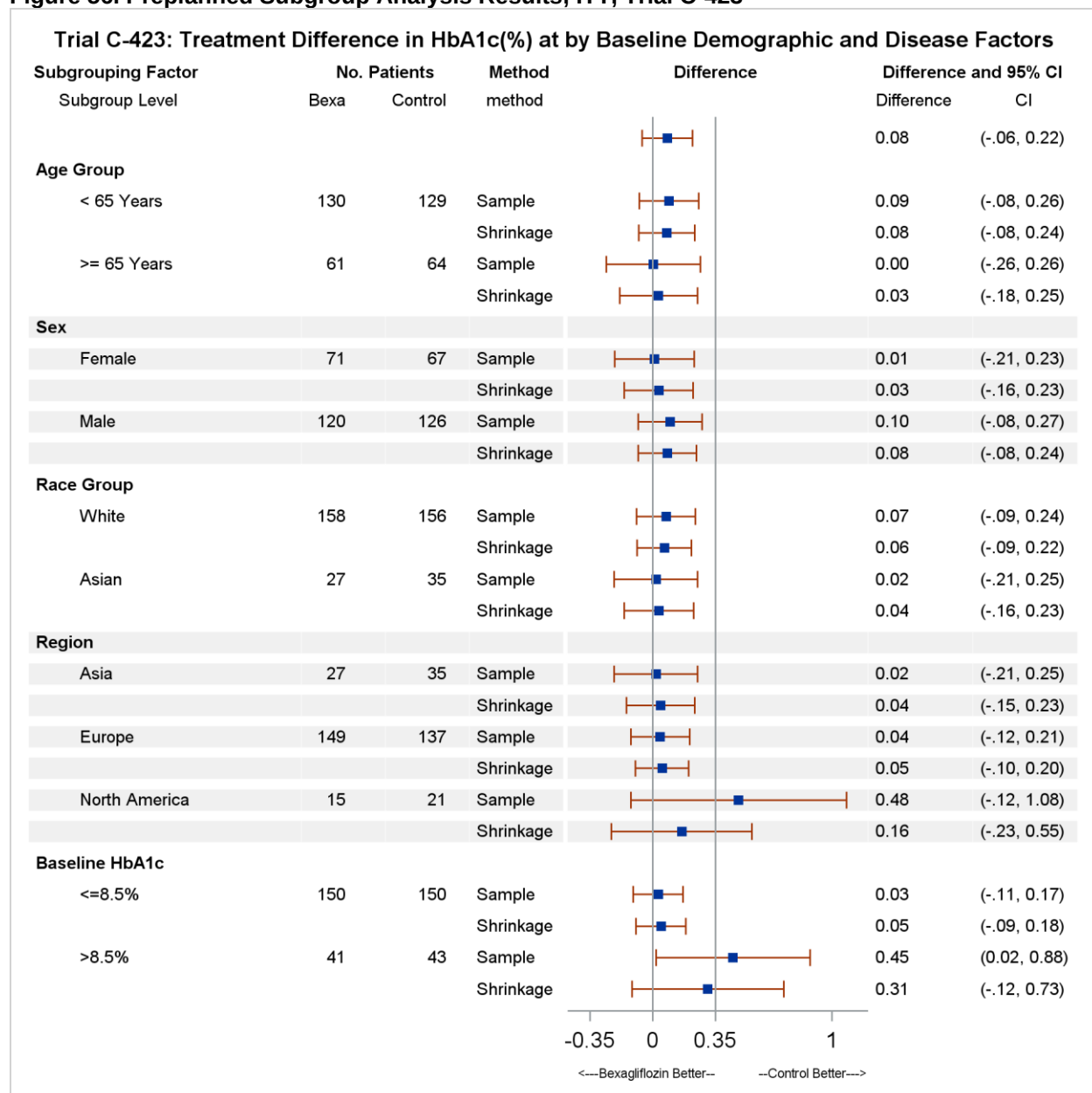
	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Endpoints		
Difference from sitagliptin 100 mg		
Difference of LS means	-2.27	
95% confidence interval	(-4.65, 0.10)	

Source: FDA statistical reviewer
Abbreviation: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; SD, standard deviation; SE, standard error; Q, quartile; SBP, systolic blood pressure.

16.4.3.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses showed that the HbA1c lowering effect was consistent across subgroups ([Figure 56](#)). All subgroups showed generally similar trend to the overall population results except small sample sized subgroups with larger variability.

Figure 56. Preplanned Subgroup Analysis Results, ITT, Trial C-423



Source: FDA statistical reviewer

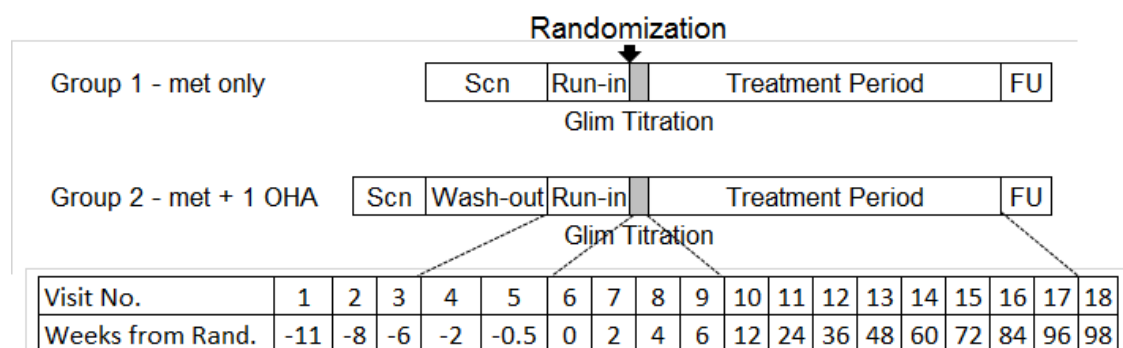
Abbreviation: Bexa, bexagliflozin; HbA1c, hemoglobin A1c; ITT, intention-to-treat; No, number of; CI, confidence interval.

16.4.4. Trial C-480

16.4.4.1. Design, Trial C-480

Trial C-480 was a phase 3, multicenter, randomized, double-blind, parallel-group study. It was designed to evaluate the hypothesis that bexagliflozin would be noninferior to glimepiride as a therapy added to metformin in subjects with disease inadequately controlled by metformin alone or by metformin plus one other OHA (see [Figure 57](#) for study design).

Figure 57. Study Plan, Trial C-480



Source: Applicant's Trial C-480 Clinical Study Report, Figure 1.

Abbreviations: met: metformin, OHA: oral hypoglycemic agent, Glim: glimepiride, FU: follow- up, SCN: screening, Rand: randomization

Treatment Duration

Different from the other five pivotal trials, both the primary endpoint and key secondary efficacy endpoints were assessed at Week 60.

Noninferiority Margin Selection

The Applicant provided the following justifications for this noninferiority margin selection:

According to FDA Guidance for Industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016), the noninferiority margin, M2, reflects the largest loss of effect that would be clinically acceptable (Section III.C.). M2 is generally accepted to be 50% of M1, or the entire effect of the active control versus placebo as seen in historical placebo-controlled trials and is assumed to be present in the noninferiority study. A double-blind, double-dummy, parallel group study with a similar study design as Trial C-480 showed subjects taking 6 mg glimepiride as an add-on to metformin for 8 weeks after a 12 week up-titration period had HbA1c values - 0.81% compared to placebo (Charpentier et al. 2001). Fifty percent of the total effect size of the placebo-controlled study is 0.41%. Based on these historical data, a noninferiority margin of 0.41% could be justified. The proposed 0.35% is a conservative and reasonable M2 noninferiority margin that represents a clinically acceptable loss of effect to demonstrate noninferiority.

Also, in justification for the noninferiority margin selection in C-423, the Applicant referred to FDA's Draft Guidance for Industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (March 2008). The guidance states, "Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials."

While the reviewer considers the noninferiority margin selection of 0.35% to be in accordance with FDA Guidance, the reviewer has one concern with the accuracy of the Applicant's quoted M1 estimate, 0.81%. In Charpentier 2001, the description was:

...Combination treatment was significantly more efficient in reducing HbA1c levels than either glimepiride alone (difference in mean change 1.04%, 95% CI

0.81 to 1.27%; $P < 0.001$) or metformin alone (difference in mean change 0.92%, 95% CI 0.63 to 1.21%; $P < 0.001$). ...

Since the primary comparison in C-480 is between bexagliflozin + metformin and glimepiride + metformin, this reviewer considers a proper reference effect size estimate should be the lower bound 0.63% of the 95% CI for the treatment effect of (glimepiride + metformin) versus metformin from the reference paper (Charpentier et al. 2001). Since 50% of 0.63% is 0.315%, while slightly lower than the selected 0.35%, it is still a reasonable choice. So, we have no further concern on this issue.

16.4.4.2. Statistical Analysis Plan, Trial C-480

16.4.4.2.1. Efficacy Endpoints

The primary and key secondary endpoints listed in this subsection are shown in the study prespecified hierarchical testing sequence.

Primary Endpoint

- Noninferiority in change from baseline in HbA1c at Week 60

Key Secondary Endpoints:

Superiority in the following endpoints in the listed order.

- Change from baseline to Week 60 in body weight in subjects with baseline BMI ≥ 25 kg/m²
- Change from baseline to Week 60 in SBP in subjects with baseline SBP ≥ 140 mm Hg
- Difference in proportion of subjects with ≥ 1 severe or documented symptomatic hypoglycemia events over 96 weeks
- Change from baseline to Week 60 in HbA1c

16.4.4.2.2. Analysis Methods

See Section [6.2.2](#) for description of the analysis methods.

16.4.4.3. Results of Analyses, Trial C-480

16.4.4.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics for Trial C-480 are summarized in [Table 151](#). Demographic and disease factors were generally balanced between the bexagliflozin 20 mg and the glimepiride groups.

Table 151. Baseline Demographic and Clinical Characteristics, ITT, Trial C-480

Characteristics	Bexagliflozin 20 mg N=213	Glimepiride N=213	Total N=426
Sex			
F	95 (45%)	83 (39%)	178 (42%)
M	118 (55%)	130 (61%)	248 (58%)
Age (years)			
Mean (SD)	59 (9)	60 (10)	60 (10)
Median (min, max)	61 (33, 87)	60 (28, 86)	60 (28, 87)
Age group			
Age <65 years	150 (70%)	146 (69%)	296 (69%)
Age ≥65 years	63 (30%)	67 (31%)	130 (31%)
Age ≥75 years	7 (3%)	16 (8%)	23 (5%)
Race			
American Indian or Alaska native			
Asian	9 (4%)	4 (2%)	13 (3%)
Black or African American	5 (2%)	4 (2%)	9 (2%)
Multiple			
Native Hawaiian or other Pacific Islander	1 (<1%)	0	1 (<1%)
Other	0	1 (<1%)	1 (<1%)
White	198 (93%)	204 (96%)	402 (94%)
Ethnicity			
Hispanic or Latino	46 (22%)	47 (22%)	93 (22%)
Not Hispanic or Latino	167 (78%)	166 (78%)	333 (78%)
Geographic region			
Europe	148 (69%)	150 (70%)	298 (70%)
North America	65 (31%)	63 (30%)	128 (30%)
Germany	28 (13%)	29 (14%)	57 (13%)
Poland	74 (35%)	79 (37%)	153 (36%)
Spain	46 (22%)	42 (20%)	88 (21%)
United States	65 (31%)	63 (30%)	128 (30%)
BMI at baseline (kg/m ²)			
Mean (SD)	31.4 (4.9)	32.2 (5.2)	31.8 (5.0)
Median (min, max)	31.1 (18.3, 44.5)	31.5 (19.8, 46.3)	31.3 (18.3, 46.3)
BMI at baseline (kg/m ²) group			
Missing	NA	NA	NA
<25 kg/m ²	12 (6%)	11 (5%)	23 (5%)
≥25 kg/m ²	201 (94%)	202 (95%)	403 (95%)
Duration of diabetes (years)			
Mean (SD)	9.3 (5.9)	8.0 (5.5)	8.7 (5.8)
Median (min, max)	8.5 (0.3, 32.9)	6.9 (0.2, 32.3)	7.4 (0.2, 32.9)
Baseline HbA1c (%) mean			
Mean (SD)	8.0 (0.8)	8.0 (0.7)	8.0 (0.7)
Median (min, max)	7.9 (6.7, 10.5)	7.9 (6.2, 10.1)	7.9 (6.2, 10.5)
Baseline HbA1c (%) group			
<8.5%	155 (73%)	159 (75%)	314 (74%)
≥8.5%	58 (27%)	54 (25%)	112 (26%)
Baseline eGFR, mL/min/1.73 m ²			
N (nonmissing)	213	211	424
Mean (SD)	91.8 (17.9)	91.1 (18.2)	91.4 (18.0)
Median (min, max)	90 (55, 146)	89 (53, 163)	90 (53, 163)

Characteristics	Bexagliflozin 20 mg N=213	Glimepiride N=213	Total N=426
Baseline eGFR group, mL/min/1.73 m ²			
Missing	0 (0)	2 (<1%)	2 (<1%)
≥45 to <60	6 (3%)	6 (3%)	12 (3%)
≥60 to <90	99 (46%)	103 (48%)	202 (47%)
≥90	108 (51%)	102 (48%)	210 (49%)
Baseline SBP, mm Hg			
Mean (SD)	133.3 (14.9)	134.2 (14.4)	133.8 (14.6)
Median (min, max)	133 (94, 185)	134 (91, 196)	134 (91, 196)
SBP group, mm Hg			
<140	135 (63%)	138 (65%)	273 (64%)
≥140	78 (37%)	75 (35%)	153 (36%)
Baseline DBP, mm Hg			
Mean (SD)	79.5 (9.4)	80.4 (8.5)	79.9 (9.0)
Median (min, max)	81 (51, 109)	80 (55, 109)	81 (51, 109)
Baseline FPG, mg/dL			
Mean (SD)	173 (34)	175 (40)	173 (36)
Median (min, max)	169 (90, 286)	166 (88, 376)	167 (88, 376)

Source: FDA statistical reviewer

Note: Two subjects: subject ID 480- (b) (6) and subject ID 480- (b) (6) had baseline GFR values missing.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intention-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SBP, systolic blood pressure.

Disposition

Subject disposition information for Trial C-480 is summarized in [Table 152](#) and [Table 153](#).

About 66% of the subjects screened for participation entered the run-in period in the trial; among subjects who entered the run-in period, 79% passed the run-in period and were randomized into the double-blind phase. Compared with the other pivotal trials, the eligibility criteria were more stringent as reflected by the fact that C-480 had the highest rate of screening failures after run-in (21%).

Table 152. Subject Screening and Randomization, Trial C-480

Disposition	Screened (%)	Entered Run-In (%)
No. subjects consented to participate and completed the screening procedures	812 (100%)	
No. screening failures before run-in	273 (34%)	
No. subjects entered run-in period	539 (66%)	539 (100%)
No. screening failures after run-in	112 (14%)	112 (21%)
No. subjects randomized	427 (53%)	426 (79%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis population and subject disposition information for Trial C-480 are summarized in [Table 153](#). Overall, 81% of the subjects completed study treatment; the bexagliflozin group had a numerically higher treatment completion rate (82%) than the active control arm (80%). The most frequent reasons for treatment discontinuation were similar in the two treatment groups: “subjects withdrew consent”, “subjects lost to follow-up” and “adverse events.” The overall study completion rate (84%) was slightly higher than the treatment completion rate (81%).

Table 153. Subject Disposition, ITT, Trial C-480

Completion Status/ Discontinuation Reason	Bexagliflozin 20 mg N=213	Glimepiride N=213	Total N=426
Analysis populations*			
Subjects randomized	214 (100%)	213 (100%)	427 (100%)
ITT population	213 (100%)	213 (100%)	426 (100%)
Per protocol population	196 (92%)	194 (91%)	390 (91%)
Safety population	213 (100%)	213 (100%)	426 (100%)
Treatment completion			
Yes	175 (82%)	171 (80%)	346 (81%)
No	38 (18%)	42 (20%)	80 (19%)
Reason for discontinuation			
Adverse event	8 (4%)	10 (5%)	18 (4%)
Other	5 (2%)	3 (1%)	8 (2%)
Protocol violation	1 (<1%)	2 (<1%)	3 (<1%)
Study terminated by investigator	0	2 (<1%)	2 (<1%)
Study terminated by Sponsor	1 (<1%)	0	1 (<1%)
Subject died	0	1 (<1%)	1 (<1%)
Subject lost to follow-up	9 (4%)	8 (4%)	17 (4%)
Subject withdrew consent	14 (7%)	16 (8%)	30 (7%)
Study completion at Week 96			
Yes	180 (85%)	177 (83%)	357 (84%)
No	33 (15%)	36 (17%)	69 (16%)
Reason for discontinuation			
Adverse event	3 (1%)	6 (3%)	9 (2%)
Entry criteria not met	1 (<1%)	2 (<1%)	3 (<1%)
Other	4 (2%)	1 (<1%)	5 (1%)
Protocol violation	1 (<1%)	0	1 (<1%)
Study terminated by investigator	0	1 (<1%)	1 (<1%)
Study terminated by Sponsor	1 (<1%)	0	1 (<1%)
Subject died	0	1 (<1%)	1 (<1%)
Subject lost to follow-up	9 (4%)	9 (4%)	18 (4%)
Subject withdrew consent	14 (7%)	16 (8%)	30 (7%)
Study completion at Week 60			
Yes	193 (91%)	192 (90%)	385 (90%)
No	20 (9%)	21 (10%)	41 (10%)
Adverse event	2 (<1%)	5 (2%)	7 (2%)
Entry criteria not met	1 (<1%)	2 (<1%)	3 (<1%)
Protocol violation	1 (<1%)	0	1 (<1%)
Subject lost to follow-up	6 (3%)	5 (2%)	11 (3%)
Subject withdrew consent	10 (5%)	9 (4%)	19 (4%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

** A randomized subject, subject 480- (b) (6) from site (b) (6) in the US was excluded from the intention-to-treat (ITT) and safety populations for misconduct.

Abbreviations: ITT, intention-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

16.4.4.3.2. Primary Endpoint and Key Secondary Efficacy Results

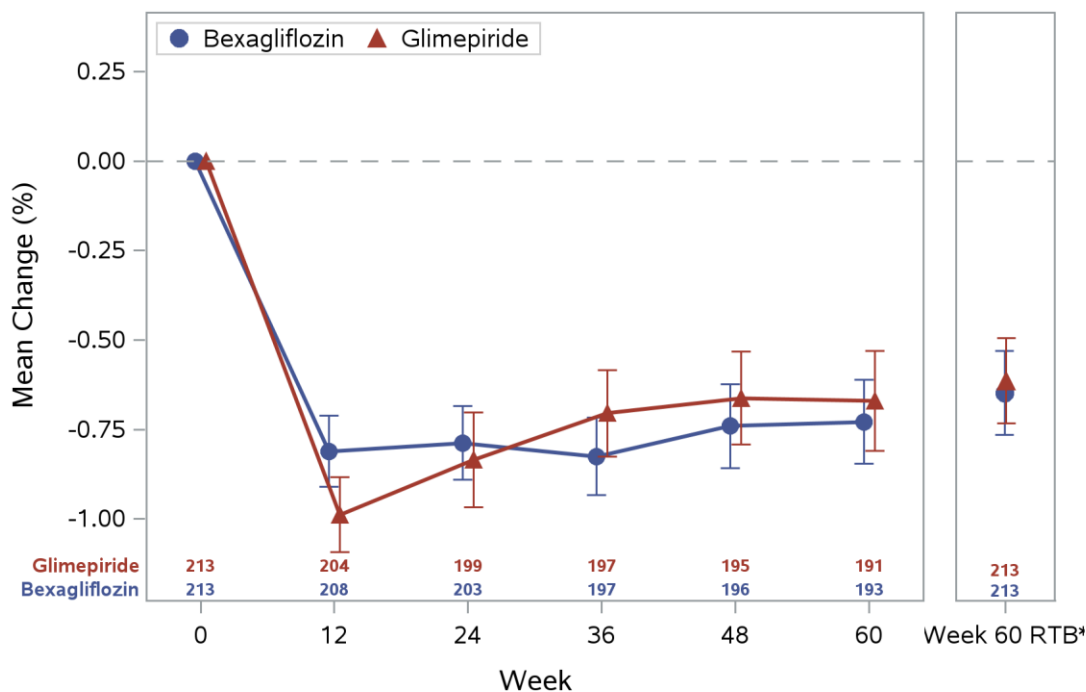
Primary Endpoint – Primary Analysis

[Table 154](#) summarizes the primary analysis results for C-480. Twenty (9.4%) and 22 (10.3%) subjects in the bexagliflozin 20 mg group and glimepiride group, respectively, had missing HbA1c data at Week 60. For lowering of HbA1c at 60 weeks, bexagliflozin 20 mg was noninferior to glimepiride (adjusted mean difference 0.03% [95% CI –0.20 to 0.13]).

[Figure 58](#) displays the mean change from baseline in HbA1c (%) over 60 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 60 is plotted separately.

Figure 58. Change From Baseline in HbA1c (%) by Time and Treatment and Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480

C-480 Mean Change from Baseline in HbA1c (%) by Time and Treatment



Note: Vertical lines represent 95% confidence intervals. *The return-to-baseline multiply imputed data was analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c at Week 60 was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c ; ITT, intention-to-treat

In addition, the one-dimensional tipping point sensitivity analysis results ([Table 187](#)) show that at the null hypothesis imputation (i.e., a penalty of size 0.35% applied to the bexagliflozin arm missing data), the primary analysis conclusion is not changed; and only under the implausible

situation, a penalty of about 2.45 applied to the bexagliflozin arm missing data, is the tipping point reached.

Table 154. Change From Baseline in HbA1c (%) at Week 60 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-480

Characteristic	Bexagliflozin 20 mg (N=213)	Glimepiride (N=213)
Number of subjects	213	213
Number (%) of values imputed for Week 60	20 (9.4)	22 (10.3)
Baseline		
Mean (SD)	8.04 (0.771)	7.98 (0.701)
Median	7.90	7.90
Q1, Q3	7.40, 8.50	7.40, 8.50
Minimum, maximum	6.7, 10.5	6.2, 10.1
Week 60 (Observed)		
Mean (SD)	7.31 (0.866)	7.34 (0.959)
Median	7.20	7.30
Q1, Q3	6.80, 7.70	6.60, 8.00
Minimum, Maximum	5.3, 10.0	4.9, 10.4
Model-adjusted change from baseline		
LS mean (SE)	-0.65 (0.060)	-0.61 (0.061)
95% confidence interval	(-0.77, -0.53)	(-0.73, -0.50)
Difference from placebo		
Difference of LS means	-0.03	
95% confidence interval	(-0.20, 0.13)	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count and proportion [N (%)] ^[1]	74 (34.7)	71 (33.3)
Model based proportion ^[2]	32.3	30.1

Source: FDA statistical reviewer

^[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

^[2] Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Also based on the multiply imputed HbA1c (%) values at Week 60, a responder defined as reaching the treatment goal of glycemic control (HbA1c (%) <7%) was derived. The logistic regression model adjusted proportions were 32.3% and 30.1% for the bexagliflozin 20 mg group and the glimepiride group, respectively.

Key Secondary Endpoints – Primary Analysis

[Table 155](#) summarizes changes from baseline in the prespecified key secondary efficacy endpoints at Week 60. Compared with glimepiride, bexagliflozin significantly decreased body mass and SBP at Week 60 ($p < 0.0001$, and $p < 0.0006$, respectively). More detailed analysis results for these two endpoints and FPG are located in Section [16.5.4](#).

Table 155. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 60, ITT , Return-to-Baseline Multiple Imputation, Trial C-480

Endpoints	Bexagliflozin 20 mg	Glimepiride
Change from baseline in body mass at Week 60 baseline BMI ≥25 kg/m ² subgroup		
Number of subjects	201	202
Number (%) of values imputed for Week 24	19 (9.5)	20 (9.9)
Model-adjusted change from baseline		
LS mean (SE)	-3.44 (0.288)	0.58 (0.292)
95% confidence interval	(-4.00, -2.87)	(0.01, 1.15)
Difference from glimepiride		
Difference of LS means	-4.01	
95% confidence interval	(-4.82, -3.21)	
One-sided p-value	<0.0001	
Change from baseline in SBP at Week 60 baseline SBP ≥140 mm Hg subgroup		
Number of subjects	78	75
Number (%) of values imputed for Week 24	4 (5.1)	7 (9.3)
Model-adjusted change from baseline		
LS mean (SE)	-12.99 (1.445)	-6.24 (1.483)
95% confidence interval	(-15.83, -10.16)	(-9.15, -3.34)
Difference from glimepiride		
Difference of LS means	-6.75	
95% confidence interval	(-10.83, -2.67)	
One-sided p-value	0.0006	

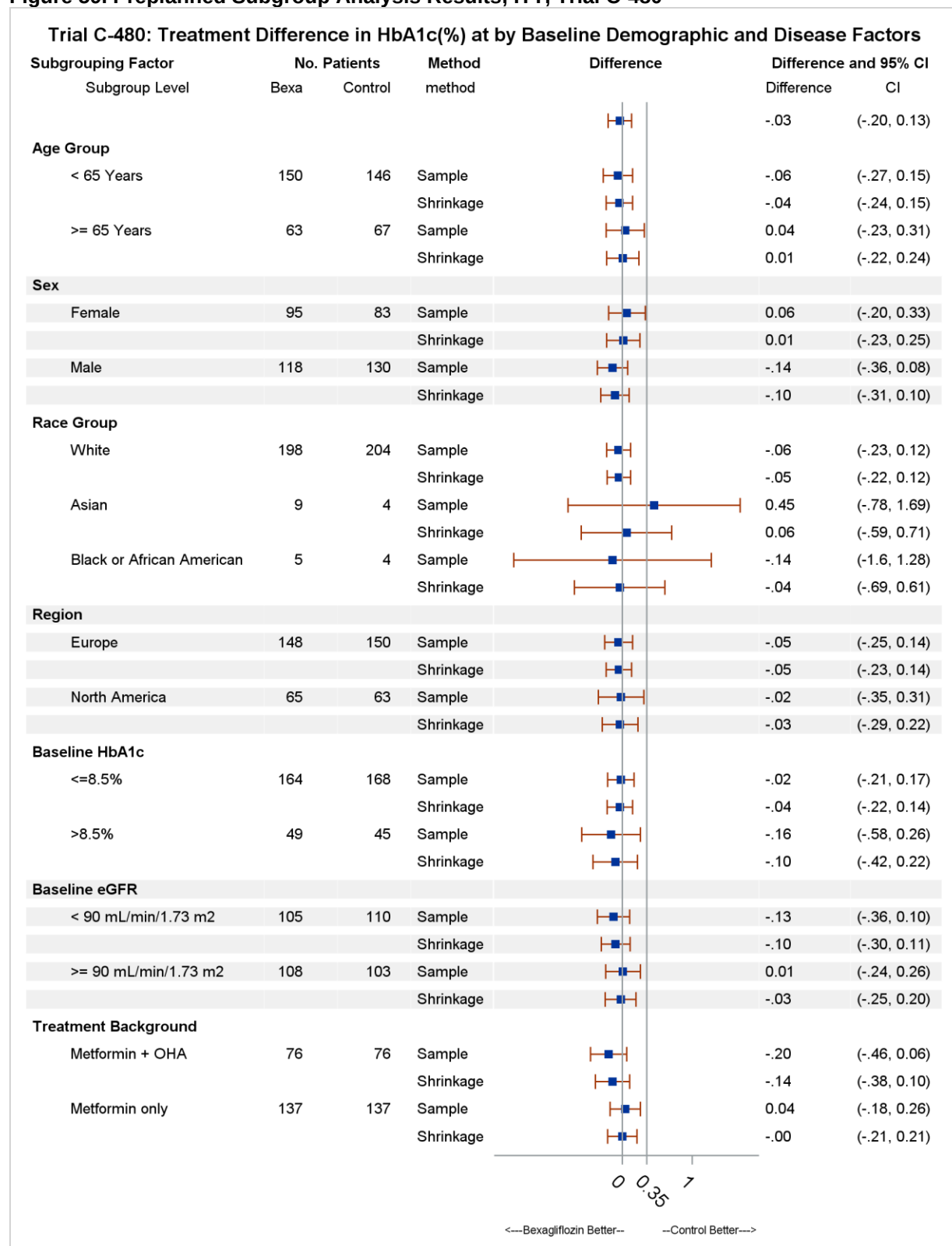
Source: FDA statistical reviewer

Abbreviation: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

16.4.4.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses showed that the HbA1c lowering effect was consistent across subgroup levels ([Figure 59](#)).

Figure 59. Preplanned Subgroup Analysis Results, ITT, Trial C-480



Source: FDA statistical reviewer

Abbreviation: Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ITT, intention-to-treat; No, number of; OHA, oral hypoglycemic agent.

16.4.5. Trial C-448

16.4.5.1. Design, Trial C-448

The primary objective is to determine the efficacy of bexagliflozin on lowering HbA1c in subjects with T2DM and moderate renal impairment after 24 weeks of treatment.

16.4.5.2. Statistical Analysis Plan, Trial C-448

16.4.5.2.1. Efficacy Endpoints

The primary and key secondary endpoints listed in this subsection are shown in the study prespecified hierarchical testing sequence.

Primary Endpoint

- Change from baseline in HbA1c at Week 24

Key Secondary Endpoints

- Change from baseline to Week 24 in body weight in subjects with baseline BMI ≥ 25 kg/m²
- Change from baseline to Week 24 in SBP in subjects with baseline SBP ≥ 130 mm Hg from baseline
- Change from baseline to Week 24 in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m²
- Change from baseline to Week 24 in HbA1c in subjects with eGFR 30 to 44 mL/min/1.73 m²

16.4.5.2.2. Analysis Methods

See Section [6.2.2](#) for description of the analysis methods.

16.4.5.3. Results of Analyses, Trial C-448

16.4.5.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics for Trial C-448 are summarized in [Table 156](#).

Compared with other trials in the bexagliflozin for T2DM program, Trial C-448's subject population was in general older in age: the median age was 70 years ranging from 39 to 88 years of age; 76% of the total population were 65 years of age or older. Overall, the majority of subjects in the trial were overweight or obese (79% of the population had a baseline BMI

≥25 kg/m²). There were more male (63%) than female subjects (37%). The demographic factors were generally balanced between the bexagliflozin 20 mg and the placebo groups.

Baseline clinical characteristics were generally balanced between the bexagliflozin 20 mg and the placebo groups.

Table 156. Baseline Demographic and Clinical Characteristics, ITT, Trial C-448

Characteristics	Bexagliflozin 20 mg N=157	Placebo N=155	Total N=312
Sex			
F	65 (41%)	51 (33%)	116 (37%)
M	92 (59%)	104 (67%)	196 (63%)
Age (years)			
Mean (SD)	69 (8)	70 (8)	70 (8)
Median (min, max)	70 (39, 88)	70 (47, 85)	70 (39, 88)
Age group			
Age <65 years	38 (24%)	37 (24%)	75 (24%)
Age ≥65	119 (76%)	118 (76%)	237 (76%)
Age ≥75 years	40 (25%)	50 (32%)	90 (29%)
Race			
Asian	61 (39%)	59 (38%)	120 (38%)
Black or African American	9 (6%)	6 (4%)	15 (5%)
Native Hawaiian or Other Pacific Islander	2 (1%)	0	2 (<1%)
Other	2 (1%)	2 (1%)	4 (1%)
White	83 (53%)	88 (57%)	171 (55%)
Ethnicity			
Hispanic or Latino	7 (4%)	17 (11%)	24 (8%)
Not Hispanic or Latino	149 (95%)	138 (89%)	287 (92%)
Not reported	1 (<1%)	0	1 (<1%)
Country			
France	12 (8%)	16 (10%)	28 (9%)
Japan	58 (37%)	58 (37%)	116 (37%)
Spain	34 (22%)	31 (20%)	65 (21%)
United States	53 (34%)	50 (32%)	103 (33%)
Geographic region			
Asia	58 (37%)	58 (37%)	116 (37%)
Europe	46 (29%)	47 (30%)	93 (30%)
North America	53 (34%)	50 (32%)	103 (33%)
BMI at baseline (kg/m ²)			
Mean (SD)	30.3 (6.0)	30.1 (5.8)	30.2 (5.9)
Median (min, max)	29.5 (19.0, 44.9)	28.8 (20.1, 44.6)	29.3 (19.0, 44.9)
BMI at baseline (kg/m ²) group			
<25 kg/m ²	32 (20%)	33 (21%)	65 (21%)
≥25 kg/m ²	125 (80%)	122 (79%)	247 (79%)
Duration of diabetes (years)			
Mean (SD)	15.5 (9.2)	16.3 (9.0)	15.9 (9.1)
Median (min, max)	15.2 (0.0, 50.2)	17.0 (0.0, 47.3)	16.2 (0.0, 50.2)
Baseline insulin, n (%)			
Insulin treated	86 (55%)	88 (57%)	174 (56%)
Not insulin treated	71 (45%)	67 (43%)	138 (44%)
Baseline HbA1c (%) mean			
Mean (SD)	8.0 (0.8)	7.9 (0.8)	8.0 (0.8)
Median (min, max)	7.8 (6.7, 10.4)	7.8 (5.9, 10.4)	7.8 (5.9, 10.4)

Characteristics	Bexagliflozin 20 mg N=157	Placebo N=155	Total N=312
Baseline HbA1c (%) group			
≤8.5%	124 (79%)	123 (79%)	247 (79%)
8.6 - 10.5%	33 (21%)	32 (21%)	65 (21%)
Baseline eGFR, mL/min/1.73 m ²			
Mean (SD)	45.4 (8.6)	44.8 (8.1)	45.1 (8.3)
Median (min, max)	46.3 (26.3, 73.3)	45.0 (25.7, 63.9)	45.6 (25.7, 73.3)
Baseline eGFR group, mL/min/1.73 m ²			
<45	71 (45%)	75 (48%)	146 (47%)
≥45	86 (55%)	80 (52%)	166 (53%)
Baseline eGFR group, mL/min/1.73 m ²			
<30	3 (2%)	4 (3%)	7 (2%)
≥30 to <45	70 (45%)	73 (47%)	143 (46%)
≥45 to <60	77 (49%)	74 (48%)	151 (48%)
≥60 to <90	7 (4%)	4 (3%)	11 (4%)
Baseline SBP, mm Hg			
Mean (SD)	135.9 (14.2)	137.6 (14.7)	136.8 (14.5)
Median (min, max)	136 (106, 174)	139 (101, 170)	137 (101, 174)
SBP group, mm Hg			
<130 mm Hg	50 (32%)	42 (27%)	92 (29%)
≥130 mm Hg	107 (68%)	113 (73%)	220 (71%)
Baseline DBP, mm Hg			
Mean (SD)	75.5 (10.0)	75.2 (10.0)	75.4 (10.0)
Median (min, max)	75 (52, 100)	75 (50, 110)	75 (50, 110)
Baseline FPG, mg/dL			
Mean (SD)	155(45)	155 (40)	155(43)
Median (min, max)	151 (68, 324)	151 (52, 281)	151(52,324)

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intention-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SBP, systolic blood pressure.

Disposition

Subject screening and randomization information for Trial C-448 are summarized in [Table 157](#). About 64% of the subjects screened for participation entered the run-in period in the trial; among subjects who entered the run-in period, 99% passed the run-in period and were randomized into the double-blind phase of the trial.

Table 157. Subject Screening and Randomization, Trial C-448

Disposition	Screened (%)	Entered Run-in (%)
No. subjects consented to participate and completed the screening procedures	490 (100%)	
No. screening failures before run-in	176 (36%)	
No. subjects entered run-in period	314 (64%)	314 (100%)
No. screening failures after run-in	2 (<1%)	2 (<1%)
No. subjects randomized	312 (64%)	312 (99%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis populations and subject disposition information for Trial C-448 are summarized in [Table 158](#). All 312 randomized subjects received at least one dose of bexagliflozin 20 mg (n=157), or placebo (n=155). The ITT analysis population and the safety population coincide.

Overall, Trial C-448 had a relatively high treatment completion rate (92%) among the bexagliflozin pivotal studies: 94% of the subjects completed study treatment; the bexagliflozin 20 mg group had a higher treatment completion rate (94%) than the placebo group (90%). Adverse event was the most frequent reason for treatment discontinuation for both treatment groups. Compared with treatment completion rate, the study completion rate was 3% higher.

Table 158. Subject Disposition, ITT, Trial C-448

Completion Status/ Discontinuation Reason	Bexagliflozin 20 mg N=157	Placebo N=155	Total N=312
Analysis populations*			
Subjects randomized	157 (100%)	155 (100%)	312 (100%)
ITT/ population	157 (100%)	155 (100%)	312 (100%)
Per protocol population	154 (98%)	150 (97%)	304 (97%)
Safety population	157 (100%)	155 (100%)	312 (100%)
Treatment completion			
Yes	147 (94%)	140 (90%)	287 (92%)
No	10 (6%)	15 (10%)	25 (8%)
Reason for discontinuation			
Adverse event	4 (2%)	7 (4%)	11 (4%)
Other	3 (%)	1 (<1%)	4 (1%)
Protocol violation: diabetes type 1	0	1 (<1%)	1 (<1%)
Study terminated by investigator: rib fracture	0	1 (<1%)	1 (<1%)
Subject lost to follow-up	1 (<1%)	3 (2%)	4 (1%)
Subject withdrew consent	2 (1%)	2 (1%)	4 (1%)
Study completion			
Yes	152 (97%)	144 (93%)	296 (95%)
No	5 (3%)	11 (7%)	16 (5%)
Reason for discontinuation			
Adverse event	1 (<1%)	4 (3%)	5 (2%)
Other	1 (<1%)	0	1 (<1%)
Protocol violation	0	1 (<1%)	1 (<1%)
Study terminated by investigator	0	1 (<1%)	1 (<1%)
Subject lost to follow-up	1 (<1%)	3 (2%)	4 (1%)
Subject withdrew consent	2 (1%)	2 (1%)	4 (1%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

Abbreviations: N, number of subjects in treatment group; n, number of subjects with given characteristic.

16.4.5.3.2. Primary Endpoint and Key Secondary Efficacy Results

Primary Endpoint – Primary Analysis

[Table 159](#) summarizes the primary analysis results for C-448. Five (3.2%) and seven (4.5%) subjects in the Bexagliflozin 20 mg group and the placebo group, respectively, had missing HbA1c data at Week 24.

In the primary analysis based on the ITT analysis set, based on the return-to-baseline multiple imputation for missing data coupled ANCOVA analysis, at Week 24, bexagliflozin statistically significantly reduced HbA1c from baseline compared with placebo. The adjusted mean difference was -0.27 (95% CI: -0.44, -0.09; one-sided p-value, 0.0017).

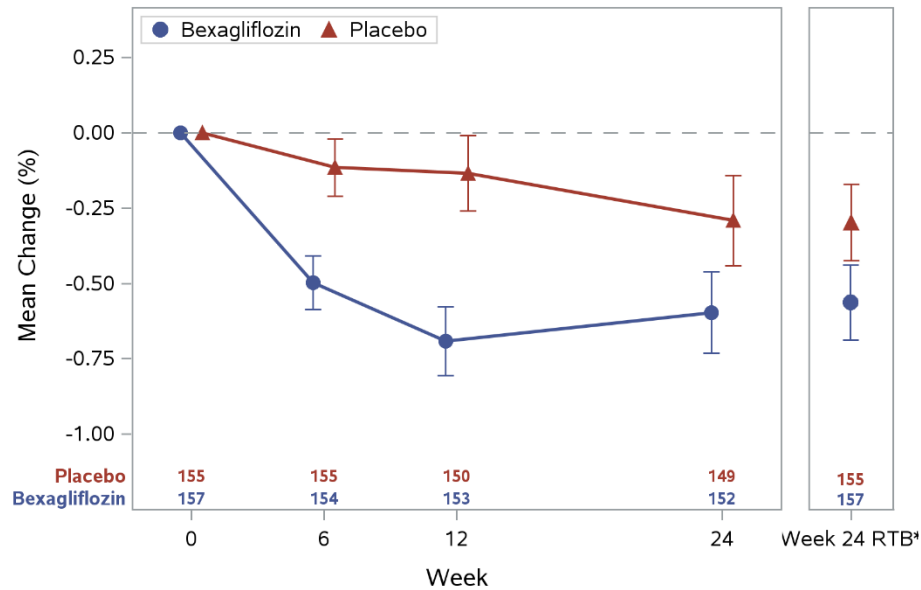
[Figure 60](#) displays the mean change from baseline in HbA1c (%) over 24 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 24 is plotted separately.

In addition, tipping point sensitivity analysis results ([Table 189](#)) show that only under an implausible situation will the treatment effect demonstrated by the primary analysis lack significance.

Also based on the return-to-baseline multiply imputed HbA1c (%) values at Week 24, a binary responder defined as subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%) variable was derived. The logistic regression model adjusted proportions were 31.3% and 18.1% for the bexagliflozin 20 mg group and the placebo group, respectively.

Figure 60. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-448

C-448 Mean Change from Baseline in HbA1c (%) by Time and Treatment



Note: Vertical lines represent 95% confidence intervals. *Data was analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c ; ITT, intention-to-treat

Table 159. Change From Baseline in HbA1c (%) at Week 24 Analysis Results, ITT, Return-to-Baseline Multiple Imputation, Trial C-448

Characteristic	Bexagliflozin 20 mg (N=157)	Placebo (N=155)
Number of subjects	157	155
Number (%) of values imputed for Week 24	5 (3.2)	7 (4.5)
Baseline		
Mean (SD)	8.01 (0.786)	7.95 (0.812)
Median	7.80	7.80
Q1, Q3	7.50, 8.40	7.40, 8.40
Minimum, maximum	6.7, 10.4	5.9, 10.4
Week 24 (Observed)		
Mean (SD)	7.40 (0.828)	7.66 (0.918)
Median	7.30	7.50
Q1, Q3	6.80, 7.90	7.00, 8.15
Minimum, maximum	5.8, 10.5	5.7, 10.8
Model-adjusted change from baseline		
LS Mean (SE)	-0.56 (0.064)	-0.30 (0.065)
95% confidence interval	(-0.69, -0.44)	(-0.42, -0.17)
Difference from placebo		
Difference of LS means	-0.27	
95% confidence interval	(-0.44, -0.09)	
One-sided p-value	0.0017	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count and proportion [N (%)] ^[1]	52 (33.1)	34 (21.9)
Model based proportion ^[2]	31.3	18.1

Source: FDA statistical reviewer

^[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

^[2] Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Key Secondary Endpoints – Primary Analysis

[Table 160](#) summarizes changes from baseline in prespecified key secondary efficacy endpoints at Week 24. Bexagliflozin significantly decreased body mass at Week 24 ($p < 0.0001$), however, bexagliflozin failed to demonstrate a treatment effect on SBP at Week 24 ($p=0.1157$). More detailed analysis results for these two endpoints and FPG are located in Section [16.5.5](#).

Table 160. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-448

Endpoints	Bexagliflozin 20 mg	Placebo
Change from baseline in body mass at Week 24 baseline BMI ≥ 25 kg/m ² subgroup		
Number of subjects	125	122
Number (%) of values imputed for Week 24	3 (2.4)	6 (4.9)
Model-adjusted change from baseline		
LS mean (SE)	-2.14 (0.263)	-0.43 (0.267)
95% confidence interval	(-2.66, -1.63)	(-0.96, 0.09)

Endpoints	Bexagliflozin 20 mg	Placebo
Difference from placebo		
Difference of LS means	-1.71	
95% confidence interval	(-2.44, -0.97)	
One-sided p-value	<0.0001	
Change from baseline in SBP at Week 24 baseline SBP $\geq$ 130 mm Hg subgroup		
Number of subjects	107	113
Number (%) of values imputed for Week 24	3 (2.8)	6 (5.3)
Model-adjusted change from baseline		
LS mean (SE)	-9.40 (1.478)	-6.92 (1.450)
95% confidence interval	(-12.30, -6.50)	(-9.76, -4.08)
Difference from placebo		
Difference of LS means	-2.48	
95% confidence interval	(-6.55, 1.58)	
One-sided p-value	0.1157	

Source: FDA statistical reviewer

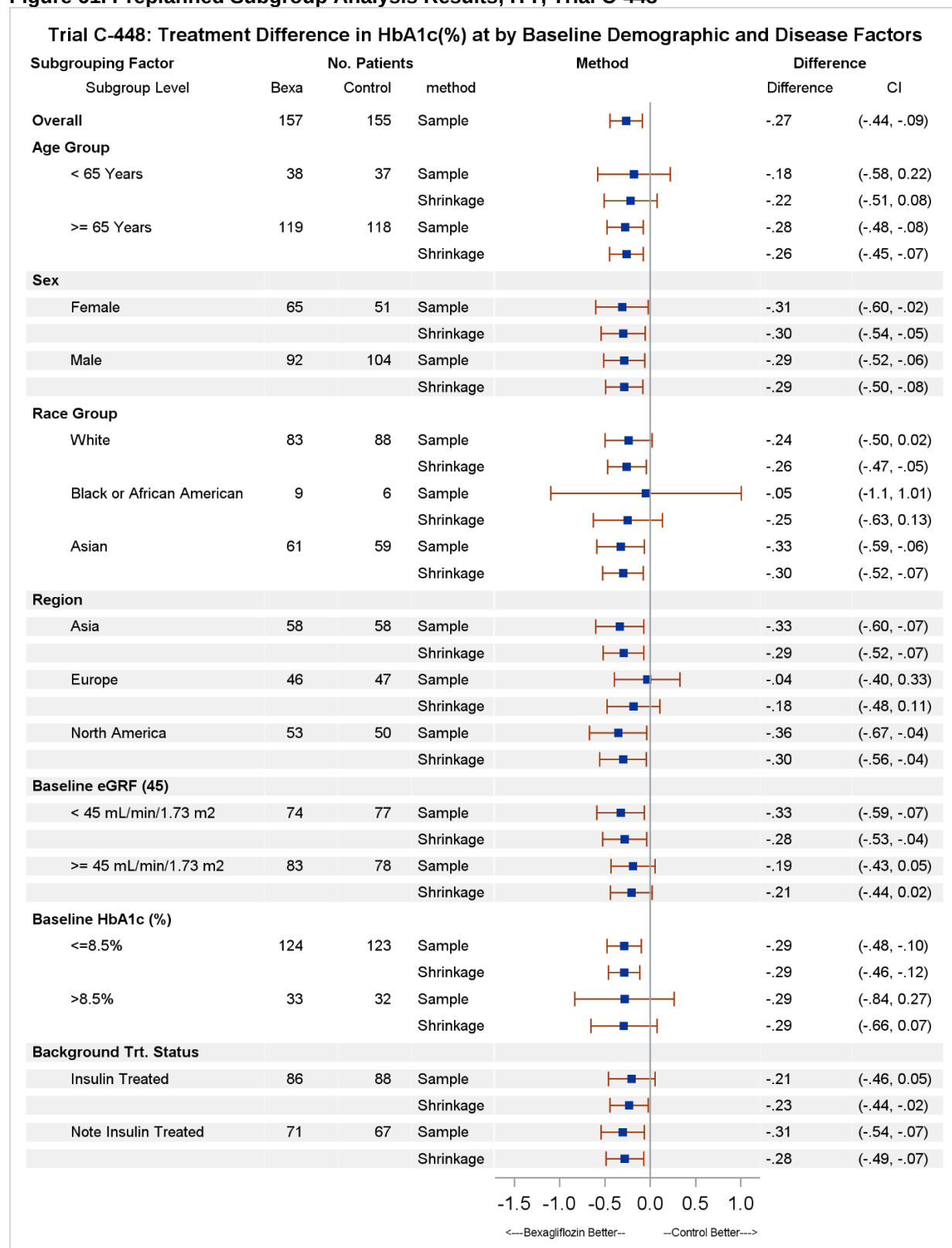
Abbreviation: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

While the sequential testing stopped at testing SBP, we know from the subgroup analysis results presented in the next subsection, bexagliflozin also failed to show significance in change from baseline to Week 24 in HbA1c in subjects with eGFR 45 to 59 mL/min/1.73 m² or 30 to 44 mL/min/1.73 m².

16.4.5.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses showed that the HbA1c lowering effect was consistent across subgroup levels ([Figure 61](#)). The subgroup level treatment effects associated with baseline renal function level are discussed as a review issue in Section [6.3.1](#).

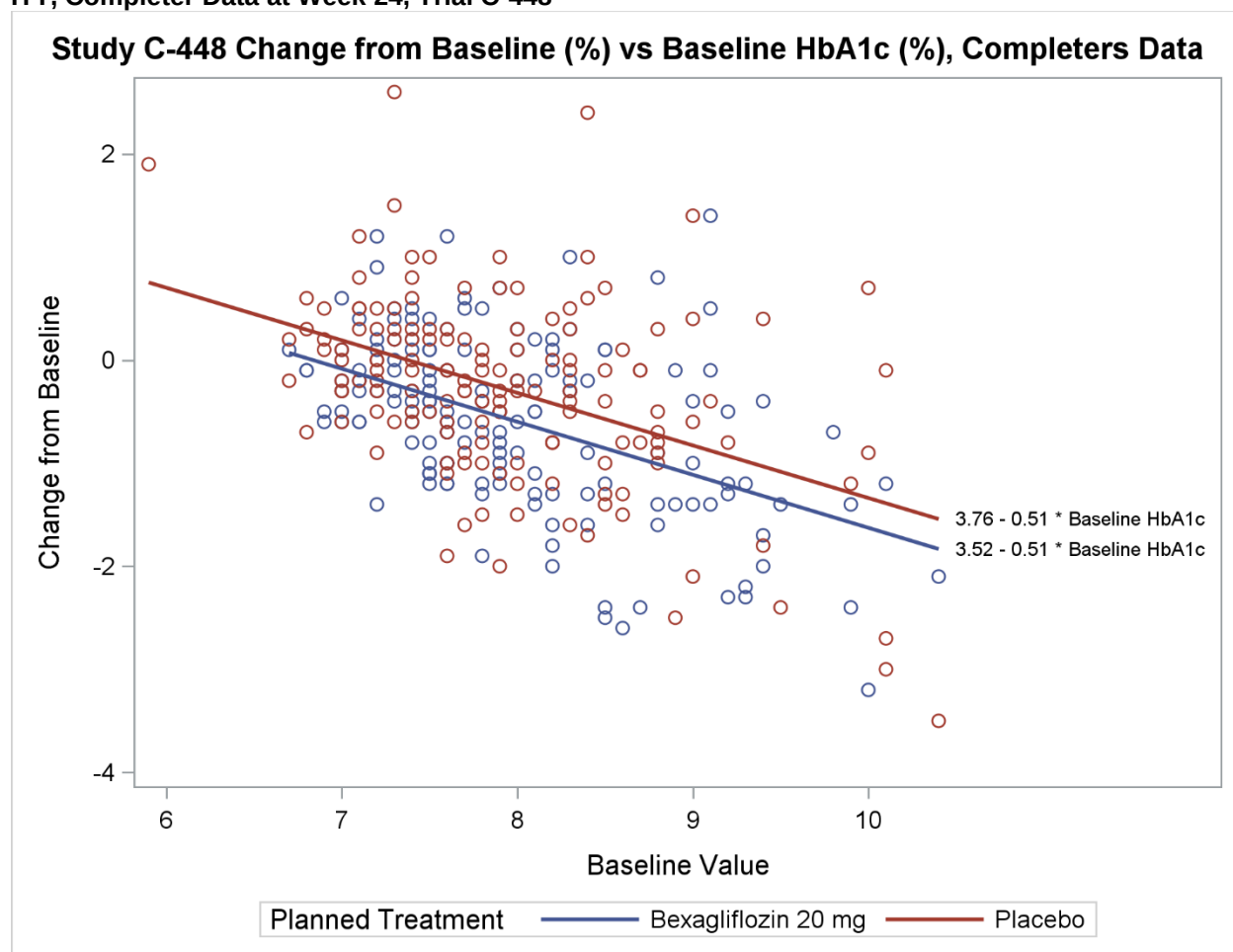
Figure 61. Preplanned Subgroup Analysis Results, ITT, Trial C-448



Source: FDA statistical reviewer
 Abbreviation: Bexa, bexagliflozin; CI, confidence interval; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration; ITT, intention-to-treat; No, number of.

To further investigate the potential modulation effect of baseline HbA1c level, a linear regression “subgroup” analysis using the continuous baseline HbA1c level based on the completers data was carried out. [Figure 62](#) shows a scatter plot of change from baseline in HbA1c at Week 24 versus baseline HbA1c data, overlaid with the estimated by-arm group regression lines. In general, in both bexagliflozin-treated subjects and in placebo subjects, higher baseline HbA1c level is associated with a bigger change from baseline HbA1c levels at Week 24. The two by-arm regression lines are near parallel, the difference in slope (slope in bexagliflozin arm - slope in placebo arm) is -0.004 (standard error=0.113, p-value=0.97). The small size of the difference and the p-value of 0.97 suggest that baseline HbA1c level is less likely to have any modulating effect on the action of this SGLT2 inhibitor drug in this study population.

Figure 62. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-448



Source: FDA statistical reviewer

Note: The estimated difference in slope between the bexagliflozin arm and the placebo arm is 0.074 (standard error [SE]=0.127, p-value=0.56). These results are derived from a simple linear regression model based on the completers data with change from baseline in HbA1c at Week 24 as the response variable, and treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction as the predictor variables.

Abbreviations: HbA1c, hemoglobin A1c; ITT, intention-to-treat.

16.4.6. Trial C-476

16.4.6.1. Design, Trial C-476

Trial C-476 was a double-blind, placebo-controlled study to evaluate the placebo-adjusted change in HbA1c from baseline after 24 weeks of exposure to bexagliflozin in type 2 diabetic subjects with increased risk of cardiovascular adverse events. The cardiovascular outcome trial (CVOT) data are reviewed by OB/DBVII and are covered in Section [17.1](#) of this review.

16.4.6.2. Statistical Analysis Plan, Trial C-476

16.4.6.2.1. Efficacy Endpoints

The primary and key secondary endpoints listed in this subsection are shown in the study prespecified hierarchical testing sequence.

Primary Endpoint

- Change from baseline in HbA1c at Week 24

Key Secondary Endpoints

- Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes*
- Change from baseline to Week 48 in body weight in subjects with baseline BMI ≥ 25 kg/m²
- Change from baseline to Week 24 in SBP in subjects with baseline SBP ≥ 140 mm Hg from baseline

** **FDA Reviewer Comment:** The Applicant newly added a key secondary endpoint: change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes in Protocol V7 (FDA reviewed) and described as a substudy in SAP V2 that was not submitted for FDA review (see Section [12](#)). The Applicant newly added HbA1c change from baseline to Week 24 in subjects who have been prescribed sulfonylurea as an exploratory endpoint in SAP V2.*

(b) (4) these subsets were not used as randomization stratification, and were retrospectively added as a key secondary endpoint and an exploratory secondary endpoint with description of a substudy in SAP V2 that was not reviewed by FDA.

16.4.6.3. Results of Analyses, Trial C-476

16.4.6.3.1. Baseline Demographic, Baseline Clinical Characteristics, and Disposition

Demographic factors and baseline clinical characteristics for Trial C-476 are summarized in [Table 161](#).

Overall, the majority of subjects in the trial were overweight or obese (92% of the population had a baseline BMI ≥ 25 kg/m²), male (70%), and white (77%). The demographic factors and baseline clinical characteristics were generally balanced between the bexagliflozin 20 mg and the placebo groups.

Table 161. Baseline Demographic and Clinical Characteristics, ITT, Trial C-476

Characteristics	Bexagliflozin 20 mg N=1133	Placebo N=567	Total N=1700
Sex			
F	341 (30%)	177 (31%)	518 (30%)
M	792 (70%)	390 (69%)	1182 (70%)
Age (years)			
Mean (SD)	64 (8)	65 (8)	64 (8)
Median (min, max)	65 (39, 91)	65 (40, 92)	65 (39, 92)
Age group			
Age <65 years	562 (50%)	276 (49%)	838 (49%)
Age ≥ 65	571 (50%)	291 (51%)	862 (51%)
Age ≥ 75 years	113 (10%)	67 (12%)	180 (11%)
Race			
American Indian or Alaska native	98 (9%)	54 (10%)	152 (9%)
Asian	108 (10%)	55 (10%)	163 (10%)
Black or African American	46 (4%)	28 (5%)	74 (4%)
Native Hawaiian or other Pacific Islander	2 (<1%)	0	2 (<1%)
White	879 (78%)	430 (76%)	1309 (77%)
Ethnicity			
Hispanic or Latino	166 (15%)	93 (16%)	259 (15%)
Not Hispanic or Latino	967 (85%)	474 (84%)	1441 (85%)
Country			
Canada	67 (6%)	24 (4%)	91 (5%)
Czech Republic	118 (10%)	52 (9%)	170 (10%)
Denmark	17 (2%)	10 (2%)	27 (2%)
Korea	48 (4%)	26 (5%)	74 (4%)
Mexico	121 (11%)	62 (11%)	183 (11%)
Netherlands	36 (3%)	18 (3%)	54 (3%)
Poland	196 (17%)	97 (17%)	293 (17%)
Russian Federation	87 (8%)	53 (9%)	140 (8%)
Taiwan	46 (4%)	20 (4%)	66 (4%)
United States	397 (35%)	205 (36%)	602 (35%)
Geographic region			
Asia	94 (8%)	46 (8%)	140 (8%)
Europe	454 (40%)	230 (41%)	684 (40%)
North America	585 (52%)	291 (51%)	876 (52%)
BMI at baseline (kg/m ²)			
Mean (SD)	32.8 (6.1)	32.2 (5.8)	32.6 (6.0)
Median (min, max)	32.0 (19.6, 61.6)	31.6 (21.2, 65.2)	31.9 (19.6, 65.2)
BMI at baseline (kg/m ²) group			
<25 kg/m ²	86 (8%)	45 (8%)	131 (8%)
≥ 25 kg/m ²	1047 (92%)	522 (92%)	1569 (92%)
Duration of diabetes (years)			
Mean (SD)	14.9 (8.6)	15.2 (9.3)	15.0 (8.8)
Median (min, max)	14.3 (0.4, 57.4)	13.7 (0.3, 53.7)	14.1 (0.3, 57.4)
Baseline insulin, n (%)			
Insulin treated	610 (54%)	292 (51%)	902 (53%)
Not insulin treated	523 (46%)	275 (49%)	798 (47%)

Characteristics	Bexagliflozin 20 mg N=1133	Placebo N=567	Total N=1700
Baseline HbA1c (%) mean			
Mean (SD)	8.3 (0.9)	8.3 (0.9)	8.3 (0.9)
Median (min, max)	8.2 (5.8, 11.0)	8.2 (5.5, 11.4)	8.2 (5.5, 11.4)
Baseline HbA1c (%) group			
≤8.5%	716 (63%)	362 (64%)	1078 (63%)
>8.5%	417 (37%)	205 (36%)	622 (37%)
Baseline eGFR, mL/min/1.73 m ²			
Mean (SD)	77.5 (19.9)	78.0 (20.3)	77.7 (20.1)
Median (min, max)	75.6 (25.2, 158.1)	75.6 (35.6, 155.7)	75.6 (25.2, 158.1)
Baseline eGFR group, mL/min/1.73 m ²			
<60	225 (20%)	109 (19%)	334 (20%)
≥60	908 (80%)	458 (81%)	1366 (80%)
Baseline eGFR group, mL/min/1.73 m ²			
<30	1 (<1%)	0	1 (<1%)
≥30 to <45	33 (3%)	17 (3%)	50 (3%)
≥45 to <60	191 (17%)	92 (16%)	283 (17%)
≥60 to <90	623 (55%)	313 (55%)	936 (55%)
≥90	285 (25%)	145 (26%)	430 (25%)
Baseline SBP, mm Hg			
Mean (SD)	134.2 (16.2)	133.7 (16.2)	134.0 (16.2)
Median (min, max)	135 (78, 227)	134 (86, 177)	135 (78, 227)
SBP group, mm Hg			
<140 mm Hg	685 (60%)	352 (62%)	1037 (61%)
≥140 mm Hg	448 (40%)	215 (38%)	663 (39%)
Baseline DBP, mm Hg			
Mean (SD)	77.1 (9.9)	76.8 (10.2)	77.0 (10.0)
Median (min, max)	78 (43, 112)	78 (47, 105)	78 (43, 112)
Baseline FPG, mg/dL			
Mean (SD)	166 (47)	162 (47)	164 (47)
Median (min, max)	162 (50, 371)	157 (43, 362)	160 (43, 371)

Source: FDA statistical reviewer

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; ITT, intention-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic; SBP, systolic blood pressure.

Disposition

Subject screening and randomization information for Trial C-476 are summarized in [Table 162](#). About 57% of the subjects screened for participation entered the run-in period in the trial; among subjects who entered the run-in period, 91% passed the run-in period and were randomized into the double-blind phase of the trial.

Table 162. Subject Screening and Randomization, Trial C-476

Disposition	Screened (%)	Entered Run-In (%)
No. subjects consented to participate and completed the screening procedures	3270 (100%)	
No. screening failures before run-in	1397 (43%)	
No. subjects entered run-in period	1873 (57%)	1873 (100%)
No. screening failures after run-in	172 (5%)	172 (9%)
No. subjects randomized	1701 (52%)	1701 (91%)

Source: FDA statistical reviewer

Abbreviations: No., number of.

Analysis populations and subject disposition information for Trial C-476 are summarized in [Table 163](#). A total of 1701 randomized subjects were randomized into the study. One randomized subject (“476- (b) (6)”) was excluded by Applicant from the ITT and safety populations because of a GCP violation. One subject (“476- (b) (6)”) was randomized to the bexagliflozin arm but did not take any investigational product and was excluded from the safety population. As a result, the ITT analysis set was composed of 1700 subjects and the safety set was composed of 1699 subjects.

A total of 428 (25%) subjects discontinued the study treatment; a slightly higher rate of discontinuation was seen with placebo (29%) than with bexagliflozin 20 mg (23%). A lower percentage of subjects treated with bexagliflozin 20 mg (2.0%) received glycemic rescue therapy compared with placebo-treated subjects (2.6%). “Other” was documented as the most frequent reason for treatment discontinuation for the two treatment groups (8% in the bexagliflozin 20 mg arm, 12% in the placebo arm). Other most frequent reasons for treatment discontinuation included “adverse event” and “subject withdrew consent.” The overall study completion rate was 86%, 11% higher than the treatment completion rate.

Table 163. Subject Disposition, ITT, Trial C-476

Completion Status/ Discontinuation Reason	Bexagliflozin 20 mg N=1133	Placebo N=567	Total N=1700
Analysis population*			
Subjects randomized**	1134 (100%)	567 (100%)	1701 (100%)
ITT population	1133 (100%)	567 (100%)	1700 (100%)
Per protocol population	1072 (95%)	548 (97%)	1620 (95%)
Safety population	1132 (100%)	567 (100%)	1699 (100%)
Treatment completion			
Yes	871 (77%)	401 (71%)	1272 (75%)
No	262 (23%)	166 (29%)	428 (25%)
Reason for discontinuation			
Adverse event	72 (6%)	34 (6%)	106 (6%)
Death	31 (3%)	21 (4%)	52 (3%)
Lost to follow-up	27 (2%)	15 (3%)	42 (2%)
Noncompliance with study drug	5 (<1%)	5 (<1%)	10 (<1%)
Other	94 (8%)	69 (12%)	163 (10%)
Protocol violation	4 (<1%)	3 (<1%)	7 (<1%)
Study terminated by investigator	6 (<1%)	3 (<1%)	9 (<1%)
Study terminated by Sponsor	6 (<1%)	2 (<1%)	8 (<1%)
Subject withdrew consent	64 (6%)	39 (7%)	103 (6%)

Completion Status/ Discontinuation Reason	Bexagliflozin 20 mg N=1133	Placebo N=567	Total N=1700
Study completion			
Yes	987 (87%)	482 (85%)	1469 (86%)
No	146 (13%)	85 (15%)	231 (14%)
Reason for discontinuation			
Adverse event	14 (1%)	5 (<1%)	19 (1%)
Death	39 (3%)	25 (4%)	64 (4%)
Lost to follow-up	31 (3%)	23 (4%)	54 (3%)
Other	1 (<1%)	0	1 (<1%)
Protocol violation	2 (<1%)	1 (<1%)	3 (<1%)
Study terminated by investigator	6 (<1%)	0	6 (<1%)
Subject withdrew consent	53 (5%)	31 (5%)	84 (5%)

Source: FDA statistical reviewer

Note: *In the "Analysis Populations" block of the table, the denominators are the corresponding number of randomized subjects. In the rest of the table, the denominators are the corresponding ITT population numbers.

** One randomized subject (476- (b) (6) in Canada) was excluded from the intention-to-treat (ITT) and safety populations for GCP violation.

Abbreviations: ITT, intention-to-treat; N, number of subjects in treatment group; n, number of subjects with given characteristic

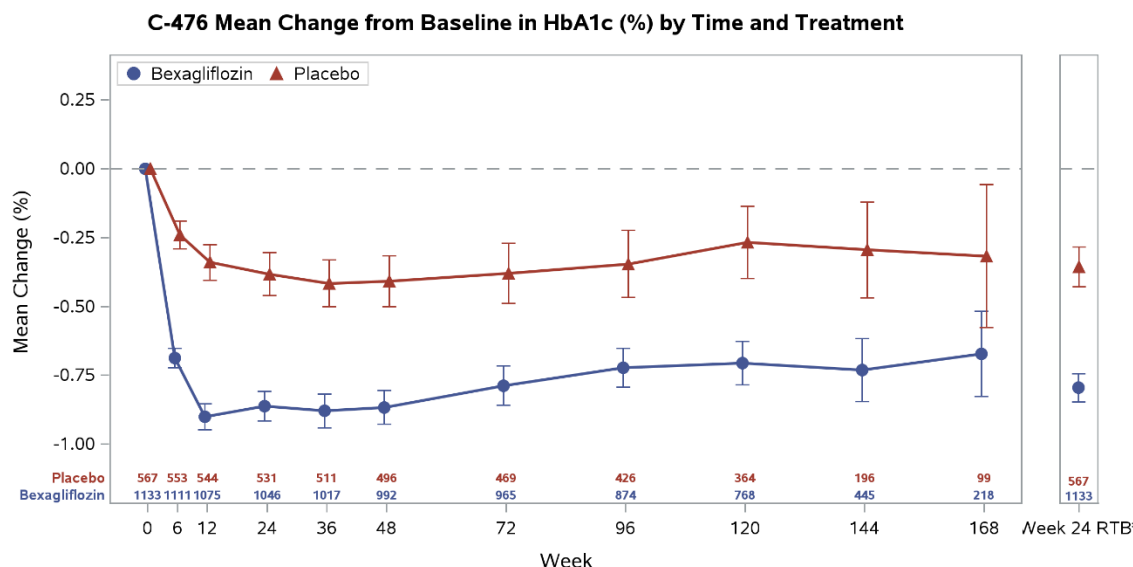
16.4.6.3.2. Primary Endpoint and Key Secondary Efficacy Results

Primary Endpoint – Primary Analysis

[Table 164](#) summarizes the primary analysis results for C-476. At Week 24, 79 (7.0%) and 34 (6.0%) subjects in the bexagliflozin 20 mg group and placebo group, respectively, had missing HbA1c data ([Table 164](#)). HbA1c was significantly reduced from baseline with bexagliflozin 20 mg compared with placebo (adjusted mean difference -0.44, 95% CI [-0.53, -0.35]; $p < 0.0001$).

[Figure 63](#) displays the mean change from baseline in HbA1c (%) over 168 weeks by time and treatment group. Data are observed values; vertical lines represent 95% confidence intervals. The primary return-to-baseline analysis results at Week 24 is plotted separately.

Figure 63. Change From Baseline in HbA1c (%) by Time and Treatment and Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476



Note: Vertical lines represent 95% confidence intervals. *The return-to-baseline multiply imputed data was analyzed with ANCOVA using fixed, categorical effects of treatment, region, screening anti-diabetic treatment regimen, baseline eGFR category, as well as the continuous fixed covariates of baseline HbA1c. Treatment group least squares means (LSMs) in change from baseline in HbA1c at Week 24 was estimated by the ANCOVA model.

Source: FDA statistical reviewer

Abbreviation: ANCOVA, analysis of covariance; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c ; ITT, intention-to-treat; RTB, return to baseline.

In addition, tipping point sensitivity analysis results ([Table 190](#)) show that only under an implausible situation will the treatment effect demonstrated by the primary analysis lack significance.

Also based on the multiply imputed HbA1c (%) values at Week 24, a responder defined as reaching the treatment goal of glycemic control (HbA1c (%) <7%) was derived. The logistic regression model adjusted proportions were 24.3% and 12.8% for the bexagliflozin 20 mg group and the placebo group, respectively.

Table 164. Change From Baseline in HbA1c (%) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476

Characteristic	Bexagliflozin 20 mg (N=1133)	Placebo (N=567)
Number of subjects	1133	567
Number (%) of values imputed for Week 24	79 (7.0)	34 (6.0)
Baseline		
Mean (SD)	8.32 (0.897)	8.33 (0.944)
Median	8.20	8.20
Q1, Q3	7.60, 8.90	7.70, 8.90
Minimum, maximum	5.8, 11.0	5.5, 11.4
Week 24 (Observed)		
Mean (SD)	7.46 (0.917)	7.93 (1.078)
Median	7.30	7.80
Q1, Q3	6.90, 8.00	7.20, 8.50
Minimum, maximum	5.1, 17.4	5.2, 13.0

Characteristic	Bexagliflozin 20 mg (N=1133)	Placebo (N=567)
Model-adjusted change from baseline		
LS mean (SE)	-0.79 (0.026)	-0.36 (0.037)
95% confidence interval	(-0.85, -0.74)	(-0.43, -0.28)
Difference from placebo		
Difference of LS means	-0.44	
95% confidence interval	(-0.53, -0.35)	
One-sided p-value	<0.0001	
Count and proportion of subjects reaching the treatment goal of glycemic control (HbA1c [%] <7%)		
Crude count and proportion [N (%)] ^[1]	325 (28.7)	96 (16.9)
Model based proportion ^[2]	24.3	12.8

Source: FDA statistical reviewer

[1] Iteration level crude counts and proportions of subjects achieving HbA1c <7.0% by arm was first derived, then crude proportion summarized across iteration by applying Rubin's rule

[2] Logistical model based by arm proportion estimates. P-value not provided as this comparison was not prespecified.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Key Secondary Endpoints – Primary Analysis

[Table 165](#) summarizes changes from baseline in prespecified key secondary efficacy endpoints. Bexagliflozin significantly decreased HbA1c at Week 24 in subjects who have been prescribed insulin, body mass index at Week 48 (in those with baseline BMI ≥ 25 kg/m²), and SBP at Week 24 (in those with baseline SBP ≥ 140 mmHg) ($p < 0.0001$, $p < 0.0001$ and $p = 0.0209$, respectively). More detailed analysis results are located in Section [16.5.6](#).

Table 165. Changes From Baseline in Prespecified Key Secondary Efficacy Endpoints at Week 24, ITT, Return-to-Baseline Multiple Imputation, Trial C-476

Endpoints	Bexagliflozin 20 mg	Placebo
Change in HbA1c from baseline to Week 24 in randomized subjects who have been prescribed insulin to control their diabetes		
Number of subjects	610	292
Number (%) of values imputed for Week 24	37 (6.0)	7 (2.3)
Model-adjusted change from baseline		
LS mean (SE)	-0.63 (0.09)	-0.15(0.10)
Difference from placebo		
Difference of LS means	-0.48	
95% confidence interval	(-0.63, -0.37)	
One-sided p-value	<0.0001	
Change from baseline in body mass index at Week 48 (baseline BMI ≥ 25 kg/m ² subgroup)		
Number of subjects	1047	522
Number (%) of values imputed for Week 48	134 (12.8)	72 (13.8)
Model-adjusted change from baseline		
LS mean (SE)	-2.66 (0.125)	-0.32 (0.174)
95% confidence interval	(-2.90, -2.41)	(-0.66, 0.02)
Difference from placebo		
Difference of LS means	-2.34	
95% confidence interval	(-2.76, -1.92)	
One-sided p-value	<0.0001	

Endpoints	Bexagliflozin 20 mg	Placebo
Change from baseline in SBP at Week 24 (baseline SBP ≥ 140 mm Hg subgroup)		
Number of subjects	448	215
Number (%) of values imputed for Week 24	26 (5.8)	9 (4.2)
Model-adjusted change from baseline		
LS mean (SE)	-9.24 (0.745)	-6.57 (1.069)
95% confidence interval	(-10.70, -7.78)	(-8.67, -4.48)
Difference from placebo		
Difference of LS means	-2.66	
95% confidence interval	(-5.23, -0.10)	
One-sided p-value	0.0209	

Source: FDA statistical reviewer

Abbreviation: BMI, body mass index; HbA1c, hemoglobin A1c; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

Exploratory Secondary Endpoint – Primary Analysis

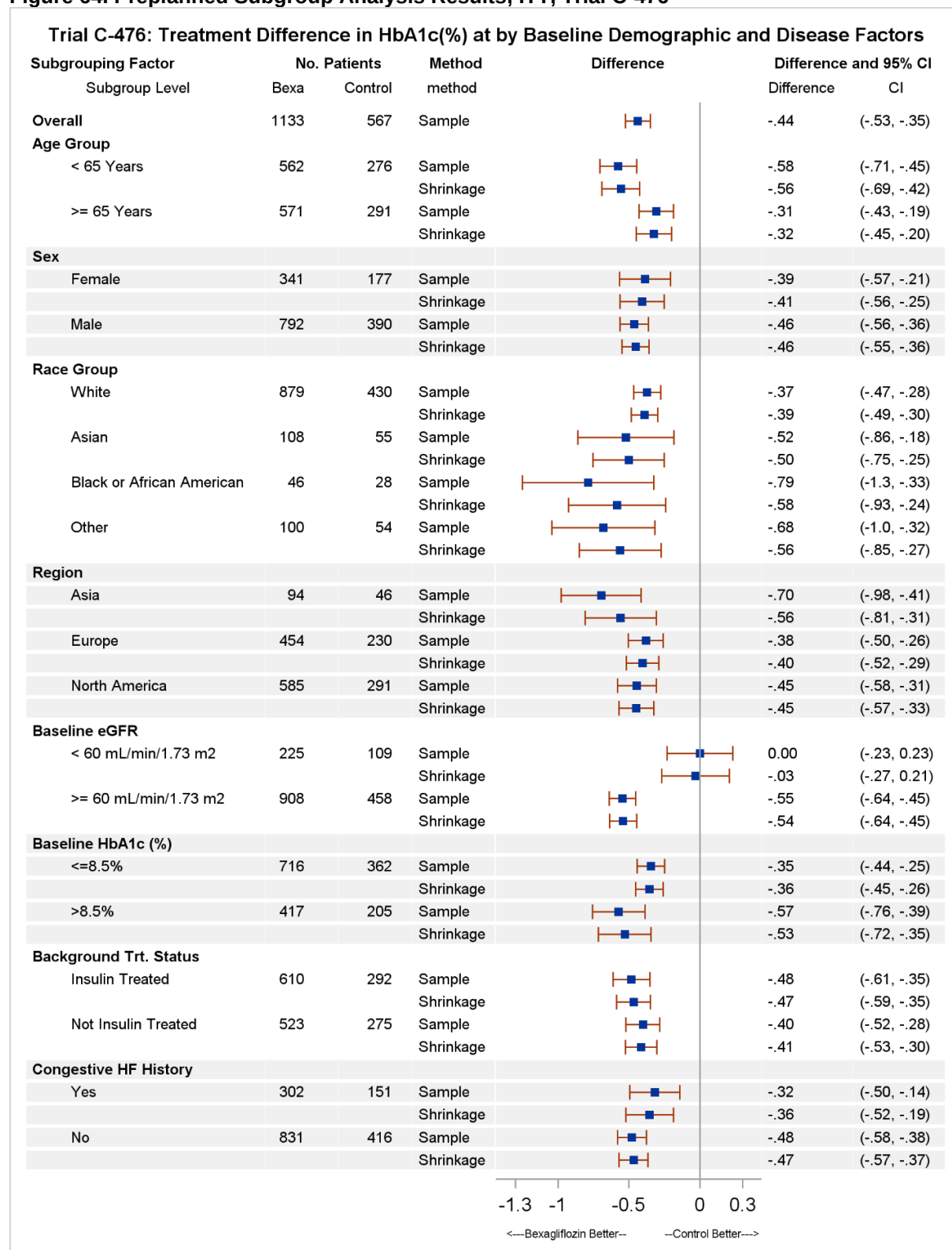
There were 313 subjects in the bexagliflozin group and 163 subjects in the placebo group who had been prescribed a sulfonylurea. There were 7% missing data in each arm (22 subjects in bexagliflozin and 12 subjects in placebo) imputed for Week 24. HbA1c change from baseline to Week 24 in subjects who had been prescribed a sulfonylurea with bexagliflozin vs. placebo was -0.39 (95% CI: -0.55, -0.24).

16.4.6.3.3. Subgroup Analyses of the Primary Endpoint

Subgroup analyses showed that the HbA1c lowering effect was generally consistent across subgroup levels ([Figure 64](#)). However, the subgroup level treatment effect associated with impaired baseline renal function (eGFR < 60 mL/min/1.73m²) has an estimated size of 0. This lack of treatment effect in a subgroup of the population is discussed as a review issue in [Section 6.3.1](#).

To further investigate the potential modulation effect of baseline HbA1c level, a linear regression “subgroup” analysis using the continuous baseline HbA1c level based on the completers data was carried out. [Figure 65](#) shows a scatter plot of change from baseline in HbA1c at Week 24 versus baseline HbA1c data, overlaid with the estimated by-arm group regression lines. In general, in both bexagliflozin-treated subjects and in placebo subjects, higher baseline HbA1c level is associated with bigger change from baseline HbA1c levels at Week 24. Compared with placebo, bexagliflozin treatment is associated with a steeper slope, the difference in slope (slope in bexagliflozin arm – slope in placebo) is -0.21 (standard error=0.05, p-value<0.001). Both the effect size and the significant p-value indicate that baseline HbA1c level may have a strong modulation effect on the action of this SGLT2 inhibitor drug in subjects at risk of cardiovascular adverse events, the higher the baseline HbA1c level, the larger the expected treatment effect at Week 24.

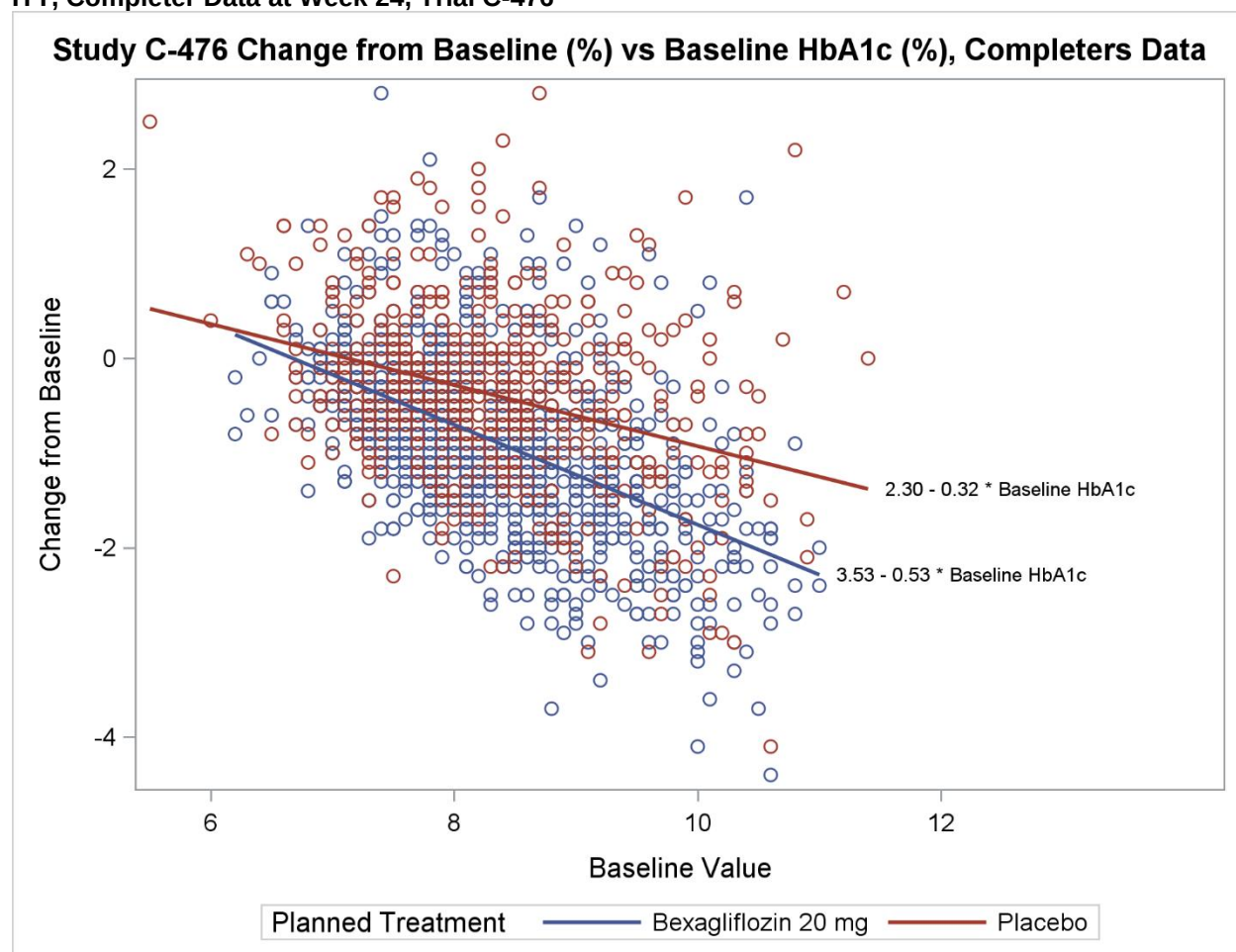
Figure 64. Preplanned Subgroup Analysis Results, ITT, Trial C-476



Source: FDA statistical reviewer

Abbreviation: Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HF, heart failure; ITT, intention-to-treat; No, number of; CI, confidence interval.

Figure 65. Exploration of the Modulation Effect of Baseline HbA1c Levels, Regression Analysis, ITT, Completer Data at Week 24, Trial C-476



Source: FDA statistical reviewer

Note: The estimated difference in slope (slope in bexagliflozin arm – slope in placebo) is -0.21 (standard error =0.05, p-value<0.001). These results is derived based on a simple linear regress model on the completers data with change from baseline in HbA1c at Week 24 as the response variable and treatment, baseline HbA1c levels, and a treatment by baseline HbA1c levels interaction as the predictor variables.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat.

16.5. Secondary Efficacy Endpoints Analysis Results

16.5.1. Trial C-450

Table 166. Change From Baseline in SBP (mmHg) at Week 24, Return-to-Baseline Analysis Results, ITT, Trial C-450

Characteristics	Bexagliflozin 20 mg (N=138)	Placebo (N=69)
Number of subjects	138	69
Number (%) of values imputed for Week 24	12 (8.7)	5 (7.2)
Baseline		
Mean (SD)	131.02 (14.351)	125.64 (13.836)
Median	130.50	126.00
Q1, Q3	122.00, 140.00	117.00, 136.00
Minimum, maximum	93.0, 188.0	98.0, 158.0
Week 24 (observed)		
Mean (SD)	128.88 (13.108)	128.75 (15.470)
Median	128.00	131.00
Q1, Q3	120.00, 137.00	120.00, 140.00
Minimum, maximum	98.0, 164.0	87.0, 163.0
Model-adjusted change from baseline		
LS mean (SE)	-0.72 (1.019)	1.03 (1.467)
95% confidence interval	(-2.72, 1.28)	(-1.85, 3.90)
Difference from placebo		
Difference of LS means	-1.75	
95% confidence interval	(-5.26, 1.77)	
One-sided p-value*	0.1649	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure. *nominal p-value

Table 167. Change From Baseline in Weight (kg) at Week 24, Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m² Subgroup, Trial C-450

Characteristics	Bexagliflozin 20 mg (N=128)	Placebo (N=62)
Number of subjects	128	62
Number (%) of values imputed for Week 24	11 (8.6)	5 (8.1)
Baseline		
Mean (SD)	92.51 (19.553)	86.94 (19.358)
Median	88.85	82.65
Q1, Q3	77.65, 103.40	73.00, 97.20
Minimum, maximum	61.6, 159.1	60.0, 151.0
Week 24 (observed)		
Mean (SD)	90.54 (19.243)	86.67 (19.548)
Median	85.60	84.00
Q1, Q3	76.00, 101.40	72.80, 97.50
Minimum, maximum	57.1, 155.9	57.7, 151.2
Model-adjusted change from baseline		
LS mean (SE)	-1.46 (0.291)	-0.76 (0.414)
95% confidence interval	(-2.03, -0.89)	(-1.58, 0.05)

	Bexagliflozin 20 mg (N=128)	Placebo (N=62)
Characteristics		
Difference from placebo		
Difference of LS means	-0.70	
95% confidence interval	(-1.69, 0.30)	
One-sided p-value*	0.0848	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. * nominal p-value

Table 168. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-450

	Bexagliflozin 20 mg (N=138)	Placebo (N=69)
Characteristics		
Number of subjects	138	69
Number (%) of values imputed for Week 24	12 (8.7)	5 (7.2)
Baseline		
Mean (SD)	169 (35)	170 (38)
Median	168	164
Q1, Q3	142, 196	144, 191
Minimum, maximum	92, 284	99, 268
Week 24 (observed)		
Mean (SD)	150 (37)	167 (41)
Median	142	159
Q1, Q3	126, 169	136, 197
Minimum, maximum	79, 326	110, 315
Model-adjusted change from baseline		
LS mean (SE)	-16 (3)	-3 (4)
95% confidence interval	(-23, -10)	(-11, 6)
Difference from placebo		
Difference of LS means	-14	
95% confidence interval	(-24, -3)	
One-sided p-value*	0.0046	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.*nominal p-value.

16.5.2. Trial C-419

Table 169. Change From Baseline in SBP (mmHg) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419

	Bexagliflozin 20 mg (N=158)	Placebo (N=159)
Characteristics		
Number of subjects	158	159
Number (%) of values imputed for Week 24	16 (10.1)	15 (9.4)
Baseline		
Mean (SD)	128.75 (14.394)	129.75 (15.096)
Median	128.50	128.50
Q1, Q3	117.50, 139.00	120.00, 140.00
Minimum, maximum	99.0, 173.0	98.0, 173.0

Characteristics	Bexagliflozin 20 mg (N=158)	Placebo (N=159)
Week 24 (observed)		
Mean (SD)	123.73 (14.831)	131.54 (16.497)
Median	122.00	132.00
Q1, Q3	114.50, 135.50	119.25, 141.00
Minimum, maximum	90.5, 171.0	95.0, 182.0
Model-adjusted change from baseline		
LS mean (SE)	-4.32 (0.995)	1.52 (0.991)
95% confidence interval	(-6.27, -2.37)	(-0.43, 3.46)
Difference from placebo		
Difference of LS means	-5.84	
95% confidence interval	(-8.60, -3.09)	
One-sided p-value*	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure. *nominal p-value.

Table 170. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m² Subgroup, Trial C-419

Characteristics	Bexagliflozin 20 mg (N=119)	Placebo (N=124)
Number of subjects	119	124
Number (%) of values imputed for Week 24	14 (11.8)	14 (11.3)
Baseline		
Mean (SD)	91.66 (20.339)	90.94 (18.578)
Median	85.80	89.75
Q1, Q3	75.70, 103.00	77.35, 101.30
Minimum, maximum	59.4, 153.0	56.5, 141.2
Week 24 (Observed)		
Mean (SD)	87.21 (20.162)	88.00 (17.065)
Median	83.60	86.15
Q1, Q3	71.60, 99.00	76.10, 98.60
Minimum, maximum	58.5, 145.5	56.7, 134.9
Model-adjusted change from baseline		
LS mean (SE)	-3.09 (0.346)	-0.82 (0.328)
95% confidence interval	(-3.77, -2.41)	(-1.46, -0.18)
Difference from placebo		
Difference of LS means	-2.27	
95% confidence interval	(-3.21, -1.34)	
One-sided p-value*	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value.

Table 171. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-419

Characteristics	Bexagliflozin 20 mg (N=158)	Placebo (N=159)
Number of subjects	158	159
Number (%) of Values imputed for Week 24	15 (9.5)	15 (9.4)
Baseline		
Mean (SD)	186 (53)	190 (49)
Median	173	184
Q1, Q3	149, 221	153, 212
Minimum, maximum	68, 326	94, 358
Week 24 (observed)		
Mean (SD)	139 (33)	163 (46)
Median	133	158
Q1, Q3	119, 153	134, 185
Minimum, maximum	65, 308	79, 382
Model-adjusted change from baseline		
LS mean (SE)	-42 (3)	-20 (3)
95% confidence interval	-48, -35	-27, -13
Difference from placebo		
Difference of LS means	-22	
95% confidence interval	-31, -12	
One-sided p-value*	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value.

16.5.3. Trial C-423

Table 172. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423

Characteristics	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Number of subjects	191	193
Number (%) of values imputed for Week 24	11 (5.8)	3 (1.6)
Baseline		
Mean (SD)	176 (42)	180 (46)
Median	169	173
Q1, Q3	148, 198	149, 202
Minimum, maximum	93, 358	94, 349
Week 24 (Observed)		
Mean (SD)	144 (27)	153 (34)
Median	144	149
Q1, Q3	127, 157	130, 167
Minimum, maximum	90, 241	88, 344
Model-adjusted change from baseline		
LS Mean (SE)	-31 (2)	-26 (2)
95% confidence interval	-35, -26	-30, -21

	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Characteristics		
Difference from sitagliptin 100 mg		
Difference of LS means	-5	
95% confidence interval	(-11, 1)	
One-sided p-value*	0.0494	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value

Table 173. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-423

	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
Characteristics		
Number of subjects	191	193
Number (%) of values imputed for Week 24	11 (5.8)	3 (1.6)
Baseline		
Mean (SD)	135.01 (12.172)	135.66 (14.321)
Median	136.00	138.00
Q1, Q3	128.00, 142.00	125.00, 145.00
Minimum, maximum	100.0, 168.0	92.0, 172.0
Week 24 (Observed)		
Mean (SD)	131.28 (12.709)	133.72 (13.968)
Median	132.00	134.00
Q1, Q3	123.00, 140.00	124.00, 141.00
Minimum, maximum	102.0, 168.0	98.0, 190.0
Model-adjusted change from baseline		
LS mean (SE)	-3.82 (0.864)	-1.55 (0.846)
95% confidence interval	(-5.52, -2.13)	(-3.21, 0.11)
Difference from sitagliptin 100 mg		
Difference of LS means	-2.27	
95% confidence interval	(-4.65, 0.10)	
One-sided p-value*	0.0304	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure. *nominal p-value

Table 174. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m² Subgroup, Trial C-423

	Bexagliflozin 20 mg (N=169)	Sitagliptin 100 mg (N=174)
Characteristics		
Number of Subjects	169	174
Number (%) of values imputed for Week 24	11 (6.5)	3 (1.7)
Baseline		
Mean (SD)	93.64 (19.391)	92.42 (17.576)
Median	91.60	90.05
Q1, Q3	80.00, 108.40	80.20, 102.60
Minimum, maximum	56.2, 140.0	58.8, 149.0
Week 24 (observed)		
Mean (SD)	90.32 (18.820)	91.64 (17.598)
Median	87.50	89.00
Q1, Q3	76.50, 103.00	78.50, 102.20
Minimum, maximum	55.7, 136.0	58.7, 153.0

	Bexagliflozin 20 mg (N=169)	Sitagliptin 100 mg (N=174)
Characteristics		
Model-adjusted change from baseline		
LS Mean (SE)	-3.02 (0.231)	-0.77 (0.223)
95% confidence interval	(-3.48, -2.57)	(-1.21, -0.34)
Difference from sitagliptin 100 mg		
Difference of LS means	-2.25	
95% confidence interval	(-2.88, -1.62)	
One-sided p-value*	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value

16.5.4. Trial C-480

Table 175. Change From Baseline in Weight (kg) at Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480

	Bexagliflozin 20 mg (N=201)	Glimepiride (N=202)
Characteristics		
Number of subjects	201	202
Number (%) of values imputed for Week 24	19 (9.5)	20 (9.9)
Baseline		
Mean (SD)	89.67 (18.216)	91.68 (16.802)
Median	88.50	89.00
Q1, Q3	76.70, 99.00	79.30, 102.50
Minimum, maximum	53.8, 151.0	63.3, 141.0
Week 24 (Observed)		
Mean (SD)	86.03 (17.901)	92.79 (17.049)
Median	84.50	90.20
Q1, Q3	74.60, 94.90	81.00, 104.00
Minimum, maximum	51.3, 147.0	58.9, 150.5
Model-adjusted change from baseline		
LS Mean (SE)	-3.44 (0.288)	0.58 (0.292)
95% confidence interval	(-4.00, -2.87)	(0.01, 1.15)
Difference from glimepiride		
Difference of LS means	-4.01	
95% confidence interval	(-4.82, -3.21)	
One-sided p-value	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Table 176. Change From Baseline in SBP (mm Hg) at Week 60 Return-to-Baseline Analysis Results, ITT, Baseline SBP $\geq$ 140 mm Hg Subgroup, Trial C-480

Characteristics	Bexagliflozin 20 mg (N=78)	Glimepiride (N=75)
Number of subjects	78	75
Number (%) of values imputed for Week 24	4 (5.1)	7 (9.3)
Baseline		
Mean (SD)	148.50 (7.320)	149.23 (8.384)
Median	147.00	148.00
Q1, Q3	143.00, 153.00	144.00, 155.00
Minimum, maximum	140.0, 185.0	140.0, 196.0
Week 24 (observed)		
Mean (SD)	134.91 (13.250)	142.38 (11.667)
Median	136.50	141.50
Q1, Q3	125.00, 143.00	135.00, 150.00
Minimum, maximum	105.0, 170.0	113.0, 181.0
Model-adjusted change from baseline		
LS Mean (SE)	-12.99 (1.445)	-6.24 (1.483)
95% confidence interval	(-15.83, -10.16)	(-9.15, -3.34)
Difference from glimepiride		
Difference of LS means	-6.75	
95% confidence interval	(-10.83, -2.67)	
One-sided p-value	0.0006	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure.

Table 177. Change From Baseline in FPG (mg/dL) at Week 60 Return-to-Baseline Analysis Results, ITT, Trial C-480

Characteristics	Bexagliflozin 20 mg (N=213)	Glimepiride (N=213)
Number of subjects	212	213
Number (%) of values imputed for Week 24	21 (9.9)	23 (10.8)
Baseline		
Mean (SD)	172 (35)	174(39)
Median	168	166
Q1, Q3	149, 191	148, 196
Minimum, maximum	90, 286	88, 376
Week 24 (observed)		
Mean (SD)	149 (29)	157 (41)
Median	144	151
Q1, Q3	130, 169	130, 180
Minimum, maximum	85, 239	70, 333
Model-adjusted change from baseline		
LS mean (SE)	-22 (2)	-14 (3)
95% confidence interval	-27, -17	-19, -9
Difference from glimepiride		
Difference of LS means	-8	
95% confidence interval	(-15, -1)	
One-sided p-value*	0.0116	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value

16.5.5. Trial C-448

Table 178. Change From Baseline in Weight (kg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m² Subgroup, Trial C-448

Characteristics	Bexagliflozin 20 mg (N=125)	Placebo (N=122)
Number of subjects	125	122
Number (%) of values imputed for Week 24	3 (2.4)	6 (4.9)
Baseline		
Mean (SD)	88.81 (18.571)	88.90 (18.963)
Median	84.10	87.60
Q1, Q3	73.70, 102.70	74.60, 101.00
Minimum, maximum	54.7, 133.3	52.7, 147.8
Week 24 (Observed)		
Mean (SD)	86.50 (18.184)	89.01 (19.104)
Median	82.65	87.60
Q1, Q3	71.50, 101.60	72.25, 102.25
Minimum, maximum	51.3, 128.7	52.1, 149.2
Model-adjusted change from baseline		
LS mean (SE)	-2.14 (0.263)	-0.43 (0.267)
95% confidence interval	(-2.66, -1.63)	(-0.96, 0.09)
Difference from placebo		
Difference of LS means	-1.71	
95% confidence interval	(-2.44, -0.97)	
One-sided p-value	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Table 179. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline SBP ≥ 130 mm Hg Subgroup, Trial C-448

Characteristics	Bexagliflozin 20 mg (N=107)	Placebo (N=113)
Number of subjects	107	113
Number (%) of values imputed for Week 24	3 (2.8)	6 (5.3)
Baseline		
Mean (SD)	143.23 (10.460)	144.33 (10.580)
Median	140.00	144.00
Q1, Q3	136.00, 150.00	136.00, 150.00
Minimum, maximum	130.0, 174.0	130.0, 170.0
Week 24 (observed)		
Mean (SD)	133.40 (16.276)	136.70 (15.170)
Median	132.00	140.00
Q1, Q3	122.00, 142.00	126.00, 148.00
Minimum, maximum	100.0, 203.0	96.0, 179.0
Model-adjusted change from baseline		
LS mean (SE)	-9.40 (1.478)	-6.92 (1.450)
95% confidence interval	(-12.30, -6.50)	(-9.76, -4.08)

	Bexagliflozin 20 mg (N=107)	Placebo (N=113)
Characteristics		
Difference from placebo		
Difference of LS means	-2.48	
95% confidence interval	(-6.55, 1.58)	
One-sided p-value*	0.1157	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure. *nominal p-value

Table 180. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-448

	Bexagliflozin 20 mg (N=157)	Placebo (N=155)
Characteristics		
Number of subjects	157	155
Number (%) of values imputed for Week 24	5 (3.2)	7 (4.5)
Baseline		
Mean (SD)	156 (46)	155 (40)
Median	151	151
Q1, Q3	128, 176	124, 182
Minimum, maximum	68, 324	52, 281
Week 24 (observed)		
Mean (SD)	133 (45)	147 (42)
Median	126	142
Q1, Q3	106, 150	119, 169
Minimum, maximum	49, 344	-2, 344
Model-adjusted change from baseline		
LS mean (SE)	-22 (3)	-8 (3)
95% confidence interval	(-28, -15)	(-14, -2)
Difference from placebo		
Difference of LS means	-14	
95% confidence interval	(-23, -5)	
One-sided p-value*	0.0012	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value

16.5.6. Trial C-476

Table 181. Change From Baseline in Weight (kg) at Week 48 Return-to-Baseline Analysis Results, ITT, Baseline BMI ≥ 25 kg/m² Subgroup, Trial C-476

	Bexagliflozin 20 mg (N=1047)	Placebo (N=522)
Characteristics		
Number of subjects	1047	522
Number (%) of values imputed for Week 48	134 (12.8)	72 (13.8)
Baseline		
Mean (SD)	97.00 (19.800)	94.86 (19.023)
Median	95.70	94.50
Q1, Q3	82.50, 109.00	80.90, 106.25
Minimum, maximum	55.1, 195.1	53.4, 171.0

Characteristics	Bexagliflozin 20 mg (N=1047)	Placebo (N=522)
Week 24 (Observed)		
Mean (SD)	94.04 (19.432)	94.68 (19.405)
Median	92.50	94.00
Q1, Q3	79.80, 105.50	80.30, 106.70
Minimum, maximum	53.4, 175.6	51.0, 175.0
Model-adjusted change from baseline		
LS Mean (SE)	-2.66 (0.125)	-0.32 (0.174)
95% confidence interval	(-2.90, -2.41)	(-0.66, 0.02)
Difference from placebo		
Difference of LS means	-2.34	
95% confidence interval	(-2.76, -1.92)	
One-sided p-value	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: BMI, body mass index; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Table 182. Change From Baseline in SBP (mm Hg) at Week 24 Return-to-Baseline Analysis Results, ITT, Baseline SBP $\geq$ 140 mm Hg Subgroup, Trial C-476

Characteristics	Bexagliflozin 20 mg (N=448)	Placebo (N=215)
Number of Subjects	448	215
Number (%) of values imputed for Week 24	26 (5.8)	9 (4.2)
Baseline		
Mean (SD)	149.83 (9.214)	150.08 (8.453)
Median	148.00	148.00
Q1, Q3	143.00, 154.00	144.00, 155.00
Minimum, maximum	140.0, 227.0	140.0, 177.0
Week 24 (observed)		
Mean (SD)	140.16 (15.905)	142.74 (16.504)
Median	140.00	142.00
Q1, Q3	130.00, 150.00	134.00, 153.00
Minimum, maximum	97.0, 192.0	100.0, 209.0
Model-adjusted change from baseline		
LS mean (SE)	-9.24 (0.745)	-6.57 (1.069)
95% confidence interval	(-10.70, -7.78)	(-8.67, -4.48)
Difference from placebo		
Difference of LS means	-2.66	
95% confidence interval	(-5.23, -0.10)	
One-sided p-value	0.0209	

Source: Statistical reviewer's analysis

Abbreviations: ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error; SBP, systolic blood pressure.

Table 183. Change From Baseline in FPG (mg/dL) at Week 24 Return-to-Baseline Analysis Results, ITT, Trial C-476

Characteristics	Bexagliflozin 20 mg (N=1133)	Placebo (N=567)
Number of subjects	1132	567
Number (%) of values imputed for Week 24	79 (7.0)	35 (6.2)
Baseline		
Mean (SD)	166 (47)	162(47)
Median	142	157
Q1, Q3	135, 194	131, 189
Minimum, maximum	50, 371	43, 362
Week 24 (observed)		
Mean (SD)	139 (39)	159 (50)
Median	135	155
Q1, Q3	115, 158	125, 187
Minimum, maximum	43, 355	52, 378
Model-adjusted change from baseline		
LS mean (SE)	-23(1)	-4 (2)
95% confidence interval	-26, -21	-7, 0
Difference from placebo		
Difference of LS means	-20	
95% confidence interval	(-24, -15)	
One-sided p-value*	<0.0001	

Source: Statistical reviewer's analysis

Abbreviations: FPG, fasting plasma glucose; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error. *nominal p-value

16.6. Primary Endpoint Sensitivity Analysis Results

16.6.1. Trial C-450

Table 184. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-450

Penalty: Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)		Award: Value (%) Subtracted From Imputed Missing Week 24 Value of Placebo Group (Delta 2)					
Mean difference							
95% CI							
P-value		0	0.4	0.8	1.2	1.6	2.0
0		-0.40 (-0.64, -0.16) 0.0006	-0.38 (-0.62, -0.14) 0.0011	-0.36 (-0.60, -0.12) 0.0019	-0.34 (-0.58, -0.10) 0.0032	-0.32 (-0.57, -0.07) 0.0053	-0.30 (-0.55, -0.05) 0.0087
0.4		-0.36 (-0.60, -0.12) 0.0017	-0.34 (-0.58, -0.10) 0.0028	-0.32 (-0.57, -0.08) 0.0045	-0.30 (-0.55, -0.06) 0.0073	-0.29 (-0.53, -0.04) 0.0116	-0.27 (-0.52, -0.02) 0.0180
0.8		-0.33 (-0.57, -0.08) 0.0044	-0.31 (-0.55, -0.06) 0.0069	-0.29 (-0.54, -0.04) 0.0107	-0.27 (-0.52, -0.02) 0.0163	-0.25 (-0.50, 0.00) 0.0244	-0.23 (-0.49, 0.02) 0.0358 ^[a]
1.2		-0.29 (-0.54, -0.04) 0.0111	-0.27 (-0.53, -0.02) 0.0164	-0.26 (-0.51, 0.00) 0.0239	-0.24 (-0.49, 0.02) 0.0342 ^[a]	-0.22 (-0.47, 0.04) 0.0482 ^[a]	-0.20 (-0.46, 0.06) 0.0665 ^[a]
1.6		-0.26 (-0.52, 0.00) 0.0252 ^[a]	-0.24 (-0.50, 0.02) 0.0352 ^[a]	-0.22 (-0.48, 0.04) 0.0484 ^[a]	-0.20 (-0.46, 0.06) 0.0656 ^[a]	-0.18 (-0.45, 0.08) 0.0873 ^[a]	-0.16 (-0.43, 0.10) 0.1140 ^[a]
2.0		-0.22 (-0.49, 0.05) 0.0513 ^[a]	-0.21 (-0.48, 0.06) 0.0678 ^[a]	-0.19 (-0.46, 0.08) 0.0885 ^[a]	-0.17 (-0.44, 0.10) 0.1138 ^[a]	-0.15 (-0.42, 0.13) 0.1439 ^[a]	-0.13 (-0.41, 0.15) 0.1787 ^[a]

Source: Statistical reviewer's analysis

^[a] Tipping point of significant results to insignificant results.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat.

16.6.2. Trial C-419

Table 185. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-419

Penalty: Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)		Award: Value (%) Subtracted From Imputed Missing Week 24 Value of Placebo Group (Delta 2)				
Mean difference						
95% CI						
P-value	0	0.5	1.0	1.5	2.0	2.5
0.0	-0.50 (-0.71, -0.30) <.0001	-0.46 (-0.67, -0.26) <.0001	-0.42 (-0.63, -0.21) <.0001	-0.38 (-0.59, -0.17) 0.0002	-0.34 (-0.55, -0.12) 0.0011	-0.30 (-0.52, -0.07) 0.0045
0.5	-0.46 (-0.67, -0.25) <.0001	-0.41 (-0.63, -0.20) 0.0001	-0.37 (-0.59, -0.16) 0.0003	-0.33 (-0.55, -0.12) 0.0012	-0.29 (-0.51, -0.07) 0.0048	-0.25 (-0.48, -0.02) 0.0155
1.0	-0.41 (-0.63, -0.19) 0.0001	-0.37 (-0.59, -0.15) 0.0004	-0.33 (-0.55, -0.11) 0.0017	-0.29 (-0.51, -0.06) 0.0058	-0.25 (-0.47, -0.02) 0.0173	-0.20 (-0.44, 0.03) 0.0441 ^[a]
1.5	-0.36 (-0.59, -0.14) 0.0008	-0.32 (-0.55, -0.10) 0.0026	-0.28 (-0.51, -0.05) 0.0077	-0.24 (-0.47, -0.01) 0.0209	-0.20 (-0.44, 0.04) 0.0496	-0.16 (-0.40, 0.09) 0.1022 ^[a]
2.0	-0.32 (-0.55, -0.08) 0.0043	-0.28 (-0.51, -0.04) 0.0110	-0.23 (-0.47, 0.00) 0.0266	-0.19 (-0.43, 0.05) 0.0582 ^[a]	-0.15 (-0.40, 0.09) 0.1133 ^[a]	-0.11 (-0.37, 0.14) 0.1952 ^[a]
2.5	-0.27 (-0.52, -0.02) 0.0162	-0.23 (-0.48, 0.02) 0.0350 ^[a]	-0.19 (-0.44, 0.06) 0.0700 ^[a]	-0.15 (-0.40, 0.11) 0.1279 ^[a]	-0.11 (-0.36, 0.15) 0.2114 ^[a]	-0.06 (-0.33, 0.20) 0.3163 ^[a]

Source: Statistical reviewer's analysis

^[a] Tipping point of significant results to insignificant results.

Abbreviation: HbA1c, hemoglobin A1c; ITT, intention-to-treat.

16.6.3. Trial C-423

Table 186. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-423

Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
0.00		
Model-adjusted change from baseline		
LS mean (SE)	-0.77 (0.051)	-0.85 (0.050)
95% confidence interval	(-0.87, -0.67)	(-0.95, -0.76)
Difference from sitagliptin 100 mg		
Difference of LS means	0.08	
95% confidence interval	(-0.06, 0.22)	
0.35 (Null Assumption Imputation)		
Model-adjusted change from baseline		
LS mean (SE)	-0.75 (0.052)	-0.85 (0.051)
95% confidence interval	(-0.86, -0.65)	(-0.95, -0.75)
Difference from sitagliptin 100 mg		
Difference of LS means	0.10	
95% confidence interval	(-0.04, 0.24)	
0.70		
Model-adjusted change from baseline		
LS mean (SE)	-0.73 (0.054)	-0.85 (0.052)
95% confidence interval	(-0.84, -0.63)	(-0.96, -0.75)
Difference from sitagliptin 100 mg		
Difference of LS means	0.12	
95% confidence interval	(-0.03, 0.27)	
1.05		
Model-adjusted change from baseline		
LS mean (SE)	-0.71 (0.055)	-0.85 (0.054)
95% confidence interval	(-0.82, -0.60)	(-0.96, -0.75)
Difference from sitagliptin 100 mg		
Difference of LS means	0.14	
95% confidence interval	(-0.01, 0.29)	
1.40		
Model-adjusted change from baseline		
LS mean (SE)	-0.69 (0.057)	-0.85 (0.056)
95% confidence interval	(-0.80, -0.58)	(-0.96, -0.75)
Difference from sitagliptin 100 mg		
Difference of LS means	0.16	
95% confidence interval	(0.01, 0.32)	
1.75 (Tipping Point)		
Model-adjusted change from baseline		
LS mean (SE)	-0.67 (0.059)	-0.86 (0.058)
95% confidence interval	(-0.79, -0.56)	(-0.97, -0.74)
Difference from sitagliptin 100 mg		
Difference of LS means	0.18	
95% confidence interval	(0.02, 0.35)	

Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)	Bexagliflozin 20 mg (N=191)	Sitagliptin 100 mg (N=193)
2.10		
Model-adjusted change from baseline		
LS mean (SE)	-0.65 (0.061)	-0.86 (0.060)
95% confidence interval	(-0.77, -0.53)	(-0.97, -0.74)
Difference from sitagliptin 100 mg		
Difference of LS means	0.20	
95% confidence interval	(0.03, 0.37)	
One-sided p-value	0.9909	

Source: Statistical reviewer's analysis

Abbreviations: HbA1c, hemoglobin A1c; ; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

16.6.4. Trial C-480

Table 187. Change From Baseline in HbA1c (%) at Week 60 Tipping Point Sensitivity Analysis, ITT, Trial C-480

Value (%) Added to Imputed Missing Week 60 Value of Bexagliflozin 20 mg Group (Delta 1)	Bexagliflozin 20 mg (N=213)	Glimepiride (N=213)
0.00		
Model-adjusted change from baseline		
LS mean (SE)	-0.65 (0.059)	-0.63 (0.059)
95% confidence interval	(-0.77, -0.54)	(-0.75, -0.52)
Difference from glimepiride		
Difference of LS means	-0.02	
95% confidence interval	(-0.19, 0.14)	
0.35 (Null Assumption Imputation)		
Model-adjusted change from baseline		
LS mean (SE)	-0.63 (0.060)	-0.63 (0.060)
95% confidence interval	(-0.74, -0.51)	(-0.75, -0.51)
Difference from glimepiride		
Difference of LS means	0.01	
95% confidence interval	(-0.16, 0.17)	
0.70		
Model-adjusted change from baseline		
LS mean (SE)	-0.60 (0.061)	-0.63 (0.062)
95% confidence interval	(-0.72, -0.48)	(-0.75, -0.51)
Difference from glimepiride		
Difference of LS means	0.03	
95% confidence interval	(-0.14, 0.20)	
1.05		
Model-adjusted change from baseline		
LS mean (SE)	-0.57 (0.063)	-0.63 (0.063)
95% confidence interval	(-0.69, -0.45)	(-0.75, -0.51)
Difference from glimepiride		
Difference of LS means	0.06	
95% confidence interval	(-0.11, 0.24)	

Value (%) Added to Imputed Missing Week 60 Value of Bexagliflozin 20 mg Group (Delta 1)	Bexagliflozin 20 mg (N=213)	Glimepiride (N=213)
1.40		
Model-adjusted change from baseline		
LS mean (SE)	-0.54 (0.065)	-0.63 (0.065)
95% confidence interval	(-0.67, -0.41)	(-0.76, -0.50)
Difference from glimepiride		
Difference of LS means	0.09	
95% confidence interval	(-0.09, 0.27)	
1.75 (Tipping Point)		
Model-adjusted change from baseline		
LS mean (SE)	-0.51 (0.067)	-0.63 (0.068)
95% confidence interval	(-0.65, -0.38)	(-0.76, -0.50)
Difference from glimepiride		
Difference of LS means	0.12	
95% confidence interval	(-0.07, 0.30)	
2.10		
Model-adjusted change from baseline		
LS mean (SE)	-0.49 (0.070)	-0.63 (0.070)
95% confidence interval	(-0.62, -0.35)	(-0.77, -0.49)
Difference from glimepiride		
Difference of LS means	0.14	
95% confidence interval	(-0.05, 0.34)	
2.45 (near or just pass the tipping point)		
Model-adjusted change from baseline		
LS mean (SE)	-0.46 (0.072)	-0.63 (0.073)
95% confidence interval	(-0.60, -0.32)	(-0.77, -0.49)
Difference from glimepiride		
Difference of LS means	0.17	
95% confidence interval	(-0.03, 0.37)	

Source Statistical reviewer's analysis

Abbreviations: HbA1c, hemoglobin A1c; ; ITT, intention-to-treat; LS, least square; N, number of subjects; Q, quartile; SD, standard deviation; SE, standard error.

Table 188. Change From Baseline in HbA1c (%) at Week 60 Tipping Point Sensitivity Analysis, ITT, Trial C-480

Penalty: Value (%) Added to Imputed Missing Week 60 Value of Bexagliflozin 20 mg Group (Delta 1)		Award: Value (%) Subtracted From Imputed Missing Week 60 Value of Glimepiride Group (Delta 2)				
Mean difference						
95% CI		0	1	2	3	4
						5
0		-0.05 (-0.21, 0.12)	0.01 (-0.16, 0.17)	0.06 (-0.11, 0.23)	0.12 (-0.07, 0.30)	0.17 (-0.02, 0.36) ^[a]
1.0		0.01 (-0.16, 0.18)	0.07 (-0.11, 0.24)	0.12 (-0.06, 0.30)	0.17 (-0.01, 0.36) ^[a]	0.23 (0.03, 0.43) ^[a]
2.0		0.07 (-0.11, 0.25)	0.12 (-0.06, 0.31)	0.18 (-0.01, 0.37) ^[a]	0.23 (0.04, 0.43) ^[a]	0.29 (0.08, 0.50) ^[a]
3.0		0.13 (-0.06, 0.32)	0.18 (-0.01, 0.38) ^[a]	0.24 (0.04, 0.44) ^[a]	0.29 (0.08, 0.50) ^[a]	0.35 (0.13, 0.57) ^[a]
4.0		0.19 (-0.02, 0.39) ^[a]	0.24 (0.03, 0.45) ^[a]	0.30 (0.08, 0.51) ^[a]	0.35 (0.13, 0.57) ^[a]	0.40 (0.17, 0.64) ^[a]
5.0		0.25 (0.02, 0.47) ^[a]	0.30 (0.07, 0.53) ^[a]	0.35 (0.12, 0.59) ^[a]	0.41 (0.17, 0.65) ^[a]	0.46 (0.21, 0.71) ^[a]

Source: Statistical reviewer's analysis

^[a] Tipping point of significant results to insignificant results.

Abbreviations: HbA1c, hemoglobin A1c; ITT, intention-to-treat.

16.6.5. Trial C-448

Table 189. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-448

Penalty: Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)		Award: Value (%) Subtracted From Imputed Missing Week 24 Value of Placebo Group (Delta 2)					
Mean difference							
95% CI							
p-value		0	0.5	1.0	1.5	2.0	2.5
0.0		-0.26	-0.25	-0.23	-0.22	-0.20	-0.19
		(-0.44, -0.09)	(-0.42, -0.07)	(-0.41, -0.06)	(-0.40, -0.04)	(-0.39, -0.02)	(-0.37, 0.00)
		0.0016	0.0027	0.0047	0.0081	0.0136	0.0222
0.5		-0.25	-0.24	-0.22	-0.21	-0.19	-0.18
		(-0.43, -0.07)	(-0.41, -0.06)	(-0.40, -0.04)	(-0.39, -0.03)	(-0.37, -0.01)	(-0.36, 0.01)
		0.0027	0.0045	0.0075	0.0123	0.0200	0.0315 ^[a]
1.0		-0.24	-0.22	-0.21	-0.19	-0.18	-0.16
		(-0.42, -0.06)	(-0.40, -0.04)	(-0.39, -0.03)	(-0.37, -0.01)	(-0.36, 0.01)	(-0.35, 0.02)
		0.0046	0.0073	0.0118	0.0188	0.0293 ^[a]	0.0444 ^[a]
1.5		-0.22	-0.21	-0.19	-0.18	-0.16	-0.15
		(-0.40, -0.04)	(-0.39, -0.03)	(-0.38, -0.01)	(-0.36, 0.00)	(-0.35, 0.02)	(-0.34, 0.04)
		0.0076	0.0119	0.0184	0.0281 ^[a]	0.0422 ^[a]	0.0615 ^[a]
2.0		-0.21	-0.20	-0.18	-0.17	-0.15	-0.14
		(-0.39, -0.03)	(-0.38, -0.01)	(-0.37, 0.00)	(-0.35, 0.02)	(-0.34, 0.04)	(-0.33, 0.06)
		0.0125	0.0188	0.0281 ^[a]	0.0413 ^[a]	0.0596 ^[a]	0.0836 ^[a]
2.5		-0.20	-0.18	-0.17	-0.15	-0.14	-0.12
		(-0.39, -0.01)	(-0.37, 0.01)	(-0.36, 0.02)	(-0.34, 0.04)	(-0.33, 0.06)	(-0.32, 0.07)
		0.0200	0.0290 ^[a]	0.0417 ^[a]	0.0590 ^[a]	0.0819 ^[a]	0.1110 ^[a]

Source: Statistical reviewer's analysis

^[a] Tipping point of significant results to insignificant results.

Abbreviations: HbA1c, hemoglobin A1c; ; ITT, intention-to-treat.

16.6.6. Trial C-476

Table 190. Change From Baseline in HbA1c (%) at Week 24 Tipping Point Sensitivity Analysis, ITT, Trial C-476

Penalty: Value (%) Added to Imputed Missing Week 24 Value of Bexagliflozin 20 mg Group (Delta 1)		Award: Value (%) Subtracted From Imputed Missing Week 24 Value of Placebo Group (Delta 2)				
Mean difference						
95% CI						
p-value	0	1	2.0	3.0	4.0	5.0
0	-0.48 (-0.57, -0.39) <.0001	-0.43 (-0.51, -0.34) <.0001	-0.37 (-0.46, -0.29) <.0001	-0.32 (-0.42, -0.23) <.0001	-0.27 (-0.37, -0.17) <.0001	-0.22 (-0.32, -0.11) <.0001
1.0	-0.42 (-0.51, -0.33) <.0001	-0.37 (-0.46, -0.28) <.0001	-0.32 (-0.41, -0.22) <.0001	-0.26 (-0.36, -0.17) <.0001	-0.21 (-0.31, -0.11) <.0001	-0.16 (-0.27, -0.05) 0.0020
2.0	-0.36 (-0.46, -0.26) <.0001	-0.31 (-0.40, -0.21) <.0001	-0.26 (-0.35, -0.16) <.0001	-0.20 (-0.31, -0.10) 0.0001	-0.15 (-0.26, -0.04) 0.0029	-0.10 (-0.21, 0.01) 0.0435 ^[a]
3.0	-0.30 (-0.41, -0.20) <.0001	-0.25 (-0.36, -0.14) <.0001	-0.20 (-0.30, -0.09) 0.0002	-0.14 (-0.26, -0.03) 0.0057	-0.09 (-0.21, 0.02) 0.0603 ^[a]	-0.04 (-0.16, 0.08) 0.2622 ^[a]
4.0	-0.24 (-0.36, -0.12) <.0001	-0.19 (-0.31, -0.07) 0.0008	-0.14 (-0.26, -0.02) 0.0125	-0.08 (-0.21, 0.04) 0.0879 ^[a]	-0.03 (-0.16, 0.09) 0.3079 ^[a]	0.02 (-0.11, 0.15) 0.6158 ^[a]
5.0	-0.18 (-0.31, -0.05) 0.0032	-0.13 (-0.26, 0.00) 0.0261 ^[a]	-0.08 (-0.21, 0.06) 0.1257 ^[a]	-0.03 (-0.16, 0.11) 0.3564 ^[a]	0.03 (-0.11, 0.17) 0.6469 ^[a]	0.08 (-0.07, 0.22) 0.8589 ^[a]

Source: Statistical reviewer's analysis

^[a] Tipping point of significant results to insignificant results.

Abbreviations: HbA1c, hemoglobin A1c; ; ITT, intention-to-treat.

17. Clinical Safety: Additional Information and Assessment

17.1. MACE Meta-Analysis

17.1.1. Data Sources

The electronic documents and subject-level data of the prespecified cardiovascular (CV) meta-analysis of the clinical development program of bexagliflozin were submitted by the Applicant as a part of the NDA submission of bexagliflozin. The Applicant's report on the meta-analysis and SAS codes used to generate the analysis results were used for comparison and verification purposes. The NDA materials utilized in the evaluation of CV safety are archived in the CDER Electronic Document Room:

Table 191. Data Sources Used to Assess Cardiovascular Safety

Study report and analysis plan	\\CDSESUB1\evsprod\NDA214373\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\cv-risk\cv-risk-meta-analysis-report.pdf
Integrated analysis datasets	
(Subject Level)	\\CDSESUB1\evsprod\NDA214373\0001\m5\datasets\cv-risk\analysis\adam\datasets\adsl.xpt
(Time-to-event)	\\CDSESUB1\evsprod\NDA214373\0001\m5\datasets\cv-risk\analysis\adam\datasets\adtte.xpt
(Adjudicated Events)	\\CDSESUB1\evsprod\NDA214373\0001\m5\datasets\cv-risk\analysis\adam\datasets\adfa.xpt
Define file	\\CDSESUB1\evsprod\NDA214373\0001\m5\datasets\cv-risk\analysis\adam\datasets\define.xml

17.1.2. Data Quality

The format, content, and documentation of the submitted data were adequate to conduct a statistical evaluation of the CV risk associated with bexagliflozin based on the prespecified meta-analysis plan. Data from individual trials were integrated into single datasets. The data define file of the integrated datasets, in combination with the submitted Analysis Data Reviewer's Guide, provides sufficient information about the variables included in each dataset. Using the submitted data, the reviewer was able to reproduce the findings included in the CV meta-analysis study report, and perform other key analyses conducted as part of this statistical review. There were no notable data quality or analysis issues discovered in this electronic submission that would impact the evaluation and conclusions regarding CV safety of bexagliflozin.

17.1.3. Summary of Study Design

During the clinical development of bexagliflozin, the CV meta-analysis was planned in accordance with the FDA Guidance for Industry: *Diabetes Mellitus – Evaluating Cardiovascular*

Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008), for a premarket CV risk assessment. The primary objective of this meta-analysis was to exclude a hazard ratio of MACE+ greater than 1.8 for subjects exposed to bexagliflozin compared to subjects exposed to comparators. MACE+ was defined as a 4-component composite endpoint with the following components: CV death (including deaths of unknown cause), nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

The meta-analysis includes all phase 2 and phase 3 randomized controlled clinical trials in which bexagliflozin tablets 20 mg once daily, or bexagliflozin capsules 20 mg once daily, were administered for a treatment period of at least 12 weeks. As a result, the meta-analysis synthesized nine phase 2 and phase 3 trials designed to evaluate the efficacy and safety of bexagliflozin. Seven of these trials included a randomized placebo control arm and two trials included an active control arm (glimepiride in Trial C-480, sitagliptin in Trial C-423). One placebo-controlled trial, Trial C-476, recruited subjects with elevated CV risk and was expected to contribute a preponderance of events for the meta-analysis.

In the clinical development program of bexagliflozin, CV events were prospectively defined, collected, and adjudicated in a consistent manner. All suspected CV events were adjudicated by an independent and blinded CEC, according to a prespecified adjudication plan.

A summary of design characteristics of these phase 2 and phase 3 trials is presented in [Table 192](#).

Table 192. Summary of Trials Included in the Meta-Analysis

Trial ID	Design Features	Treatment Arms	No. of Subjects	Treatment Duration	Population	Region
Monotherapy						
C-418	R, DB, PC, PG, MC Phase 2b	Bexa capsules 20 mg Placebo	145 141	96 weeks	T2DM	Multinational
C-449	R, DB, PC, PG, MC Phase 2b	Bexa tablets 5 mg Bexa tablets 10 mg Bexa tablets 20 mg Placebo	72 72 76 72	12 weeks	T2DM	United States, Japan
C-450	R, DB, PC, PG, MC Phase 3	Bexa tablets 20 mg Placebo	138 69	24 weeks	T2DM	United States, Canada
Combination Therapy: add-on to metformin						
C-419	R, DB, PC, PG, MC Phase 3	Bexa tablets 20 mg Placebo	158 159	24 weeks	T2DM	United States, Japan
C-423	R, DB, AC, PG, MC Phase 3	Bexa tablets 20 mg Sitagliptin	191 193	24 weeks	T2DM	Multinational
C-480	R, DB, AC, PG, MC Phase 3	Bexa tablets 20 mg Glimepiride	213 213	96 weeks	T2DM	Multinational

Trial ID	Design Features	Treatment Arms	No. of Subjects	Treatment Duration	Population	Region
Special Populations						
C-448	R, DB, PC, PG, MC Phase 3	Bexa tablets 20 mg Placebo	157 155	24 weeks	T2DM with CKD	Multinational
C-476 (CVOT)	R, DB, PC, PG, MC Phase 3	Bexa tablets 20 mg Placebo	1132 567	Event driven	T2DM with CV risk	Multinational
THR-1442-C-603A	R, DB, PC, PG, MC Phase 2/3	Bexa tablets 20 mg Placebo	83 84	12 weeks	hypertension ^a	US

Source: Generated by Reviewer.

^aOnly subjects with a history of diabetes were included in the CV meta-analysis.

Abbreviations: AC, active-controlled; Bexa, bexagliflozin; CV, cardiovascular; DB, double-blind; MC, multicenter; PC, placebo-controlled; PG, parallel-group; R, randomized; T2DM, type 2 diabetes mellitus.

The main eligibility criteria by study are summarized in [Table 193](#) below. All subjects had inadequate glycemic control at baseline, except for some enrolled in Study C-603A. Most of the study participants had normal renal function or mild impairment with an eGFR of ≥ 60 mL/min/1.73 m², while Trial C-448 recruited subjects with stage 3 chronic kidney disease ($30 \leq$ eGFR < 60 mL/min/1.73 m²).

Table 193. Main Inclusion Criteria for Trials Included in the Meta-Analysis

Protocol	Age (y)	BMI (kg m ⁻²)	GFR	Baseline HbA _{1c} (%)	SBP (mm Hg)	DBP (mm Hg)	Hepatic/Renal
Monotherapy							
THR-1442-C-449	≥ 20	≤ 40	≥ 60	7 to 8.5	≤ 160	≤ 95	ALT/AST $< 2.5 \times$ ULN, TSB $< 1.5 \times$ ULN; UACR ≤ 2000
THR-1442-C-418	≥ 18	≤ 45	≥ 50	7 to 10	≤ 160	≤ 95	$< 3 \times$ ULN
THR-1442-C-450	≥ 18	≤ 45	≥ 60	7 to 10.5	≤ 160	≤ 95	ALT/AST $< 2.5 \times$ ULN, TSB $< 1.5 \times$ ULN; UACR ≤ 2000
Combination Therapy							
THR-1442-C-419	≥ 20	≤ 45	≥ 60	7.5 to 10.5	≤ 180	≤ 110	ALT/AST $< 2.5 \times$ ULN, TSB $< 1.5 \times$ ULN
THR-1442-C-423	≥ 18	≤ 45	≥ 60	7 to 11	≤ 160	≤ 95	ALT/AST $\leq 2.5 \times$ ULN, ALP/TSB $\leq 1.5 \times$ ULN; UACR ≤ 1500
THR-1442-C-480	≥ 18	≤ 45	≥ 60	7 to 10.5	≤ 160	≤ 95	ALT/AST $\leq 2.5 \times$ ULN; ALP/TSB $\leq 1.5 \times$ ULN; UACR ≤ 1500
Special Populations							
THR-1442-C-448	≥ 20	≤ 45	≥ 30 & < 60	7 to 10.5	≤ 170	≤ 110	ALT/AST $\leq 2.5 \times$ ULN; ALP/TSB $\leq 1.5 \times$ ULN
THR-1442-C-476	≥ 40	Not specified	≥ 45	7 to 11	< 170	< 110	ALT/AST $\leq 2.5 \times$ ULN; ALP/TSB $\leq 1.5 \times$ ULN; UACR < 2000
THR-1442-C-603A	≥ 20	Not specified	≥ 45	≤ 9.5	ABPM ≥ 135	≤ 110	ALT/AST $\leq 2.5 \times$ ULN; ALP/TSB $\leq 1.5 \times$ ULN

Abbreviations: y: years; BMI: body mass index; GFR: glomerular filtration rate (mL min⁻¹ per 1.73 m²); HbA_{1c}: hemoglobin A_{1c}; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; TSB: total serum bilirubin; ALP: alkaline phosphatase; UACR: urine albumin/creatinine ratio; ABPM: ambulatory blood pressure monitoring

Source: Table 2, page 12, Bexagliflozin Cardiovascular Risk Assessment Statistical Report.

As Trial C-476 was expected to provide the majority of CV events for the meta-analysis, the study design of the trial is described below in more detail. Please refer to Sections [6.2](#) and [15.1](#) of the integrated review for study design details of the other phase 2/3 trials included in the meta-analysis.

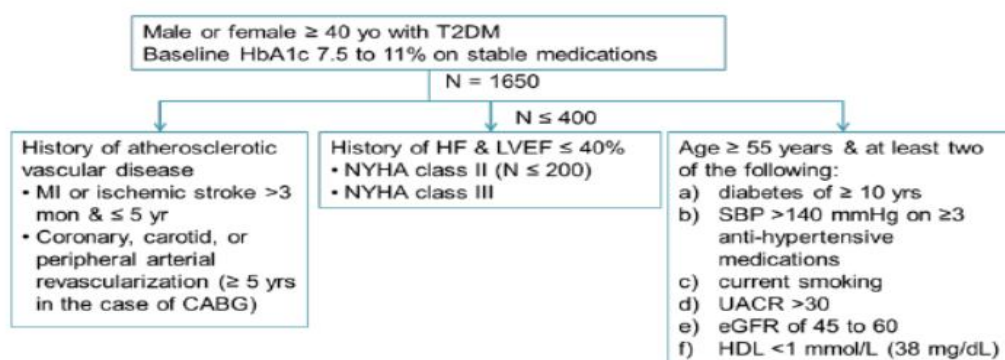
CVOT: Trial C-476

C-476 was a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group trial conducted to evaluate the effect of bexagliflozin on hemoglobin A1c in T2DM subjects with increased risk for CV adverse events. The primary safety objective of this study was to contribute at least 134 MACE+ to be pooled with CV events data from other phase 2/3 studies in the prespecified CV meta-analysis to exclude a hazard ratio of 1.8 or greater for subjects exposed to bexagliflozin compared to subjects exposed to comparators.

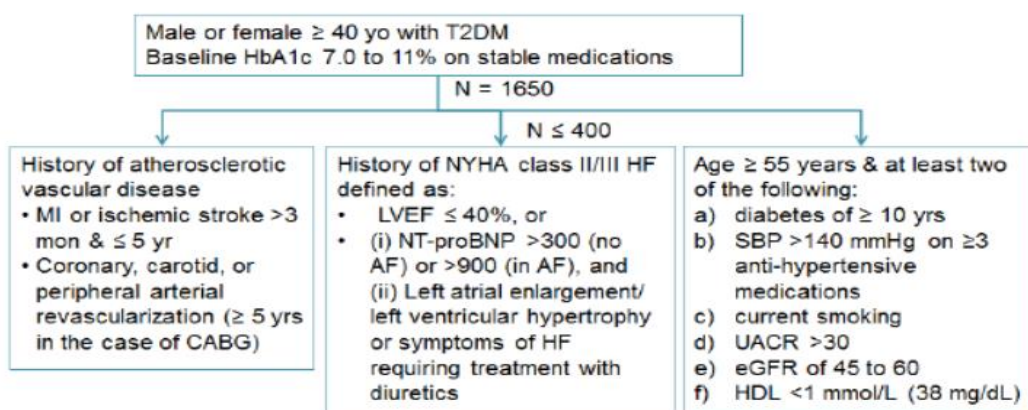
Trial C-476 planned to randomize approximately 1650 male and female subjects aged 40 years or older with T2DM and elevated CV risk from any of the following three groups: (1) a history of atherosclerotic vascular disease, (2) a history of the NYHA class II or class III heart failure, or (3) an age of ≥ 55 years plus at least two additional risk factors including: diabetes of long duration, hypertension, smoking, renal impairment, or dyslipidemia. If a subject qualified for more than one risk group, she or he was to be assigned to the group with the anticipated highest risk. To ensure that subjects with diverse CV risks were adequately represented, at least 352 subjects (21%) from each of the three risk groups were to be enrolled and at most 400 subjects with a history of class II or III heart failure were to be randomized. The definition of group 2 was modified to include subjects with preserved ejection fraction in Protocol Amendment 8 dated October 28, 2016, due to difficulties recruiting the desired numbers of participants in the heart failure group. The definitions of CV risk groups are presented in [Figure 66](#) below.

Figure 66. Cardiovascular Risk Eligibility Criteria for the Study Population, Trial C-476

(A) CV Risk Group Definition in Protocol Version 5



(B) CV Risk Group Definition in Protocol Version 8



Source: Figure 1, page 17, Bexagliflozin Cardiovascular Risk Assessment Statistical Report.

Abbreviations: AF, atrial fibrillation/flutter; CABG, coronary artery bypass grafting; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high density lipoprotein-associated cholesterol concentration; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NT-proBNP, N-terminal probrain natriuretic peptide; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; UACR, urinary albumin/creatinine ratio.

During a two-week run-in period, subjects were to self-administer placebo run-in product once daily. Adjustments of treatment for hypertension or dyslipidemia were not permitted during the screening and run-in periods. Eligible subjects were randomly assigned in a 2:1 ratio to take either bexagliflozin tablets 20 mg/day or placebo as an add-on therapy to other antidiabetic medications. Randomization was stratified by HbA1c ($>$ or $\leq 9.5\%$), eGFR ($<$ or ≥ 60 mL/min/1.73 m²), BMI ($<$ or ≥ 25 kg/m²), and history of heart failure.

The study subjects were to be contacted by the site at Weeks 2 and 18 by phone. At Weeks 6, 12, 24, 36 and 48 postrandomization, clinic visits were to be scheduled. After Week 48, clinic visits were to be scheduled every 24 weeks followed by a phone interview 12 weeks after each visit until the last randomized subject had completed at least 52 weeks of treatment and a total of 134 subjects had experienced an adjudicated MACE+ event. A follow-up visit was to be conducted 4 weeks after the conclusion of treatment.

During the first 24 weeks of the treatment period, hyperglycemia was to be managed with diet and exercise counseling and only with changes in antidiabetic therapy if clinically indicated.

After 24 weeks, the investigators were to prescribe adjustment of the antidiabetic therapies if deemed necessary. Any approved antidiabetic medications were allowed except an SGLT2 inhibitor.

At every visit, including the phone interviews, participants were queried regarding adverse events. Information on all events that potentially represented MACE+ was to be adjudicated by an independent CV CEC. All potential MACE+ were to be captured as serious adverse events (SAEs). The SAE listing was reviewed periodically by the CEC members to identify potential unreported MACE+. All subjects were to be followed by investigators for CV events assessment during the study, including during the post-treatment follow-up period after permanent cessation of randomized treatment.

Sample Size Calculation of Trial C-476

The sample size of Trial C-476 was determined based on the required number of MACE+ for the program-wide meta-analysis of CV safety, where nonexcess risk of bexagliflozin versus combined control was to be formally assessed based on a 1.8 risk margin for the hazard ratio of MACE+.

To ensure the meta-analysis would be adequately powered, it was assumed that no MACE+ events would be contributed by other studies. Assuming a true underlying hazard ratio of 1.0 between bexagliflozin and control, 134 positively adjudicated MACE+ events would be required to provide 87% power to demonstrate nonexcess risk using a 1.8 risk margin, at a 2-sided α level of 0.05.

Approximately 1650 randomized subjects would be needed in Trial C-476, based on the following assumptions:

- An enrollment period of 1 year
- A follow-up period of 1 to 3 years, except for premature withdrawals
- An annual premature withdrawal rate of 6.5%
- A randomization ratio of 2:1 (bexagliflozin versus placebo)
- A true underlying hazard ratio of 1.0 and a monthly event rate of 0.308% in placebo arm

17.1.4. Statistical Methodology

17.1.4.1. Analysis Populations and Cardiovascular Events Ascertainment

The prespecified primary analysis population used in the CV meta-analysis was the full analysis set (FAS) which included all subjects who were randomized in the phase 2 and phase 3 studies ([Table 192](#)) and received at least one dose of investigational product. Subjects were analyzed according to their randomized treatment.

Per the SAP of the CV meta-analysis, the prespecified primary endpoint was the time-to-first confirmed occurrence of a 4-component composite MACE+: CV death (including deaths of unknown cause), nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.

The SAP also lists the following key secondary endpoints for the assessment of CV safety:

- Time-to-first confirmed occurrence of any event in a 3-component composite endpoint of MACE: CV death (including deaths of unknown cause), nonfatal MI, or nonfatal stroke;
- Time-to-first confirmed occurrence of hospitalization for heart failure or CV death.

Additional exploratory endpoints included the time-to-first 6-component MACE consisting of CV death (including deaths of unknown cause), nonfatal MI, nonfatal stroke, hospitalization for unstable angina, unplanned coronary revascularization, and hospitalization for nonfatal heart failure. Time-to-first occurrence of each component of the 6-component MACE were considered exploratory endpoints and analyzed individually.

All CV events listed above were defined, identified, and adjudicated consistently across the phase 2 and phase 3 clinical development program of bexagliflozin. Suspected CV events occurring subsequent to randomization were reported by investigators and sent for adjudication by the independent CEC. Additionally, serious adverse event listings were reviewed monthly for any unreported potential events by the CEC members. If such events were identified, the information required for adjudication was provided by the clinical investigators and assembled by the Applicant for delivery to the CEC. The CEC was responsible for reviewing and adjudicating suspected CV endpoints in a blinded manner, according to a prespecified adjudication process outlined in the CEC Manual of Operation (Appendix 1 of the CV-meta-analysis study report).

The following censoring schemes were used for CV event ascertainment in time-to-event analyses:

- On-study: Events that occurred during the course of the study from the date of first dose following randomization (including both on- and off-treatment periods) were captured. Subjects who had not experienced such an event were censored on their last date of observation;
- On-treatment +7 days: Events that occurred while a subject was on the study treatment or within 7 days after the last date of treatment were captured; those who had not experienced such an event were censored on the last date of treatment +7 days, or their last date of observation, whichever was earlier;
- On-treatment +30 days: Events that occurred while a subject was on the study treatment or within 30 days after the last date of treatment were captured; those who had not experienced such an event were censored on the last date of treatment +30 days, or their last date of observation, whichever was earlier.

17.1.4.2. Analysis Methods for Cardiovascular Endpoints

Meta-Analysis Treatment Group

In the CV meta-analysis, all bexagliflozin dose levels were combined to form the bexagliflozin treatment group (referred to as “bexagliflozin”), and all the comparators were combined into the pooled comparator group (referred to as “control”). The analyses of the primary and secondary CV endpoints were based on the comparison of these two combined groups. Note that all trials in the meta-analysis included a single bexagliflozin treatment arm, bexagliflozin 20 mg once daily,

expect for Trial C-449, which randomized subjects to bexagliflozin 5 mg (n=72), 10 mg (n=72), and 20 mg once daily (n=76).

Meta-Analysis Study Group

The meta-analysis was not stratified by individual study. It was stratified by a dichotomous study group variable: C-476 versus other phase 2 and phase 3 studies combined, since a majority of the primary cardiovascular events were anticipated to occur in Trial C-476, which enrolled a population with elevated CV risk. The other eight studies were combined as only a few MACE events in total were anticipated to occur in these studies of a shorter duration and a population of low CV risk.

17.1.4.2.1. Analysis Methods for Primary Endpoint

The prespecified primary analysis was based upon time-to-event methods for MACE+, using the FAS and on-study censoring, which included positively adjudicated events that occurred during study participation. The following hypothesis was to be tested on MACE+:

H_0 : hazard ratio (HR) ≥ 1.8 ; versus

H_a : HR < 1.8 .

A stratified Cox proportional hazards regression model that included the meta-analysis treatment group (bexagliflozin or control) as a fixed effect and the meta-analysis study group (C-476 or other phase 2/3 studies) as the stratification factor was to be used. The between-treatment difference in time-to-first MACE+ was assessed by the hazard ratio estimate of bexagliflozin versus control. The two-sided 95% confidence interval for the hazard ratio was calculated using the Cox model and its upper bound was compared with the 1.8 risk margin. If the upper bound is below 1.8, nonexcess risk of bexagliflozin versus control would be met for MACE+.

A Cox regression model with the meta-analysis treatment group as the only independent variable was fitted to the time-to-first on-study adjudicated MACE+ for Trial C-476 and for the combined phase 2/3 studies excluding Trial C-476, separately. Kaplan-Meier (K-M) estimates and plots of time-to-first MACE+ would be presented by meta-analysis treatment groups for Trial C-476 and for other studies combined, respectively.

FDA Reviewer Comment: *Kaplan-Meier curves were provided in the Bexagliflozin Cardiovascular Risk Assessment Statistical Report submitted by the Applicant to visually compare the observed survival functions of the primary and secondary endpoints between the two meta-analysis treatment groups. However, due to the varying randomization ratios and baseline CV risks across trials included in the meta-analysis, the overall K-M plot may be subject to Simpson's Paradox and may be confounded by imbalance of baseline characteristics of the two combined groups for comparison. Therefore, while the K-M plots for CVOT C-476 are presented by treatment arms, the overall K-M plots of the CV meta-analysis are not included in this review.*

For the primary endpoint MACE+, sensitivity analyses were done on the FAS using “on-treatment +7 days” and “on-treatment +30 days” censorings, respectively. The same Cox model as that used for the primary analysis was applied in these sensitivity analyses to compare the two groups.

Other sensitivity analyses included:

- MACE+ censored upon other SGLT2 inhibitor initiation
- MACE+ before and after Trial C-476 amendment
- MACE+ tipping point analysis using multiple imputations for early withdrawal subjects who had not experienced an event prior to study withdrawal
- MACE+ with unknown death from control group excluded

17.1.4.2.2. Analysis Methods for Secondary Endpoints

Per the meta-analysis SAP, a hierarchical testing procedure was to be used for the primary and key secondary endpoints to preserve the family-wise type I error at a two-sided significance level of 0.05.

If the null hypothesis was rejected for the primary endpoint MACE+, nonexcess risk for the first key secondary endpoint time-to-first 3-component MACE was to be evaluated against a preset risk margin for the hazard ratio of 1.3. If the risk margin was met for MACE, superiority for the time-to-first occurrence of hospitalization for heart failure or CV death was to be tested.

All secondary and exploratory CV outcomes described in Section [17.1.4.1](#), including composite endpoints and their individual components, were analyzed in a similar manner as the primary endpoint using a Cox proportional hazard model, with the meta-analysis treatment group as the independent variable, stratified by meta-analysis study group. The estimated HR and its associated 95% CI were to be reported for these outcomes. The upper bound of the 95% CI for the hazard ratio was to be compared with 1.3. If the null hypothesis was rejected for both the primary and first key secondary endpoints, the upper bound of the 95% CI for the hazard ratio was to be compared with 1.0 to conclude whether exposure to bexagliflozin resulted in a reduced risk of CV death or hospitalization for heart failure in T2DM subjects.

Time-to-event analysis was conducted for Trial C-476 and for the combined phase 2/3 studies excluding Trial C-476, separately for the secondary CV endpoints.

17.1.5. Subject Disposition, Demographics and Baseline Characteristics

17.1.5.1. Subject Disposition

The FAS consisted of 4090 T2DM subjects, with 2437 (59.6%) randomized to receive bexagliflozin and 1653 (40.4%) randomized to receive active comparator drugs or placebo. An aggregate summary of the disposition including reasons for study dropout and premature discontinuation of study drug is provided in [Table 194](#).

The disposition of subjects in the combined bexagliflozin group was similar to that of the combined comparator group. Among the 4090 FAS subjects, 2148 (88.1%) in the combined bexagliflozin arm and 1442 (87.2%) in the comparators arm were followed until the completion of the studies, regardless of their adherence to randomized treatment. Across both arms, 500 subjects (12.2%) discontinued study participation prior to the end of the studies; premature study dropout was similar in both arms in terms of percentages (11.9% in bexagliflozin versus 12.8%

in control), as well as reasons for study dropout. The most common reason given for study discontinuation was withdrawal of consent which occurred in 122 subjects (5%) in bexagliflozin group and 91 subjects (5.5%) in control group, followed by lost to follow-up for 59 subjects (2.4%) in the bexagliflozin group and 48 subjects (2.9%) in the comparators group. The percentages of early study withdrawal due to adverse events are comparable between the two arms (bexagliflozin: 1.5%; control: 1.4%).

Reasons for treatment discontinuation were also provided in [Table 194](#). Fractions of premature treatment discontinuations were generally similar across the two comparison arms; a slightly larger fraction (108; 4.4%) of subjects on the bexagliflozin arm ceased doses due to adverse events compared to that in the control arm (59; 3.6%).

Table 194. Aggregate Summary of Subject Disposition, Full Analysis Set

Disposition	Bexagliflozin	Control
Number of subjects (FAS)	2437 (100%)	1653 (100%)
Completed Study	2148 (88.1%)	1442 (87.2%)
Discontinued from Study	289 (11.9%)	211 (12.8%)
Consent Withdrawal	122 (5.0%)	91 (5.5%)
Lost to follow up	59 (2.4%)	48 (2.9%)
Death	40 (1.6%)	27 (1.6%)
Adverse event	37 (1.5%)	23 (1.4%)
Withdrawal by investigator/Sponsor	13 (0.5%)	9 (0.5%)
Other	11 (0.5%)	7 (0.4%)
Major protocol violation	7 (0.3%)	6 (0.4%)
Completed treatment	2015 (82.7%)	1347 (81.5%)
Prematurely discontinued treatment	422 (17.3%)	306 (18.5%)
Consent withdrawal	133 (5.5%)	99 (6.0%)
Adverse event	108 (4.4%)	59 (3.6%)
Other	60 (2.5%)	58 (3.5%)
Lost to follow up	55 (2.3%)	40 (2.4%)
Death	31 (1.3%)	23 (1.4%)
Withdrawal by investigator/Sponsor	12 (0.5%)	12 (0.7%)
Major protocol violation	9 (0.4%)	8 (0.5%)
Noncompliance with study drug	5 (0.2%)	5 (0.3%)
Missing	9 (0.4%)	2 (0.1%)

Source: Generated by Reviewer.

Abbreviations: FAS, full analysis set

Among the FAS, 1699 (41.5%) were enrolled in the dedicated CVOT Trial C-476 which recruited a T2DM population with elevated CV risk. Trial C-476 was initiated on November 5, 2015 (first subject first visit) and was completed on November 6, 2019 (last subject last visit). The database was locked on November 22, 2019. A summary of subject disposition in Trial C-476 is presented in [Table 195](#) below. A total of 1469 subjects (86.4%) completed all protocol-specified study visits. A slightly larger proportion of subjects in the placebo arm (15%) discontinued study participation compared to that in the bexagliflozin group (12.8%). A higher proportion of subjects in the placebo group (29.3%) prematurely discontinued treatment compared with the bexagliflozin group (23.1%).

Table 195. Summary of Subject Disposition, Full Analysis Set, Trial C-476

Disposition	Bexagliflozin	Placebo
Number of subjects (FAS)	1132 (100%)	567 (100%)
Completed study	987 (87.2%)	482 (85.0%)
Discontinued from study	145 (12.8%)	85 (15.0%)
Consent withdrawal	53 (4.7%)	31 (5.5%)
Lost to follow up	31 (2.7%)	23 (4.1%)
Death	39 (3.4%)	25 (4.4%)
Adverse event	14 (1.2%)	5 (0.9%)
Withdrawal by investigator/Sponsor	6 (0.5%)	0 (0.0%)
Major protocol violation	2 (0.2%)	1 (0.2%)
Completed treatment	871 (76.9%)	401 (70.7%)
Prematurely discontinued treatment	261 (23.1%)	166 (29.3%)
Consent withdrawal	64 (5.7%)	39 (6.9%)
Adverse event	72 (6.4%)	34 (6.0%)
Other	45 (4.0%)	45 (7.9%)
Lost to follow up	27 (2.4%)	15 (2.6%)
Death	31 (2.7%)	21 (3.7%)
Withdrawal by investigator/Sponsor	4 (0.4%)	2 (0.4%)
Major protocol violation	4 (0.4%)	3 (0.5%)
Noncompliance with study drug	5 (0.4%)	5 (0.9%)
Missing	9 (0.8%)	2 (0.4%)

Source: Generated by Reviewer
Abbreviations: FAS, full analysis set

The aggregate summary of study follow-up in the FAS is depicted in [Table 196](#). In the pool of all studies, subjects in the bexagliflozin arm were followed for an average of 2 months longer than subjects in the comparator arm. The reason for this apparent imbalance is that subjects in Trial C-476 had longer mean follow-up time (approximately 900 days) than any of the other trials and Trial C-476 contributed twice as many subjects to the bexagliflozin arm than to the comparator arm in the pool of all studies due to its 2:1 randomization ratio. The mean and median follow-up duration was comparable between bexagliflozin and placebo in Trial C-476 as shown in the lower panel of [Table 196](#).

Approximately 54% of subjects had at least 48 weeks of study follow-up, 48% had 96 weeks or longer of follow-up, and around 16% had a follow-up duration longer than 144 weeks. The CVOT Trial C-476 contributed about 69% of the total subject-years of follow-up in the meta-analysis.

Table 196. Subject Follow-Up Until Study Discontinuation, Full Analysis Set
All Studies Included in the Meta-Analysis

Variable	Bexagliflozin (N=2437)	Control (N=1653)
Days of Follow-up		
Mean (SD)	567.6 (401.3)	508.3 (377.2)
Median	657	444
Min, max	1, 1407	2, 1394
Total subject-years of follow-up	3786.9	2300.6
Subjects with follow-up, n (%)		
≥48 weeks	1381 (56.7%)	845 (51.1%)
≥96 weeks	1205 (49.5%)	746 (45.1%)
≥144 weeks	440 (18.1%)	208 (12.6%)

Trial C-476		
Variable	Bexagliflozin (N=1132)	Placebo (N= 567)
Days of Follow-up		
Mean (SD)	901.4 (278.5)	895.0 (281.1)
Median	916.5	917
Min, max	20, 1407	14, 1394
Total subject-years of follow-up	2793.7	1389.3
Subjects with follow-up, n (%)		
≥48 weeks	1063 (93.9%)	533 (94.0%)
≥96 weeks	913 (80.7%)	456 (80.4%)
≥144 weeks	440 (38.9%)	208 (36.7%)

Source: Generated by the reviewer.

Summary statistics in [Table 197](#) below shows the distribution of treatment exposure by arm for all studies combined and for Trial C-476 only.

In the pool of all studies, subjects in the bexagliflozin arm had a longer average treatment exposure than subjects in the comparator arm. The reason for this imbalance is that subjects in Trial C-476 had longer mean treatment exposure (approximately 800 days) than any of the other trials and Trial C-476 contributed twice as many subjects to the bexagliflozin arm than to the comparator arm in the pool of all studies due to its 2:1 randomization ratio. The mean and median treatment exposure was comparable between bexagliflozin and placebo in Trial C-476 as shown in the lower panel of [Table 197](#).

Table 197. Summary of Treatment Exposure, Full Analysis Set
All Studies Included in the Meta-Analysis

Variable	Bexagliflozin (N=2437)	Control (N=1653)
Days of treatment exposure		
Mean (SD)	516.2 (391.0)	461.9 (361.2)
Median	558	227.5
Min, max	1, 1379	1, 1358
Subjects with treatment exposure, n (%)		
≥48 weeks	1312 (53.8%)	801 (48.5%)
≥96 weeks	1016 (41.7%)	613 (37.1%)
≥144 weeks	356 (14.6%)	156 (9.4%)
Trial C-476		
Variable	Bexagliflozin (N=1132)	Placebo (N=567)
Days of treatment exposure		
Mean (SD)	812.7 (323.4)	791.8 (326.7)
Median	863.5	852
Min, max	1, 1379	2, 1358
Subjects with treatment exposure, n (%)		
≥48 weeks	1002 (88.5%)	495 (87.3%)
≥96 weeks	819 (72.4%)	407 (71.8%)
≥144 weeks	356 (31.5%)	156 (27.5%)

Source: Generated by reviewer.

17.1.5.2. Demographics and Baseline Characteristics

[Table 198](#) summarizes the demographics and baseline characteristics of the FAS subjects pooled across all studies included in the CV meta-analysis and in Trial C-476 alone. The demographics for the 4090 subjects in the FAS were generally well-balanced between the comparison groups in all studies combined and in the standalone Trial C-476.

For all studies combined, imbalances between comparison arms were observed for baseline cardiovascular history and history of insulin prescription, due to the 2:1 randomization ratio in Trial C-476 which enrolled an enriched population with elevated CV risk or insulin use. Besides higher proportions of prior CV disease, subjects in C-476 had a longer history of T2DM diagnosis, older age, and a greater proportion of insulin use at baseline, compared to subjects from other studies included in the meta-analysis.

In the FAS, there were more male subjects than female subjects (63% versus 37%). Approximately 70% of subjects were white and about 7% were black, while 17% were Asian and 6% of subjects belong to other races. About 41% of subjects were at least 65 years of age, while the mean age was about 61.7 years. About 40% of subjects were from the United States. The mean BMI was 31.6 kg/m². The mean HbA1c at baseline was 8.1%. The mean duration of T2DM was 11.6 years with baseline insulin usage in 26% of the FAS subjects.

Table 198. Summary of Demographics and Baseline Characteristics, Full Analysis Set

Characteristics	All Studies Combined		Trial C-476	
	Bexagliflozin (N=2437)	Control (N=1653)	Bexagliflozin (N=1132)	Placebo (N=567)
Age ± SD (years)	61.9±9.7	61.4±10.4	64.4±7.9	64.6±8.0
<65	58.2%	59.5%	49.6%	48.7%
≥65	41.8%	40.5%	50.4%	51.3%
Female	36.6%	38.4%	30.1%	31.2%
Race				
White	69.9%	71.1%	77.7%	75.8%
Black	6.9%	6.8%	4.1%	4.9%
Asian	17.1%	16.7%	9.5%	9.7%
Other	6.1%	5.3%	8.8%	9.5%
Region				
North America	50.9%	49.1%	51.7%	51.3%
Latin America	1.4%	1.6%		
Europe	32.7%	34.1%	40.1%	40.6%
Asia	15.1%	15.2%	8.2%	8.1%
United States	40.1%	40.1%	35.1%	36.2%
BMI ± SD (kg/m ²)	31.7±6.0	31.5±5.7	32.8±6.1	32.2±5.8
Duration of T2DM ± SD (years)	11.7±8.5	11.3±8.4	14.9±8.6	15.2±9.3
CV history				
Myocardial infarction	24.1%	20.6%	45.9%	48.2%
Stroke	5.5%	5.1%	9.0%	9.4%
Arterial revascularization	24.2%	20.9%	45.0%	46.2%
Congestive heart failure	13.7%	10.5%	26.7%	26.6%
Baseline HbA1C ± SD (%)	8.2±0.9	8.1±0.9	8.3±0.9	8.3±0.9
Baseline insulin use	28.6%	23.0%	53.9%	51.5%

Source: Generated by Reviewer.

Abbreviations: BMI, body mass index; CV, cardiovascular; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes mellitus.

17.1.6. Meta-Analysis Results and Conclusion

17.1.6.1. Descriptive Summary of Safety Outcomes

As described in Section 17.1.4.1, the prespecified primary endpoint is the 4-component MACE+. Table 199 provides a descriptive summary of first-occurrence of on-study MACE+ and its individual components, broken down by meta-analysis study group and treatment group. A total of 159 subjects experienced at least one positively-adjudicated MACE+ in the pooled studies (96 in the bexagliflozin group and 63 in the control group). Among these subjects, 146 were from Trial C-476 (89 in the bexagliflozin group and 57 in the placebo group) and 13 were from other phase 2/3 studies (7 in the bexagliflozin group and 6 in the control group).

Table 199. First MACE+ by Meta-Analysis Study and Treatment Group, Full Analysis Set, On-Study

Trial	Treatment Arm	N	MACE+ n (%)	Nonfatal	Nonfatal	CV Death n (%)	Hosp. for UA n (%)
				MI n (%)	Stroke n (%)		
C-476	Bexagliflozin	1132	89 (7.9)	41 (3.6)	22 (1.9)	25 (2.2)	1 (0.1)
	Placebo	567	57 (10.1)	29 (5.1)	9 (1.6)	17 (3.0)	2 (0.4)
Other	Bexagliflozin	1305	7 (0.5)	4 (0.3)	2 (0.2)	1 (0.1)	-
	Control	1086	6 (0.6)	4 (0.4)	1 (0.1)	1 (0.1)	-

Source: Generated by reviewer.

Abbreviations: CV cardiovascular; MACE, major adverse cardiac event; UA, unstable angina.

17.1.6.2. Meta-Analysis Results

17.1.6.2.1. Analysis Results for Primary Endpoint MACE+

The prespecified primary analysis for MACE+ was based on a Cox proportional hazards model stratified by the meta-analysis study group with a fixed effect for the meta-analysis treatment group using all first MACE+ events observed during the study participation (on-study censoring) in the FAS subjects.

As shown in Table 200 below, the estimated hazard ratio of MACE+ associated with bexagliflozin relative to control was 0.80 with a 95% confidence interval of (0.58, 1.09). The upper bound of the 95% CI for the hazard ratio was 1.09 which is lower than the CV risk margin of 1.8.

Table 200. Primary Analysis Results of MACE+, Full Analysis Set, On-Study

Variable	Bexagliflozin N=2437 PY =3705.8	Control N=1653 PY =2249.3
MACE+ [IR/100PY a]	96 [2.5]	63 [3.1]
HR _{Bexa/Control} (95% CI) *	0.80 (0.58, 1.09)	

Source: Generated by reviewer.

^a Study-size adjusted incidence rate.

* Hazard ratio was estimated based upon a Cox model stratified by meta-analysis study group with a fixed effect for the meta-analysis treatment group.

Abbreviations: Bexa, bexagliflozin; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

Table 201. Analysis Results of MACE+ in Full Analysis Set, On-Study, Trial C-476

Variable	Bexagliflozin N=1132 PY =2716.3	Placebo N=567 PY =1342.8
MACE+ [IR/100PY]	89 [3.3]	57 [4.2]
HR _{Bexa/Placebo} (95% CI) *	0.77 (0.56, 1.08)	

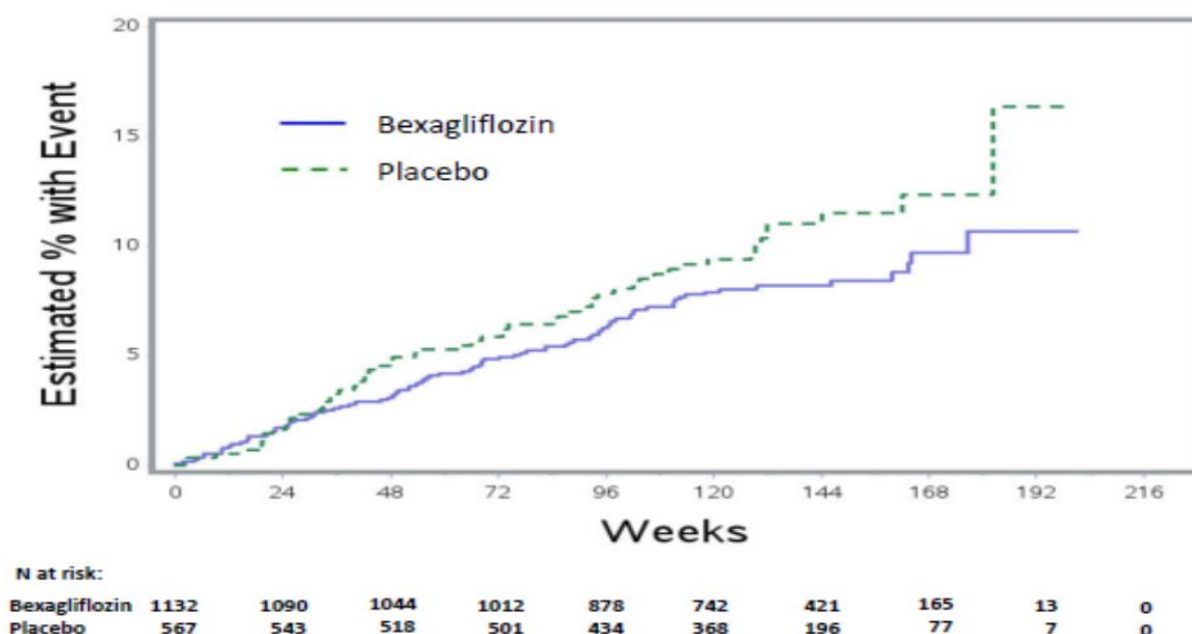
* Hazard ratio was estimated based upon a Cox model with a fixed effect for treatment.

Source: Generated by reviewer.

Abbreviations: Bexa, bexagliflozin; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

Figure 67 shows the Kaplan-Meier cumulative probability of developing a MACE+ during on-study follow-up for the two arms in C-476. The K-M curves for the two groups are very close to each other until around Week 30 then started exhibiting divergence with higher incidence of MACE+ observed for the placebo curve through the remainder of Trial C-476.

Figure 67. Kaplan-Meier Plot of Time-to-First MACE+ in, Full Analysis Set, On-Study, Trial C-476



Source: Generated by reviewer.

Abbreviations: MACE, major adverse cardiac event.

As described in Section 17.1.4.2.1, proximity of MACE+ to treatment exposure was evaluated by two alternate censoring schemes in the FAS: on-treatment analyses that included events observed while on treatment or within an extended observation window of 30 days (on-treatment +30 days) and 7 days (on-treatment +7 days) after permanent treatment discontinuation, respectively.

These on-treatment analyses of MACE+ were performed using the same stratified Cox regression model as that for the primary analysis, with the results presented in Table 202 below for all studies combined and for Trial C-476 only. With slightly fewer events observed on treatment, results were generally in line with the results of the prespecified primary analysis and were driven by the CV data in C-476. The upper bounds of the associated 95% CIs ranged from

1.14 to 1.25, which are consistent with the conclusion that the risk margin of 1.8 can be ruled out for MACE+.

Table 202. On-Treatment Analysis Results for MACE+, Full Analysis Set

All Studies Combined			
Variable		Bexagliflozin N=2437	Control N=1653
On-Treatment +30 days	MACE+ [IR/100PY ^a] HR (95% CI) *	86 [2.3]	55 [2.9] 0.81 (0.58, 1.14)
On-Treatment +7 Days	MACE+ [IR/100PY ^a] HR (95% CI) *	81 [2.2]	48 [2.6] 0.87 (0.61, 1.25)
Trial C-476			
		Bexagliflozin N=1132	Placebo N=567
On-Treatment +30 days	MACE+ [IR/100PY] HR (95% CI) **	80 [3.2]	49 [4.0] 0.80 (0.56, 1.14)
On-Treatment +7 Days	MACE+ [IR/100PY] HR (95% CI) **	75 [3.0]	43 [3.6] 0.86 (0.59, 1.25)

Source: Generated by reviewer.

^a: Study-size adjusted incidence rate.

*: Hazard ratio and 95% CI are based on a Cox proportional hazards model, stratified by meta-analysis study group, with meta-analysis treatment group as explanatory variable.

**: Hazard ratio and 95% CI are based on a Cox proportional hazards model with treatment group as explanatory variable.

Abbreviations: HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

FDA Reviewer Comment: Other sensitivity analyses of MACE+ conducted by the Applicant are described and listed in Section 17.1.4.2.1. The results were generally consistent and supportive of the conclusion of the primary analysis of MACE+. The tipping point analysis showed that for the upper bound of the 95% CI to exceed 1.8, the imputed risk for subsequent MACE+ following study discontinuation in subjects who withdrew from the bexagliflozin arm needs to elevate by a factor of 4.5 to 5. The results of these sensitivity analyses are not presented in this review.

In examination of the ADFA dataset (adjudicated events), the reviewer identified that four subjects (as shown below) had experienced adjudicated CV deaths after their last date of study participation but were included in the analyses of the primary and secondary CV endpoints. All four deaths occurred within 6 days of their last date of study participation (three on bexagliflozin and one on control).

Table 203. Subjects Who Experienced Adjudicated CV Death after Last Date of Study Participation, ADFA Dataset

USUBJID		Treatment Group	Date of Death	Last Date of Study Participation
THR-1442-C-418	(b) (6)	Bexagliflozin		(b) (6)
THR-1442-C-476		Bexagliflozin		
THR-1442-C-476		Bexagliflozin		
THR-1442-C-476		Comparator		

Source: Generated by reviewer.

Abbreviations: CV, cardiovascular; ADFA, finding about analysis dataset.

The Applicant stated the following on page 3 of their IR response submitted on May 31, 2022
(\CDSESUB1\evsprod\NDA214373\0030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\type-2-

[diabetes-mellitus\5351-stud-rep-contr\thr-1442-c-476\resp-info-req-vital-status-deaths-20220506-02.pdf](#)):

“As stated in the C-476 analysis data reviewer’s guide (NDA 214373, seq 0001, m5/datasets/THR-1442-C-476/analysis/adam/datasets/adrg), subject 476- (b) (6) withdrew consent on (b) (6). Since the death of the subject occurred more than 30 days after the last study participation, the patient was excluded from C-476 ADDTTE dataset. For the same reason, as stated in the CV-risk analysis data reviewer’s guide (NDA 214373, seq 0001, m5/datasets/cv-risk/analysis/adam/datasets/adrg), the patient was also excluded from the MACE meta-analysis. The only patient in the adjudication record impacted by the exclusion of death events greater than 30 days after last study participation was subject 476- (b) (6).”

As implied in the response cited above, the Applicant’s time-to-event analyses included CV deaths that occurred within 30 days past the last day of study participation. This 30-day window was not prespecified in the CV-risk analysis data reviewer’s guide or in the SAP of CV meta-analysis. However, the exclusion of these four deaths from the analyses does not alter the conclusions of the CV assessment of bexagliflozin. Therefore, this review does not present sensitivity analysis that exclude these four deaths.

17.1.6.2.2. Analysis Results for Secondary Endpoints

In this section, analysis results for the following secondary endpoints will be presented in the order of:

- Time-to-first confirmed occurrence of any event in the 3-component MACE: CV death (including deaths of unknown cause), nonfatal MI, or nonfatal stroke;
- Time-to-first confirmed occurrence of hospitalization for heart failure or CV death;
- Time-to-first confirmed occurrence of any event in the 6-component MACE: CV death (including deaths of unknown cause), nonfatal MI, nonfatal stroke, hospitalization for unstable angina, unplanned coronary revascularization, or hospitalization for nonfatal heart failure.

Time to 3-Component MACE

Since the null hypothesis for the primary endpoint was rejected, the first prespecified secondary endpoint in the hypothesis testing hierarchy could be evaluated. [Table 204](#) below presents the time-to-event analysis results based upon on-study censoring for MACE. The hazard ratio estimates for MACE were generally similar to that calculated for the primary MACE+ endpoint. There were 95 subjects in the bexagliflozin arm and 61 subjects in the comparator arm who experienced at least one adjudicated 3-component MACE. The hazard ratio was 0.82 with a 95% CI of 0.59 to 1.13. The upper bound of the 95% CI was less than the prespecified margin of 1.3 for MACE.

Table 204. Analysis Results for 3-Component MACE, Full Analysis Set, On-Study

All Studies Combined		
Variable	Bexagliflozin N=2437	Control N=1653
3-component MACE [IR/100PY]	95 [2.6]	61 [2.7]
HR (95% CI) *	0.82 (0.59, 1.13)	
Trial C-476		
	Bexagliflozin N=1132	Placebo N=567
3-component MACE [IR/100PY]	88 [3.2]	55 [4.1]
HR (95% CI) **	0.79 (0.57, 1.11)	

Source: Generated by reviewer.

*: Hazard ratio and 95% CI are based on a Cox proportional hazards model, stratified by meta-analysis study group, with meta-analysis treatment group as explanatory variable.

**: Hazard ratio and 95% CI are based on a Cox proportional hazards model with treatment group as explanatory variable.

Abbreviations: HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

Time to Hospitalization for Heart Failure or CV Death

As prespecified in the hierarchical testing procedure, superiority for the time-to-first occurrence of hospitalization for heart failure or CV death was to be evaluated if nonexcess risk of MACE+ and MACE were both met.

[Table 205](#) below depicts the time-to-event analysis results for the composite endpoint of hospitalization for heart failure and CV death using on-study censoring. The hazard ratio estimate was 0.74 with a 95% confidence interval of (0.48, 1.15) for the overall meta-analysis. Covering the null value of 1, the confidence interval does not indicate a statistically significant benefit associated with bexagliflozin use, compared to the combined control group; therefore, superiority of bexagliflozin over the comparators was not reached.

Table 205. Analysis Results for HHF or CV Death, Full Analysis Set, On-Study

All Studies Combined		
Variable	Bexagliflozin N=2437	Control N=1653
HHF/CV Death [IR/100PY]	49 [1.3]	34 [1.5]
HR (95% CI) *	0.74 (0.48, 1.15)	
Trial C-476		
	Bexagliflozin N=1132	Placebo N=567
HHF/CV Death [IR/100PY]	47 [1.7]	31 [2.3]
HR (95% CI) **	0.75 (0.48, 1.18)	

Source: Generated by reviewer.

*: Hazard ratio and 95% CI are based on a Cox proportional hazards model, stratified by meta-analysis study group, with meta-analysis treatment group as explanatory variable.

**: Hazard ratio and 95% CI are based on a Cox proportional hazards model with treatment group as explanatory variable.

Abbreviations: CV, cardiovascular; HHF hospitalization for heart failure; HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

Time to 6-Component MACE

[Table 206](#) below summarizes the time-to-event analysis results for adjudicated 6-component MACE, which was not included in the hierarchical testing procedure and was considered supportive. With the addition of unplanned coronary revascularization and hospitalization for

nonfatal heart failure, the hazard ratio estimate was similar to that of the primary MACE+ and its confidence interval was slightly narrower.

Table 206. Analysis Results for 6-Component MACE, Full Analysis Set, On-Study

All Studies Combined		
Variable	Bexagliflozin N=2437	Control N=1653
6-component MACE [IR/100PY]	126 [3.4]	82 [3.7]
HR (95% CI) *	0.80 (0.60, 1.06)	
Trial C-476		
	Bexagliflozin N=1132	Placebo N=567
6-component MACE [IR/100PY]	117 [4.4]	73 [5.6]
HR (95% CI) **	0.79 (0.59, 1.06)	

Source: Generated by reviewer.

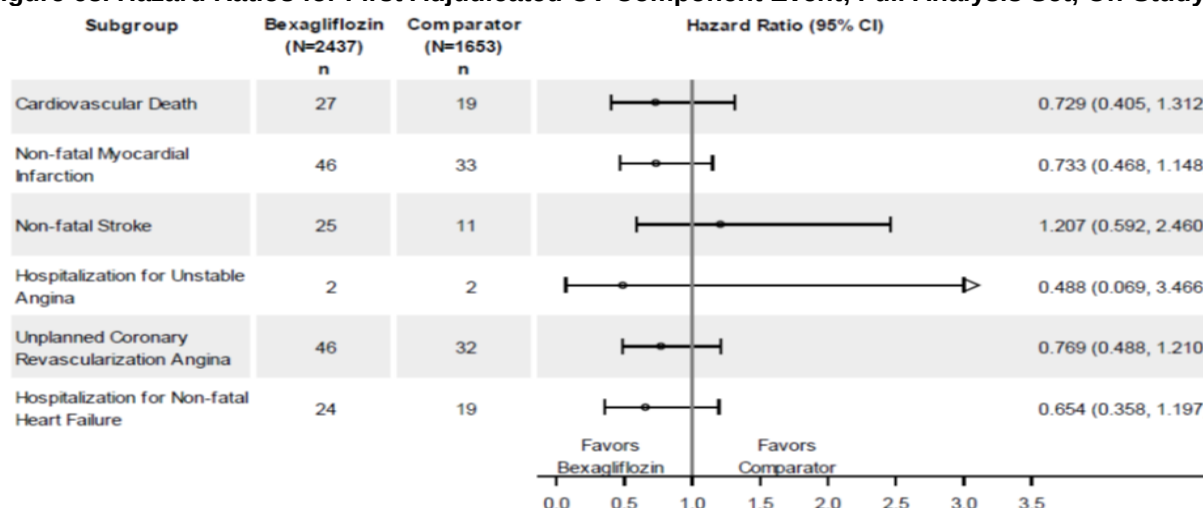
*: Hazard ratio and 95% CI are based on a Cox proportional hazards model, stratified by meta-analysis study group, with meta-analysis treatment group as explanatory variable.

**: Hazard ratio and 95% CI are based on a Cox proportional hazards model with treatment group as explanatory variable.

Abbreviations: HR, hazard ratio; IR, incidence rate; MACE, major adverse cardiac event; PY, person years.

For each individual component event of the 6-component MACE, an exploratory analysis was conducted using a similar stratified Cox regression model as that used in the primary analysis. The hazard ratio and its corresponding 95% confidence interval for each component event is depicted in a forest plot (Figure 68). The estimated hazard ratios for CV death (0.73), nonfatal MI (0.73), hospitalization for unstable angina (0.49), unplanned coronary revascularization (0.77) and hospitalization for nonfatal heart failure (0.65) were all smaller than 1, except for nonfatal stroke (1.21). The 95% confidence intervals for each component include the null value of 1. The hazard ratio for unstable angina could not be assessed with precision because there were only four adjudicated events.

Figure 68. Hazard Ratios for First Adjudicated CV Component Event, Full Analysis Set, On-Study*



Source: Figure 9, page 55, Bexagliflozin Cardiovascular Risk Assessment Statistical Report.

* Hazard ratio and 95% CI are based on a Cox proportional hazards model, stratified by meta-analysis study group, with meta-analysis treatment group as explanatory variable.

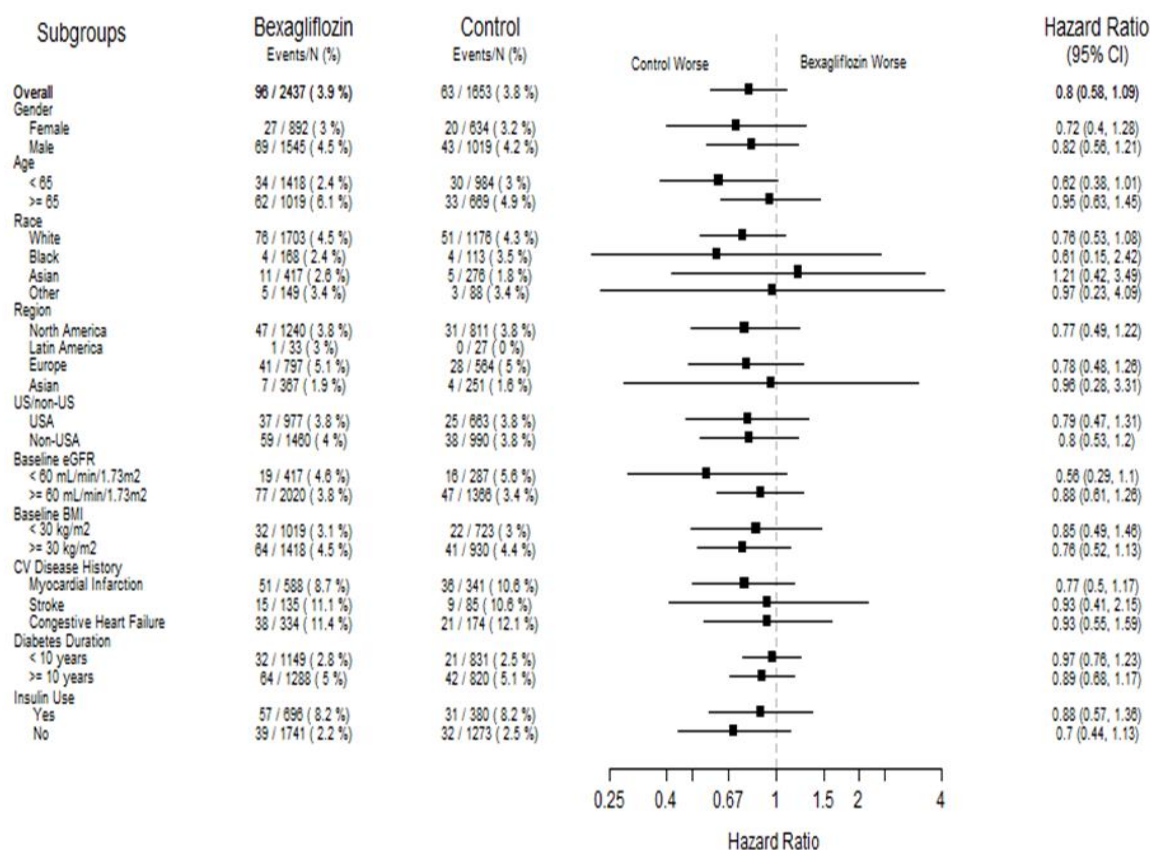
Abbreviations: CV, cardiovascular.

17.1.7. Findings in Subgroup Populations

In this section, analysis results for the primary CV endpoint MACE+ are presented for specific subgroups in the FAS based on the on-study censoring scheme. Subgroups presented in this section are defined by baseline demographic factors and clinical factors including age, gender, race, region, baseline eGFR, baseline BMI, history of CV disease, duration of T2DM diagnosis, and insulin use at baseline. Analyses of subgroups were based upon a Cox proportional hazards model stratified by meta-analysis study group (C-476 or not) with a fixed effect for treatment group to estimate the hazard ratio and its corresponding 95% confidence interval. There were no protocol-defined multiplicity corrections for these exploratory analyses and as such results are presented using unadjusted 95% confidence intervals for each of the subgroups.

A forest plot of the hazard ratio and its corresponding 95% confidence interval is provided in [Figure 69](#) below as a summary of the findings for the subgroup analyses. The results of subgroup analyses were generally consistent with the primary analysis. None of the confidence intervals excluded 1. All hazard ratio estimates were below 1 except for the estimate of the race category “Asian” (1.21); however, the number of events is relatively low and the confidence interval was wide for this subgroup.

Figure 69. Forest Plot of Hazard Ratios for MACE+ by Baseline Subgroups, Full Analysis Set, On-Study



Source: Generated by reviewer.

Abbreviations: BMI, body mass index; CV, cardiovascular; eGFR, estimated glomerular filtration; MACE, major adverse cardiac event.

17.1.8. Summary and Conclusions

17.1.8.1. Statistical Issues

There were no significant statistical concerns identified in this review on the design, conduct, and analyses of the primary and secondary CV endpoints.

17.1.8.2. Collective Evidence

In the NDA submission, data from nine randomized controlled phase 2/3 trials were synthesized to evaluate the cardiovascular risk associated with the use of bexagliflozin, according to a prespecified CV meta-analysis plan. Eight of the nine trials are efficacy trials with fixed treatment period, while Trial C-476 is a dedicated event-driven cardiovascular outcomes trial with a primary objective to collect CV events to be combined with other efficacy trials in the CV meta-analysis.

A total of 4090 subjects were included in the FAS for the CV meta-analysis, with 2437 in the bexagliflozin arm and 1653 in the combined control arm. Among them, a total of 1699 subjects were randomized in Trial C-476, which enrolled a population with elevated CV risk and contributed about 69% of the total follow-up time in the CV meta-analysis.

The prespecified primary composite endpoint for CV safety evaluation was MACE+, comprised of CV death (including deaths of unknown cause), nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina. Among the 4090 FAS subjects, a total of 159 subjects experienced at least one adjudicated MACE+ event during the course of the trials, with 96 subjects in the pooled bexagliflozin group and 63 subjects in the pooled control group. Most of these events (89 in the bexagliflozin arm and 57 in the placebo arm) were observed in Trial C-476. The primary analysis was a time-to-event analysis based on a stratified Cox proportional hazards model with the meta-analysis study group (C-476 or not) as the stratification factor. The primary analysis resulted in a hazard ratio estimate of 0.80 with an associated 95% confidence interval of (0.58, 1.09). The upper bound of 1.09 was lower than the 1.8 risk margin preset for the nonexcess risk hypothesis on this endpoint, and it can be concluded that the analysis for MACE+ successfully ruled out the 1.8 risk margin. Analyses with on-treatment censoring schemes, analysis of an expanded 6-component MACE endpoint and each of its component events support the conclusion for MACE+. Analyses of MACE+ across a range of subgroups were generally consistent and showed no evidence of increased risk associated with bexagliflozin.

According to a prespecified hierarchical testing procedure, the first key secondary endpoint 3-component MACE (CV death including deaths of unknown cause, nonfatal myocardial infarction, or nonfatal stroke) was then evaluated for nonexcess risk against a preset margin of 1.3. Prespecified time-to-event analysis using a similar Cox model as that used for MACE+, resulted in a hazard ratio estimate of 0.82 with a 95% confidence interval (0.59, 1.13). Therefore, the analysis for strict MACE successfully ruled out the 1.3 risk margin.

The second key secondary endpoint, which was the composite of CV death and hospitalization for heart failure was tested for superiority as the next step of the testing hierarchy. The null

hypothesis was not rejected; therefore, the objective of demonstrating superiority was not achieved for this endpoint.

In this CV meta-analysis, the overall results were highly influenced by the single CV outcomes Trial C-476 due to its population of high CV risk, large sample size and long follow up for CV events. Only 13 adjudicated MACE+ events out of the 159 primary CV events were contributed by other phase 2/3 trials. This is expected and preplanned. Analysis results of the primary and secondary endpoints were also examined for Trial C-476 alone and they are consistent with the overall results of the meta-analysis.

17.1.8.3. Conclusions and Recommendations

Theracos evaluated the cardiovascular safety of bexagliflozin through a prespecified CV meta-analysis of its phase 2/3 programs. The prespecified stratified Cox proportional hazards model obtained an estimated hazard ratio for the primary cardiovascular endpoint MACE+ (4-component: cardiovascular death including deaths of unknown cause, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina) of 0.80 with an associated 95% confidence interval of (0.58, 1.09). The upper bound of this confidence interval was smaller than 1.8 and therefore met the preset risk margin for MACE+. The stratified Cox proportional hazards model obtained an estimated hazard ratio for the key secondary endpoint MACE (3-component: cardiovascular death including deaths of unknown cause, nonfatal myocardial infarction, or nonfatal stroke) of 0.82 with a 95% confidence interval of (0.59, 1.13). The upper bound was smaller than 1.3 and therefore met the preset risk margin for strict MACE.

In conclusion, based on our statistical review on results of the prespecified CV meta-analysis, bexagliflozin is not associated with an unacceptable increase in cardiovascular risk.

17.2. Applicant's Approach to the Safety Review

The Applicant performed their integrated safety analysis primarily utilizing a pool that consisted of all phase 2b/3 trials conducted in the clinical development program for bexagliflozin for improved glycemic control enrolling subjects with diabetes, as well as a subset of diabetic subjects enrolled in trials conducted in the clinical program of bexagliflozin for the treatment of essential hypertension (C-603A and C-603B), termed the "overall diabetic pool." C-603A was randomized, controlled trial where hypertensive subjects were randomized 1:1 to receive bexagliflozin 20 mg or placebo for 12 weeks. Subjects who completed C-603A immediately initiated C-603B, which was a randomized withdrawal trial. For both trials, AEs that occurred while subjects were randomized to placebo were not defined as treatment emergent in the Applicant's analysis. To address this, a modified pool was created, termed the "broad pool," which included all studies in the Applicant's overall diabetic pool; however, only data from the placebo-controlled portion of C-603A (including both diabetic and nondiabetic subjects) was included. As the broad pool combines trials of different study design, patient population, and drug formulation (i.e., C-418), this pool was used for exploratory purposes in this safety review.

In addition, the Applicant also utilized a pool consisting of placebo-controlled trials where bexagliflozin was evaluated as monotherapy or as add-on to metformin, termed the "general diabetic population," which consisted to C-418, C-419, C-449, and C-450. However, as C-418 used a noncommercial formulation of bexagliflozin and had differing trial design features as

compared to the other trials (e.g., longer duration, lack of a washout period for subjects taking one oral antihyperglycemic agent prior to randomization, etc.), the review team concluded it was not appropriate for labeling purposes. A modified pool, consisting of C-419, C-449, and C-450, termed the placebo-controlled pool, was used in FDA's review to inform product labeling.

Lastly, to identify adverse events associated with bexagliflozin treatment in the integrated summary of safety (ISS), the Applicant utilized statistical strategies (e.g., Fisher's exact test). The review team did not agree with the Applicant's use of statistical methods for identifying safety signals and this approach was not utilized in the FDA's safety review.

Overall, the FDA's safety review utilized modified data pools as compared to the pools utilized by the Applicant and did not rely on statistical testing to identify safety signals. The impact of these differences in the approach to the safety review is reflected in the modifications made to the proposed labeling (see Section [21](#) for a summary of labeling negotiations).

17.3. Submission-Specific Safety Issues

The following sections detail submission-specific safety issues, including the following AESIs: DKA, diuretic effects, fractures, falls, GMI, hepatotoxicity, rash, hypoglycemia, hypotensive episodes, malignancies, acute kidney injury (AKI), pyelonephritis/urosepsis, and hypersensitivity reactions. Hypoglycemia, with and without concurrent use with insulin or an insulin secretagogue, is also discussed. C-476 was the largest and longest trial in the bexagliflozin clinical development program, enrolling subjects who were older and with a longer diabetes duration and more comorbidities as compared to other trials. Therefore, Trial C-476 was considered the most relevant trial to inform events that may occur at a low frequency, events that may be more likely to occur with prolonged drug exposure, and/or events that may have a latency period. Additional trial data are reviewed where relevant.

17.3.1. Fracture

Conflicting evidence exists with regards to whether SGLT2 inhibitor treatment may increase the risk of fracture events. Bone safety was initially an area of possible concern for this drug class due to the potential for altered renal tubule reabsorption of calcium and phosphorus, the potential for altered vitamin D metabolism, the tendency for weight loss, and preclinical bone findings of hyperostosis in rats. In the approval letter for canagliflozin, a postmarketing requirement (PMR) was issued to assess the impact of canagliflozin on bone mineral density (BMD) and markers of bone turnover (PMR 2027-4). To address the PMR, the Applicant was required to complete trial DIA3010. This trial, which was intended to evaluate glycemic efficacy in older adults, was a placebo-controlled, double-blind trial randomizing subjects who were ≥ 55 to ≤ 80 years of age to placebo, canagliflozin 100 mg, or canagliflozin 300 mg (Bilezikian et al. 2016). The primary efficacy endpoint was change in HbA1c from baseline to Week 26, with a placebo-controlled extension period for the assessment of secondary safety endpoints, including those related to bone safety. BMD was measured by dual-energy X-ray absorptiometry in 714 older adults (mean age 64 years). At 2 years, subjects randomized to canagliflozin 100 mg and 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Of the CVOTs conducted for this drug class, including CANVAS and CANVAS-R for canagliflozin, EMPA-REG for empagliflozin, DECLARE for

dapagliflozin, and VERTIS for ertugliflozin, an increased risk of fracture was only observed in the CANVAS trial (HR: 1.55; 95% CI: 1.21, 1.97). However, no increased risk was observed in the CANVAS-R trial (HR: 0.86; 95% CI: 0.62, 1.19), despite the enrollment of similar subject populations. Currently, the US prescribing information for canagliflozin includes a Warnings and Precautions statement for risk of bone fracture risk. While other SGLT2 inhibitor labeling does not include a similar Warnings and Precautions statement, the dapagliflozin US prescribing information reports that in a placebo-controlled study of subjects with an eGFR ≥ 30 to < 60 mL/min/1.73 m² with a 2:1 randomization allocation, 13 subjects receiving dapagliflozin experienced bone fractures compared to none receiving placebo over a 104-week treatment period. Investigation of this imbalance revealed that all fractures were related to falls and that 7/13 subjects had a history of orthostatic hypotension or diabetic neuropathy. Although small, inconsistent changes in bone biomarkers were observed, including parathyroid hormone concentration, calcium, 25-OH vitamin D, phosphorus and magnesium, the imbalance was not reproduced when all subjects with moderate renal dysfunction in the phase 2b and phase 3 trials were pooled. A consult from the Division of Bone, Reproductive and Urologic Products concluded that there was insufficient evidence that dapagliflozin was associated with bone loss or increased fracture risk.

As identified by Food and Drug Administration Medical Dictionary for Regulatory Activities query (FMQ), there was no imbalance in the overall frequency of fracture events in C-476 (4.0% and 3.9% of subjects reporting at least one fracture event in the bexagliflozin and placebo groups, respectively, as identified by the “Fracture” FMQ). However, more subjects in the bexagliflozin group (15 subjects (1.3%)) experienced a serious fracture event as compared to the placebo group (2 subjects (0.4%)), including serious events of hip and femur fracture ([Table 207](#)). The narratives for serious fracture events were reviewed, which did not reveal any overt trends that indicated drug relatedness (e.g., falls and fractures due secondary to hypotensive episodes) ([Table 208](#)). The majority of fracture events occurred in C-476, and other trials did not accrue enough events to meaningfully inform this signal.

As discussed in Section [17.3.2](#), there was no imbalance of fall events in C-476, although undercoding of fall events in the ADaM adverse events analysis (ADAE) dataset limits interpretability of these findings (see Section [7.7.3](#)). There was a lower incidence of osteoporosis events in the bexagliflozin group in C-476 as identified by the “Osteoporosis” FMQ, although data were limited (3 (0.3%) versus 5 (0.9%) subjects experiencing an event in the bexagliflozin and placebo groups, respectively). The majority of serious fracture events in C-476 occurred in subjects older than 65 years with baseline eGFR > 60 mL/min/1.73 m²; however, the low number of events in each subgroup limits meaningful conclusions. There was no imbalance in fracture events in the dedicated renal impairment trial in the bexagliflozin clinical program, although data were limited (1.9% of subjects with a fracture event in each treatment group).

Table 207. Serious Fracture Events as Identified by FMQ, Safety Population, Trial C-476

FMQ Preferred Terms	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Fracture	15 (1.3)	2 (0.4)	1.0 (0.1, 1.8)
Femur fracture	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Foot fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Lower limb fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Patella fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Rib fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Spinal fracture	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Fibula fracture	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Humerus fracture	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Hip fracture	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Spinal compression fracture	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

Table 208. Serious Fracture Events With ≥2 Cases in Bexagliflozin Arm, By Anatomic Location, Safety Population, Trial C-476

Location	Abbreviated Narrative
Femur fracture	Subject 476- (b) (6) (bexagliflozin) was a 66-year-old American Indian or Alaska Native male with past medical history notable for left ventricular failure, Parkinson's disease, CAD s/p revascularization, T2DM complicated by neuropathy and LBBB. On Day 577, the subject sustained a left hip (femur) fracture due to a fall . He fell on his left hip when his chair broke while changing positions. The subject underwent intramedullary trochanteric nail insertion.
Femur fracture	Subject 476- (b) (6) (bexagliflozin) was an 82-year-old Asian female with past medical history notable for CAD s/p PCI, COPD, CHF, T2DM complicated by retinopathy, hypertension, and osteoporosis . On Day 407, the subject was hospitalized with left femoral fracture and was treated with open reduction internal fixation.
Femur Fracture	Subject 476- (b) (6) (bexagliflozin) was a 71-year-old Caucasian female with past medical history notable for CAD s/p PCI, CHF, hypertension, and rheumatoid arthritis. On Day 78, the subject sustained a displaced trochanteric fracture of the right femur due to a fall . She was treated nonsurgically.
Rib Fracture	Subject 476- (b) (6) (bexagliflozin) was a 53-year-old Caucasian male with past medical history notable for CAD s/p revascularization, STEMI, hypertension and T2DM complicated by neuropathy . On Day 548, the subject sustained a rib fracture after being hit by a crane hook . He was treated with a thoracic lumbar sacral orthosis brace.
Rib Fracture	Subject 476- (b) (6) (bexagliflozin) was a 66-year-old Caucasian male with past medical history notable for atrial fibrillation, hypertension and T2DM complicated by nephropathy. On Day 971, the subject sustained multiple costal fractures following a snowmobile accident . He was treated with morphine for pain control.
Foot Fracture	Subject 476- (b) (6) (bexagliflozin) was a 56-year-old Caucasian male with past medical history notable for T2DM complicated by retinopathy, neuropathy and nephropathy, hypertension, CKD, and TIA. On Day 450, he sustained a left foot fracture after his first toe was caught under a rug . The subject was treated nonsurgically.
Foot Fracture	Subject 476- (b) (6) (bexagliflozin) was a 72-year-old American Indian/Alaska Native male with past medical history notable for hypertension, dyslipidemia and BPH. On Day 123, he sustained an open fracture of the distal phalanx of the second right toe due to direct trauma from a heavy object .

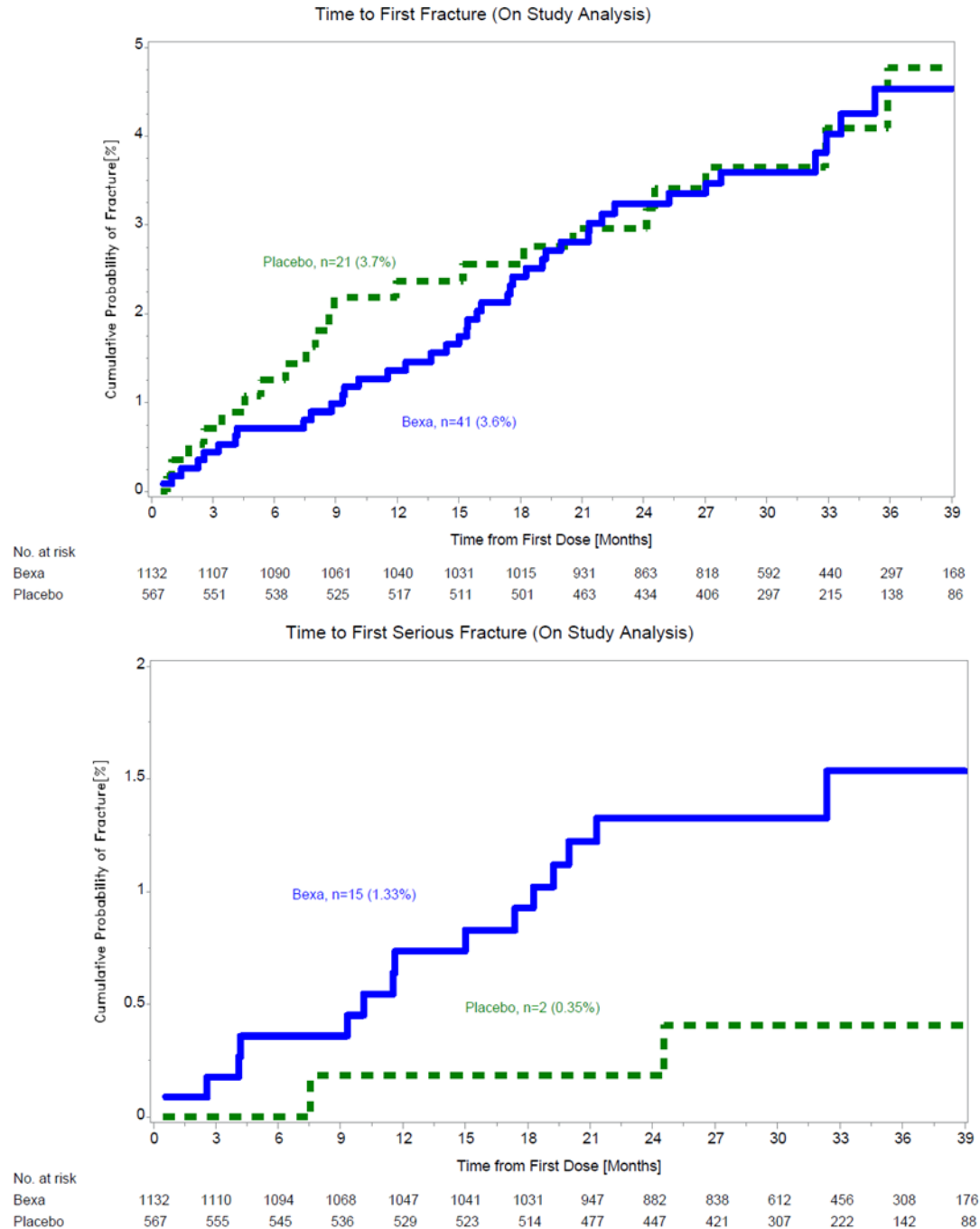
Location	Abbreviated Narrative
Lower Limb	Subject 476- (b) (6) (bexagliflozin) was a 48-year-old American Indian/Alaska Native male with past medical history notable for CHF, CAD s/p PCI, STEMI, and hypertension. On Day 522, the subject sustained right patellar fracture as a result of a motorcycle accident . He was treated surgically by right knee osteosynthesis.
Lower Limb	Subject 476- (b) (6) (bexagliflozin) was a 68-year-old Caucasian female with past medical history notable for CAD s/p revascularization, STEMI, CHF, hypertension, and humerus fracture . On Day 303, she sustained a left lower leg fracture after falling on a slick road . The subject was treated nonsurgically with plaster immobilization.
Spinal Fracture	Subject 476- (b) (6) (bexagliflozin) was a 53-year-old Caucasian male with past medical history notable for CAD s/p revascularization, STEMI and T2DM complicated by neuropathy . On Day 548, he sustained a spinal fracture of T9 and T10 after being hit by a crane hook . The subject was treated with thoracic lumbar sacral orthosis brace.
Spinal Fracture	Subject 476- (b) (6) (bexagliflozin) was a 71-year-old Caucasian male with past medical history notable for CAD s/p CABG, hypertension and T2DM complicated by retinopathy. On Day 126, the subject sustained a fracture of transverse process from T12 to L4 after he fell from an excavator and landed on his left chest. He was treated nonsurgically.

Source: Adapted from ISS

Abbreviations: BPH, benign prostatic hyperplasia; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus; TIA, transient ischemic attack.

A time-to-event analysis was also performed for both all fracture events and serious fracture events ([Figure 70](#)). When considering all fracture events, more events are observed in the placebo group within the first 15 months; however, curves converge upon longer treatment duration (HR 0.97, 95% CI (0.57, 1.64)). In contrast, for serious fracture events, curves separate early in the trial (i.e., within the first 6 months of treatment), with more events of serious fracture occurring in the bexagliflozin group at a seemingly constant rate over time (HR 3.76, 95% CI (0.86, 16.4)).

Figure 70. Time-to-First Fracture (Top*) and Serious Fracture (Bottom) Event, Safety Population, Trial C-476



Source: adae.xpt; Software: SAS; Generated by Clinical Reviewer

*This analysis relied on the Applicant's CMQ for Fracture events (i.e., the CQ01NAM Flag) and therefore the data varies slightly from the FMQ analysis performed (3.7% versus 3.6% of subjects with a fracture event as identified by CMQ as compared to 4.0% versus 3.9% subjects with a fracture event as identified by FMQ in the bexagliflozin and placebo groups, respectively). Results for serious events did not differ between analysis method.

Abbreviations: Bexa, bexagliflozin; CMQ, customized Medical Dictionary for Regulatory Activities query; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

While fracture events were prespecified AEs in the bexagliflozin clinical program, monitoring for these events beyond passive reporting did not occur. For example, the Applicant did not employ a specific data collection form, any prespecified follow-up investigations in the study protocol, or independent review. While standard chemistry laboratory parameters were collected, more specific markers for bone turnover (e.g., parathyroid hormone, collagen type 1 beta-carboxy telopeptide) were not evaluated, nor was an assessment of BMD carried out. Lack of additional information complicates the assessment of the noted imbalance in serious fracture events observed in C-476. Only one event indicative of increased parathyroid hormone was observed in C-476; an event of “Hyperparathyroidism secondary” that occurred in the bexagliflozin group. Regarding the available laboratory data, there were no clinically meaningful differences between bexagliflozin and placebo in terms of changes in serum calcium or alkaline phosphatase; however, bexagliflozin treatment mildly increases serum magnesium and phosphate (see Section 17.4 for additional information on laboratory analyses). The meaningfulness of these laboratory changes on long-term bone safety is uncertain.

FDA Reviewer Comment: Case narratives for the serious fracture events identified a substantial number of causes that were associated with high-impact trauma (e.g., snowmobile accident, hit by crane hook, motorcycle accident, fall from excavator, direct trauma from heavy object) that appear unrelated to the drug. Restricting the data to nontraumatic serious fractures significantly diminishes the imbalance. However, when evaluating osteoporosis trials, fractures of the vertebrae, hip, forearm and humerus (other than pathologic) are generally considered potentially relevant to bony integrity regardless of trauma severity, and fractures of the hand, foot, skull or face are typically disregarded (see dapagliflozin DBRUP consult for further information). Furthermore, despite the lack of data on parathyroid hormone levels and bone mineral density, the laboratory biomarkers related to bone health that were collected (calcium, magnesium, phosphorus, alkaline phosphatase) were not consistent with decreased substrate concentrations for bone mineralization or suggested increased bone fragility. Despite unclear drug-relatedness, labeling in Section 6 to inform providers of the potential risk of increased fracture with bexagliflozin treatment is proposed given that fracture events were serious in nature, including events of serious hip and femur fracture.

17.3.2. Falls

Similar to fracture events, conflicting evidence exists with regards to whether SGLT2 inhibitor treatment may increase the risk of falls, with only canagliflozin currently labeled for increased risk of fall events. Specifically, in a pool of nine clinical trials with mean duration of exposure to canagliflozin of 85 weeks, the proportion of subjects who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, canagliflozin 100 mg, and canagliflozin 300 mg, respectively. The higher risk of falls for subjects treated with canagliflozin was observed within the first few weeks of treatment.

As detailed in Section 7.7.3, fall events were found in narrative descriptions of SAEs that were not included in the ADAE dataset originally submitted to this application, and an updated ADAE dataset utilizing natural language processing (NLP) found a significant number of additional events. The reason fall events were not adequately captured in the original ADAE dataset appears multifactorial, including lack of specific protocol-driven procedures to collect fall events, fall events potentially being incorrectly assessed as a symptom of an event as opposed to

a stand-alone event or sequelae of a separate event, and inappropriate Medical Dictionary for Regulatory Activities (MedDRA) coding (i.e., “left ankle pain due to fall” coded as “pain ankle” without coding of “fall”). Despite these issues, no imbalance in fall events was observed in the ADAE dataset submitted with the application or with the NLP-modified dataset ([Table 209](#)). As discussed in [Section 7.7.3](#), there is no evidence of systemic bias with regards to missed events, including fall events, in the ADAE dataset. Bexagliflozin does not appear to be associated with increased risk of fall events based on the available data. In addition, the imbalance in fracture events is proposed for the labeling in Section 6, despite the limitations of the study/dataset.

Table 209. Fall Events in Original and NLP-Modified Safety Datasets, Safety Population, Trial C-476

	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
FMQ			
Fall (original safety dataset)	31 (2.7)	17 (3.0)	-0.3 (-2.0, 1.4)
Fall (NLP-modified safety dataset)	71 (6.3)	36 (6.3)	-0.1 (-2.5, 2.4)

Source: tadae.xpt and adae.xpt; Software: R; Generated by CDS
Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query; NLP, natural language processing.

17.3.3. Malignancy

At the time the bexagliflozin clinical program was initiated, it was unknown whether SGLT2 inhibitor treatment was associated with malignancy. Given this, malignancy events were considered AESIs. Premarket and postmarket data from other approved drugs in the class generally appears to support that SGLT2 inhibitor treatment does not increase malignancy risk; however, canagliflozin includes labeling to inform providers on imbalances observed in renal cell carcinoma events that occurred in the CANVAS trial.

Given that malignancies typically have a long latency period, C-476 was determined to be the most relevant trial for the assessment of malignancy. As identified by the FMQ for “Malignancy,” there were 39 (3.4%) and 18 (3.2%) subjects having at least one malignancy event in the bexagliflozin and placebo groups, respectively ([Table 210](#)). As shown in [Table 210](#), most events occurred in two or fewer subjects, limiting interpretability. As discussed below, several categories of malignancies (i.e., lung cancers, skin cancers) demonstrated imbalances unfavorable to drug when preferred terms (PTs) of similar medical concept were grouped.

An imbalance in nonmelanoma skin cancers was apparent in C-476, with more subjects having an event of “squamous cell carcinoma,” “basal cell carcinoma,” “squamous cell carcinoma of skin,” and “skin cancer” in the bexagliflozin group (17 (1.5%) subjects with an event) as compared to the placebo group (3 (0.5%) subjects with an event). A time-to-event analysis showed events mostly occurred within the first 18 months of treatment in the bexagliflozin group ([Figure 71](#)). Importantly, the time-to-event analysis also highlights that multiple lesions were also reported for some subjects, and that there were 11 (0.97%) versus 3 (0.57%) subjects who had a nonmelanoma event in C-476 therefore lessening the imbalance between groups, particularly when accounting for the 2:1 randomization.

Risk factors for squamous cell and basal cell carcinoma include fair skin, older age, male gender, UV exposure, and history of skin cancer. Demographics for these subjects were reviewed, and subjects were generally Caucasian, over 65 years of age, and male. The anatomical location of the lesion was generally in a location where sun exposure would be expected (e.g., face, neck,

arm, etc.). In nonclinical studies, bexagliflozin did not absorb UV light between 290 to 700 nm, and therefore nonclinical studies to investigate potential photosensitivity effects were not conducted. Events in the “Photosensitivity and photodermatosis conditions” HLT were reviewed; however, only three events occurred in C-476, limiting interpretability. Carcinogenicity studies were conducted in rats and mice, with no treatment-related tumor findings in either species. A meta-analysis that utilized a systematic search of electronic databases did not show an increased risk of melanoma and nonmelanoma skin cancers with SGLT2 inhibitor use (Tang et al. 2018). While canagliflozin is labeled for photosensitivity events, nonclinical studies demonstrated UV absorption of the compound, prompting additional characterization of potential photosensitivity reactions. Overall, the clinical meaningfulness of this signal is unclear; however, there were no events resulting in death, they were not judged as serious by the investigator, and did not result in treatment discontinuation.

In C-476, there was a minor unfavorable imbalance in events of lung cancer (PTs of “Lung adenocarcinoma,” “Squamous cell carcinoma of lung,” “Lung neoplasm malignant,” and “Nonsmall cell lung cancer”; 5 (0.4%) versus 1 (0.2%) events in the bexagliflozin and placebo groups, respectively). All subjects had a history of heavy smoking, ranging from 28 to 60 pack-years, except for one subject where smoking history was not reported. Conclusions are limited when considering the 2:1 randomization and low event rate.

In the Applicant’s analysis of the overall diabetic pool, they note a minor imbalance in events of non-Hodgkin’s Lymphoma, with four events occurring in bexagliflozin exposed subjects (0.10 cases per 100 subject-years of exposure) as compared to none in placebo- or active-comparator-exposed subjects. Based on the available data, causality cannot be assessed.

With regard to malignancy signals from other SGLT2 inhibitor programs, pheochromocytoma, Leydig cell tumor, and renal cell carcinoma were concerns with canagliflozin treatment upon approval. Currently, the US prescribing information for canagliflozin described an imbalance unfavorable to drug in renal cell carcinoma events in the CANVAS trial, although the label states that a causal relationship could not be established due to the limited number of cases. There was no imbalance in renal cell carcinoma events in C-476 (2 (0.2%) versus 1 (0.2%) subjects with an event in the bexagliflozin and placebo groups, respectively), although few events limits interpretability. No events of Leydig cell tumor or pheochromocytoma were observed in the bexagliflozin clinical program.

Bladder cancer was initially a concern with dapagliflozin treatment and a PMR was issued to assess the risk of bladder cancer associated with dapagliflozin in the DECLARE trial (PMR 2121-6). As discussed in the clinical review for the DECLARE trial, this trial excluded an unacceptable increased risk of bladder cancer in the studied population and the US prescribing information was updated accordingly (see Dr. Carey’s review in DARRTS dated October 15, 2019). Three events of transitional cell carcinoma were observed in C-476, which upon narrative review appear to also have involved the bladder. Limited data impedes interpretability of this finding.

Overall, the available data do not support increased risk of malignancy with bexagliflozin treatment, although it is acknowledged that data was limited. As stated above, there is no known causal relationship with SGLT2 inhibitor treatment and malignancy.

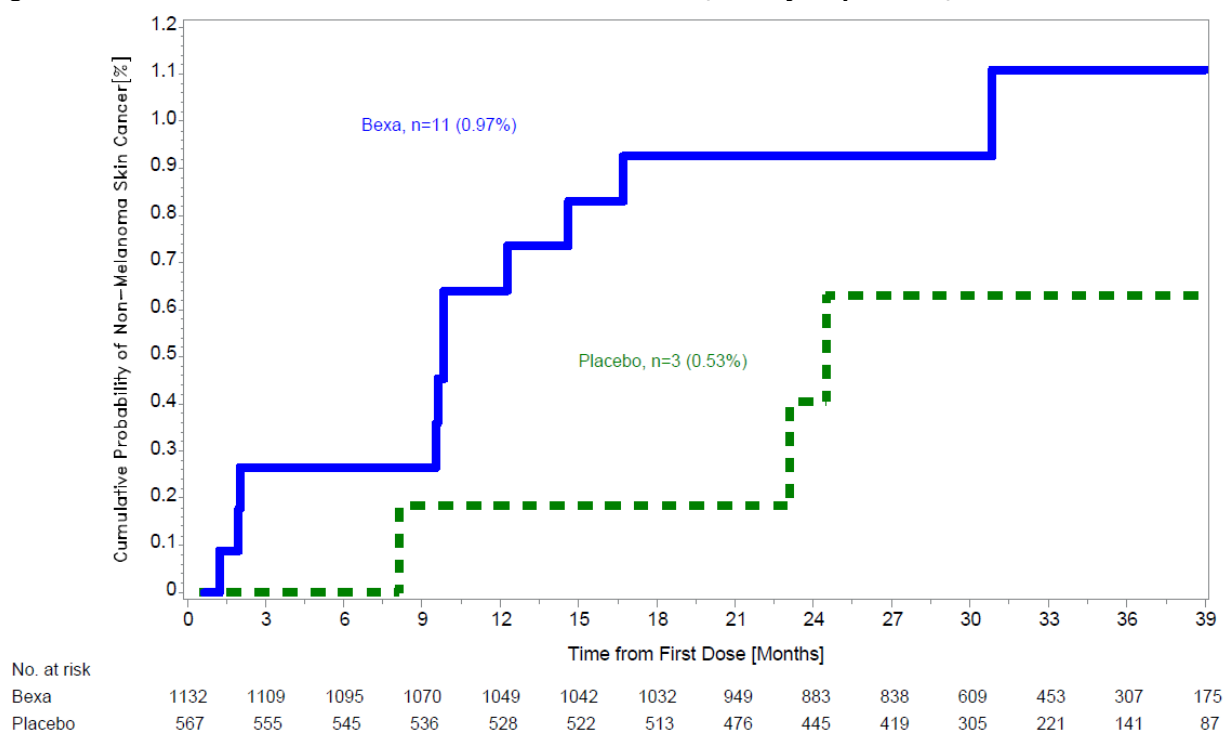
Table 210. Malignancy Events (FMQ), Safety Population, Trial C-476

FMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Malignancy	39 (3.4)	18 (3.2)	0.3 (-1.5, 2.1)
Squamous cell carcinoma	5 (0.4)	0 (0)	0.4 (0.1, 0.8)
Basal cell carcinoma	7 (0.6)	2 (0.4)	0.3 (-0.4, 0.9)
Squamous cell carcinoma of skin	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Transitional cell carcinoma	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
B-cell lymphoma	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Lung adenocarcinoma	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Lung neoplasm malignant	2 (0.2)	0 (0)	0.2 (-0.1, 0.4)
Adenocarcinoma gastric	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Adenocarcinoma pancreas	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Bile duct cancer	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Chronic lymphocytic leukemia	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Gastrointestinal stromal tumor	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Hepatocellular carcinoma	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Myeloproliferative neoplasm	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Ovarian epithelial cancer	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Prostate cancer	5 (0.4)	2 (0.4)	0.1 (-0.5, 0.7)
Renal cell carcinoma	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Squamous cell carcinoma of lung	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Skin cancer	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Adenocarcinoma of colon	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Invasive ductal breast carcinoma	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Malignant melanoma	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Metastatic renal cell carcinoma	1 (0.09)	1 (0.2)	-0.1 (-0.5, 0.3)
Cervix carcinoma	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Colorectal adenocarcinoma	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Malignant neoplasm of ampulla of Vater	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Non-small cell lung cancer	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Ovarian cancer	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Papillary cystadenoma lymphomatosum	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)
Colon cancer	0 (0)	2 (0.4)	-0.4 (-0.8, 0.1)
Pancreatic carcinoma	0 (0)	3 (0.5)	-0.5 (-1.1, 0.1)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

Figure 71. Time-to-Event for Nonmelanoma Skin Cancers, Safety Population, Trial C-476



Source: adae.xpt; Software: SAS; Generated by Clinical Reviewer
Abbreviations: Bexa, bexagliflozin.

17.3.4. Hypersensitivity and Rash

(b) (4)

(b) (4) The Applicant describes that rash was a concern early in the bexagliflozin development program because one subject in the multiple ascending dose segment of the phase 1 Trial C-328 developed a rash and withdrew, and another subject of the phase 2b Trial C-418 developed a moderate severity event of rash that was likely due to bexagliflozin exposure based on a withdrawal and rechallenge test. In addition, a scientist working on formulation development developed a rash that was addressed by use of personal protective garments. All events occurred with exposure to the noncommercial, capsule formulation of bexagliflozin. In response to this safety signal, the Applicant reformulated the drug to the proposed, to-be-commercialized tablet formulation that employs a gastroretentive mechanism. Following the introduction of the tablet formulation, the Applicant reports one moderate event of allergic dermatitis that resolved with interruption of dosing and recurred upon resumption of dosing in Trial C-603A. The Applicant states that events of rash/dermatitis should be considered confirmed adverse reactions associated with exposure to bexagliflozin based on these findings.

FMQs for “Rash,” “Urticaria,” “Erythema,” “Angioedema,” “Hypersensitivity,” and “Anaphylactic reaction” were utilized to investigate rash and hypersensitivity events. In C-476, 5.4% and 3.4% of subjects in the bexagliflozin and placebo groups experienced at least one event of rash, respectively, as determined by the Rash FMQ (Table 211). Some events of genital rash were captured in this query, which may be more likely related to cases of GMI as compared to

generalized rash events; however, exclusion of this preferred term from the analysis did not significantly impact the results (data not shown). Events of rash were generally evaluated as mild to moderate intensity by the investigator, with only one event being evaluated as serious. The narrative for this SAE was reviewed. Subject 476- (b) (6), assigned to the bexagliflozin group, experienced events of “dermatitis allergic” and “dermatitis contact” after the initiation of afatinib for the treatment of metastatic lung adenocarcinoma. Cutaneous reactions are known adverse reactions associated with afatinib treatment as described in the US prescribing information, and therefore this event may not be related to bexagliflozin exposure. More events of rash led to treatment discontinuation in the placebo group as compared to the bexagliflozin group of C-476 (1 event (<0.1%) versus 3 events (0.5%) in the bexagliflozin and placebo groups, respectively). A time-to-event analysis showed that rash events appear to occur at a somewhat constant rate over time (Figure 72). While data from other trials was limited, an imbalance unfavorable to drug for events of rash as identified by FMQ was also observed in the placebo-controlled pool (1.3% versus 0% in the bexagliflozin and placebo groups, respectively). No rash events in the placebo-controlled pool were serious or lead to discontinuation from the trial.

A higher incidence of hypersensitivity events was observed in the bexagliflozin group (1.3%) as compared to the placebo group (0.7%) in C-476. No events were serious or led to discontinuation. Few events were captured in the FMQs for “Erythema,” “Urticaria,” and “Anaphylactic reaction” limiting interpretability (Table 211).

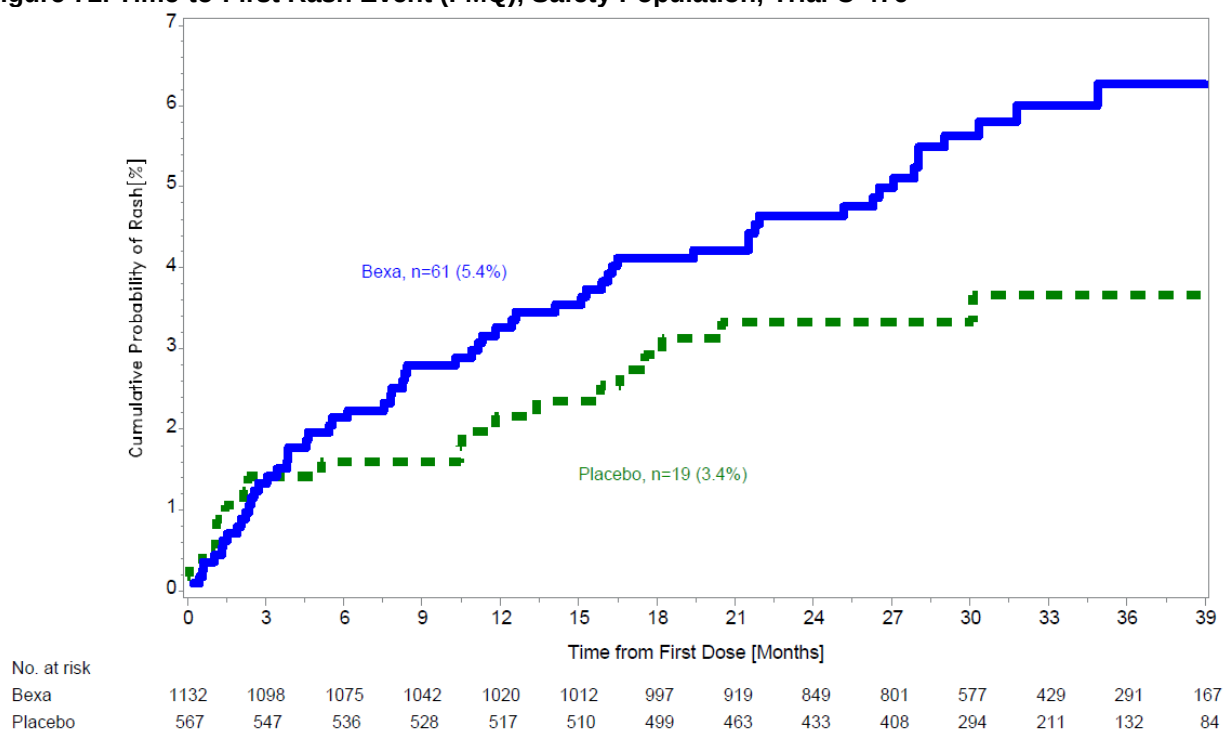
Table 211. Rash Events (FMQ), Safety Population, Trial C-476

FMQ	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Rash	61 (5.4)	19 (3.4)	2.0 (0.1, 4.0)
Hypersensitivity	15 (1.3)	4 (0.7)	0.6 (-0.3, 1.6)
Erythema	6 (0.5)	4 (0.7)	-0.2 (-1.0, 0.6)
Urticaria	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Angioedema	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Anaphylactic reaction	0 (0)	0 (0)	NA

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

Figure 72. Time-to-First Rash Event (FMQ), Safety Population, Trial C-476



Source: adae.xpt; Software: SAS; Generated by Clinical Reviewer

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

FDA Reviewer Comment: Overall, an increased incidence of rash was observed in C-476 and the placebo-controlled pool. This observation in combination with the Applicant's description of the rechallenge events may support drug relatedness. However, rash events were generally not serious, nor did they typically lead to discontinuation. Skin reactions including rash and urticaria have been identified in postmarketing reports for dapagliflozin and empagliflozin, and these events are reported in the current US prescribing information for these products. Several literature reports also seem to support the possibility of increased skin reactions associated with SGLT2 inhibitor exposure (Damiani et al. 2016; Raschi et al. 2017; Sakaeda et al. 2018). It is appropriate that information regarding rash be described in Section 6 of the labeling for bexagliflozin. A Warnings and Precautions statement is not necessary to describe the rash events observed, which, as noted above, were generally not serious nor did they typically lead to discontinuation.

While no serious hypersensitivity or anaphylactic reactions were characterized, the frequency of these events may be too low to evaluate in a premarket setting. Hypersensitivity to the drug and any excipients is included as a contraindication in labeling for SGLT2 inhibitors, which also appears appropriate for bexagliflozin.

17.3.5. Hepatic Injury

Hepatic injury events were evaluated as AESIs in the bexagliflozin clinical program to assess the relationship between bexagliflozin and drug-induced liver injury (DILI). For any increase in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3x upper limit of

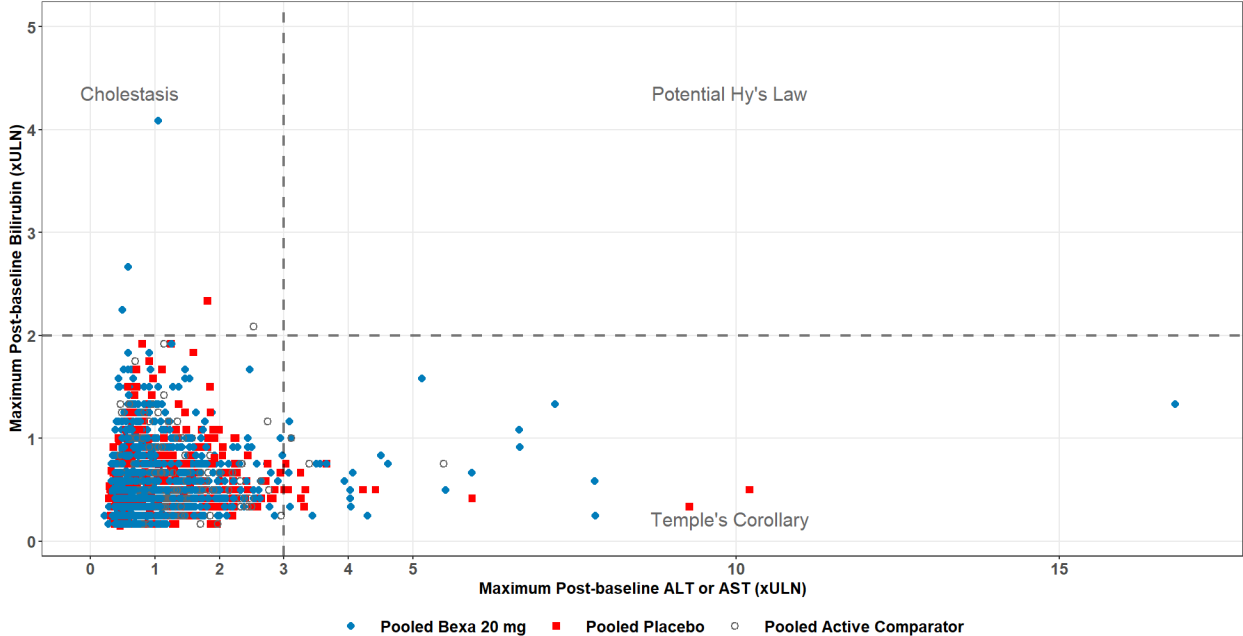
normal (ULN), investigators were instructed to confirm the hepatic enzyme elevation within 48 to 72 hours and to assess the clinical situation at least every 96 hours until ALT and/or AST return to $<2.5\times$ ULN. Investigators were advised to stop study medication and report the event as an AE if the enzyme elevation was confirmed or worsening. Hepatotoxicity was entered as an AE should any of the following have occurred:

- ALT or AST $>8\times$ ULN
- ALT or AST $>3\times$ ULN and total bilirubin $>2\times$ ULN or international normalized ratio (INR) >1.5
- ALT or AST $>3\times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$)

Investigators were instructed to permanently discontinue the study medication should a hepatotoxicity event occur. Note, the Applicant's hepatotoxicity definition did not consider elevations in ALP that could be indicative of cholestasis, and ALP was not systematically assessed in all trials. For trials where ALP data were not available (i.e., C-448 and C-450), Hy's law analysis was completed irrespective of ALP information for the assessment of DILI.

The broad pool, which pools all data from phase 2b/3 trials utilizing the 20 mg dosage strength (see Section 17.2 for additional information), was used to identify potential Hy's Law cases (Figure 73 and Table 212). No Hy's Law cases were identified from available lab data. Enzyme elevations in the cholestasis and Temple's Corollary quadrants were generally balanced between bexagliflozin and placebo groups (Table 212). There were 0.64 versus 1.08 subjects per 100 patient-years in the pooled bexagliflozin and placebo groups of the broad pool, respectively, that experienced at least one hepatic injury event as assessed by FMQ. While there were no overall concerning trends indicating DILI, selected narratives of subjects with outlier values were reviewed. Narratives reviewed indicated potentially alternative etiologies and were inconclusive with regards to drug relatedness. For example, Subject 476- (b) (6) was a 53-year-old Asian male assigned to the bexagliflozin group who had a history of hepatic steatosis, dyslipidemia, cholelithiasis, and hepatitis B infection. The subject experienced a solitary elevation of ALT and AST to $16.8\times$ and $14.7\times$ ULN, respectively, with an increase in total bilirubin to $1.29\times$ ULN (this subject represents the most extreme LFT observed in the clinical program as observed as the rightmost point in Temple's Corollary quadrant in Figure 73). In addition to chronic active hepatitis B, the subject experienced recurrent infectious cholecystitis during the trial, indicating a potential alternative etiology for the LFT elevations observed. Lastly, as discussed in Section 17.4, there were no noteworthy mean changes in bilirubin over time, and modest decreases in mean ALT and AST in the placebo-controlled pool, and subjects with one or more liver chemistry analyte values exceeding specified levels was also generally balanced between treatment arms in the placebo-controlled pool, Trial C-476, and Trial C-448. Overall, there does not appear to be a signal for DILI based on the information available.

Figure 73. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Broad Pool



Source: adlb.xpt; Software: R; Generated by CDS
Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.
All patients with at least one postbaseline ALT or AST and bilirubin are plotted.
Data for studies C-448 and C-450 plotted without regards to ALP values.

Table 212. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Broad Pool

Quadrant	Bexa 20 mg N=2578	Placebo N=1478	Active Comparator N=406
Potential Hy's law (right upper)	0/2134 (0)	0/994 (0)	0/193 (0)
Cholestasis (left upper)	3/2488 (0.1)	1/1131 (0.1)	1/403 (0.2)
Temple's corollary (right lower)	26/2488 (1)	13/1131 (1.1)	3/403 (0.7)
Total	29/2488 (1.2)	14/1131 (1.2)	4/403 (1)

Source: adlb.xpt; Software: R; Generated by CDS
Abbreviations: Bexa, bexagliflozin; DILI, drug-induced liver injury; N, number of subjects in treatment arm.

17.3.6. DKA

DKA is a serious, acute complication of diabetes that may be potentially life-threatening. The association between SGLT2 inhibitor treatment and increased risk of DKA was identified from postmarketing reports for approved products while the clinical development program for bexagliflozin was ongoing. A “DKA Monitoring and Adjudication Plan” was initiated January 2016 to enable relevant data to be captured and consistently adjudicated in the bexagliflozin clinical program. Trials C-450, C-448, C-480, and C-476 were ongoing at the time the monitoring plan was initiated. For these trials, protocols were updated via protocol amendments to include DKA as an AESI, to describe the DKA monitoring procedures to investigators, and to add a dedicated DKA case report form (CRF). These monitoring and documentation procedures were incorporated into protocols for all trials initiated after January 2016 (i.e., C-419, C-423, C-603). Trials C-418 and C-449 were completed prior to initiation of the DKA Monitoring and

Adjudication Plan, and data from adverse event logs, SAE reports, and laboratory parameters were used to identify potential DKA events retrospectively.

As detailed in the DKA Monitoring and Adjudication Plan, suspected DKA cases could be identified based on subject-reported events, investigator-reported events, or adjudicator-identified events. Subjects were informed of the signs and symptoms of DKA and were instructed to call the study site and seek treatment should such signs or symptoms occur, although ketone monitoring via home-use meter was not carried out in any trial. Investigators were informed that DKA may occur in the absence of highly elevated plasma glucose (i.e., euglycemic DKA). DKA CRFs were to be completed by the investigators at all subject visits (i.e., scheduled visits, unscheduled visits, phone consultations, etc.). The eCRFs were designed to document whether a suspected DKA had occurred and to ensure the collection of relevant clinical information to allow for adjudication. All potential DKA events underwent blinded adjudication by an endocrinologist. In addition, a listing of SAEs was sent to the adjudicator to identify DKA events potentially missed by investigators.

As shown in [Table 213](#), DKA was categorized by the adjudicator as either confirmed DKA, probable DKA, possible DKA, unlikely DKA, or intermediate DKA. The Applicant's DKA monitoring plan, including DKA case definitions, were discussed with the agency and agreed to during IND interactions (see Written Response Only dated September 21, 2016 in DARRTS).

Table 213. DKA Case Definitions

Case Term	Case Definition
Confirmed DKA	An episode consisting of symptoms of DKA with ketonuria or ketonemia AND one or more biochemical findings of acidosis, which responds to fluid replenishment and, if needed, insulin
Probable DKA	An episode consisting of moderate/severe symptoms of DKA, which responds to fluid replenishment and, if needed, insulin; OR An episode consisting of moderate/severe symptoms of DKA with moderate to large ketonuria and/or ketonemia without biochemical findings of acidosis, which responds to fluid replenishment and, if needed, insulin
Possible DKA	An episode consisting of mild to moderate symptoms of DKA with small to moderate ketonuria, condition self-managed, and resolves with or without change in diabetic medications; OR An episode of 4+ (40 mg/dL) or greater ketonuria with mild symptoms of DKA; OR An episode of 5+ (80 mg/dL) or greater ketonuria without symptoms of DKA
Unlikely DKA	An episode consisting of mild symptoms of DKA with negative to small ketonuria; OR Small to moderate (2+) ketonuria without symptoms
Indeterminant DKA	Mild to moderate symptoms of DKA without ketosis that are self-managed and/or self-resolving

Source: ISS

Abbreviations: DKA diabetic ketoacidosis.

The following definitions were specified in the DKA Monitoring and Adjudication Plan:

- One or more biochemical findings of acidosis shall mean one or more of: (i) a venous pH <7.3 or an arterial pH ≤7.3; (ii) a plasma bicarbonate <18 mM; or (iii) an albumin-corrected anion gap >10 mM.

- Symptoms of DKA shall mean exhibiting: (i) nausea with or without vomiting; (ii) abdominal pain; (iii) tachypnea and/or hyperpnea; (v) polydipsia; (vi) polyuria; (vii) malaise and/or asthenia; or (viii) confusion and/or disorientation.
- Ketonuria shall mean a moderate or large urine nitroprusside reaction (color matches or exceeds 3+ or 40 mg/dL sample swatch for test strip).
- Ketonemia shall mean a capillary blood β -hydroxybutyrate concentration >3.0 mM or a moderate or large plasma nitroprusside reaction (>1.0 mM).

Overall, 19 suspected events were sent for adjudication ([Table 214](#)). There were few confirmed DKA events in the clinical program for bexagliflozin (two and three confirmed DKA events in bexagliflozin and placebo-exposed subjects, respectively). In trial C-476, there were more events of confirmed DKA in the placebo group as compared to the bexagliflozin group (bexagliflozin: one event (0.09%), placebo: three events (0.5%)). This imbalance became increasingly favorable to drug when events adjudicated as confirmed or probable DKA were pooled (bexagliflozin: one event (0.09%), placebo: five events (0.9%)). Only one event of confirmed DKA occurred in the remainder of the bexagliflozin program in Trial C-419 (bexagliflozin: one event (0.6%), placebo: zero events (0%)).

Narratives for the two confirmed DKA events in the bexagliflozin group were reviewed. Subject 419- (b) (6) was a 37-year-old white male enrolled in C-419. The narrative reports that the subject presented to the hospital on Day 33 with epigastric pain, nausea, dehydration, and emesis following a binge drinking episode. The subject's severe anion gap metabolic acidosis was accompanied by high blood lactic acid levels, thought to be exacerbated by hypoperfusion and possible sepsis as well as concurrent metformin use. The discharge diagnosis was DKA/lactic acidosis secondary to alcohol abuse and metformin. Subject 476- (b) (6) was a 40-year-old white female enrolled in C-476. On Day 39, the subject presented to the hospital with diffuse abdominal pain, nausea, vomiting and diarrhea, and was hospitalized. The subject was rehydrated with intravenous fluid plus bicarbonate.

As discussed in Section [17.4](#), transient decreases in mean serum bicarbonate occurred in the placebo-controlled pool starting at Week 2 and recovering by Week 18, with a maximum mean decrease of -1.4 mEq/L in the bexagliflozin group compared to -0.5 mEq/L in the placebo group at Week 6. Transient decreases in serum bicarbonate were also observed in C-476 and C-448 although to a lesser extent. In line with these results, there were also more subjects who experienced at least one level 1 (<20 mEq/L), 2 (<18 mEq/L), and 3 (<15 mEq/L) low bicarbonate values in the bexagliflozin group of the placebo-controlled pool compared to the placebo group. As few events of DKA occurred in the clinical program, the meaningfulness of this laboratory data is unclear.

FDA Reviewer Comment: *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 was not observed with bexagliflozin exposure. As with other SGLT2 inhibitors, premarket programs are unlikely to adequately assess DKA risk, and class labeling appears warranted.*

Table 214. Adjudicated DKA Cases

Subject ID	Trial	Treatment	Reported PT	Adjudication Result
419- (b) (6)	C-419	Bexa	Diabetic Ketoacidosis	Confirmed DKA
448-	C-448	Bexa	Metabolic Acidosis	Unlikely DKA
476-	C-476	Bexa	Metabolic Acidosis	Confirmed DKA
476-		Bexa	Metabolic Acidosis	Unlikely DKA
476-		Bexa	Lactic Acidosis	Unlikely DKA
476-		Bexa	Respiratory Acidosis	Unlikely DKA
476-		Bexa	Metabolic Acidosis	Unlikely DKA
476-		Bexa	Hyperkalemia	Unlikely DKA
476-		Bexa	Diabetes Mellitus Inadequate Control	Unlikely DKA
476-		Bexa	Renal Tubular Acidosis	Indeterminant DKA
476-		Bexa	Hyperkalemia	Downgraded*
480-	C-480	Bexa	Pyelonephritis acute	Unlikely DKA
476-	C-476	Placebo	Diabetic Ketoacidosis	Confirmed DKA
476-		Placebo	Diabetic Ketoacidosis	Confirmed DKA
476-		Placebo	Diabetic Ketoacidosis	Confirmed DKA
476-		Placebo	Diabetic Ketoacidosis	Probable DKA
476-		Placebo	Diabetes Mellitus Inadequate Control	Probable DKA
476-		Placebo	Lactic Acidosis	Unlikely DKA
476-		Placebo	Metabolic Acidosis	Unlikely DKA

Source: Modified from Applicant; SD0008

*The clinical site confirmed that the CRF indicating DKA was sent in error

Abbreviations: Bexa, bexagliflozin; DKA, diabetic ketoacidosis.

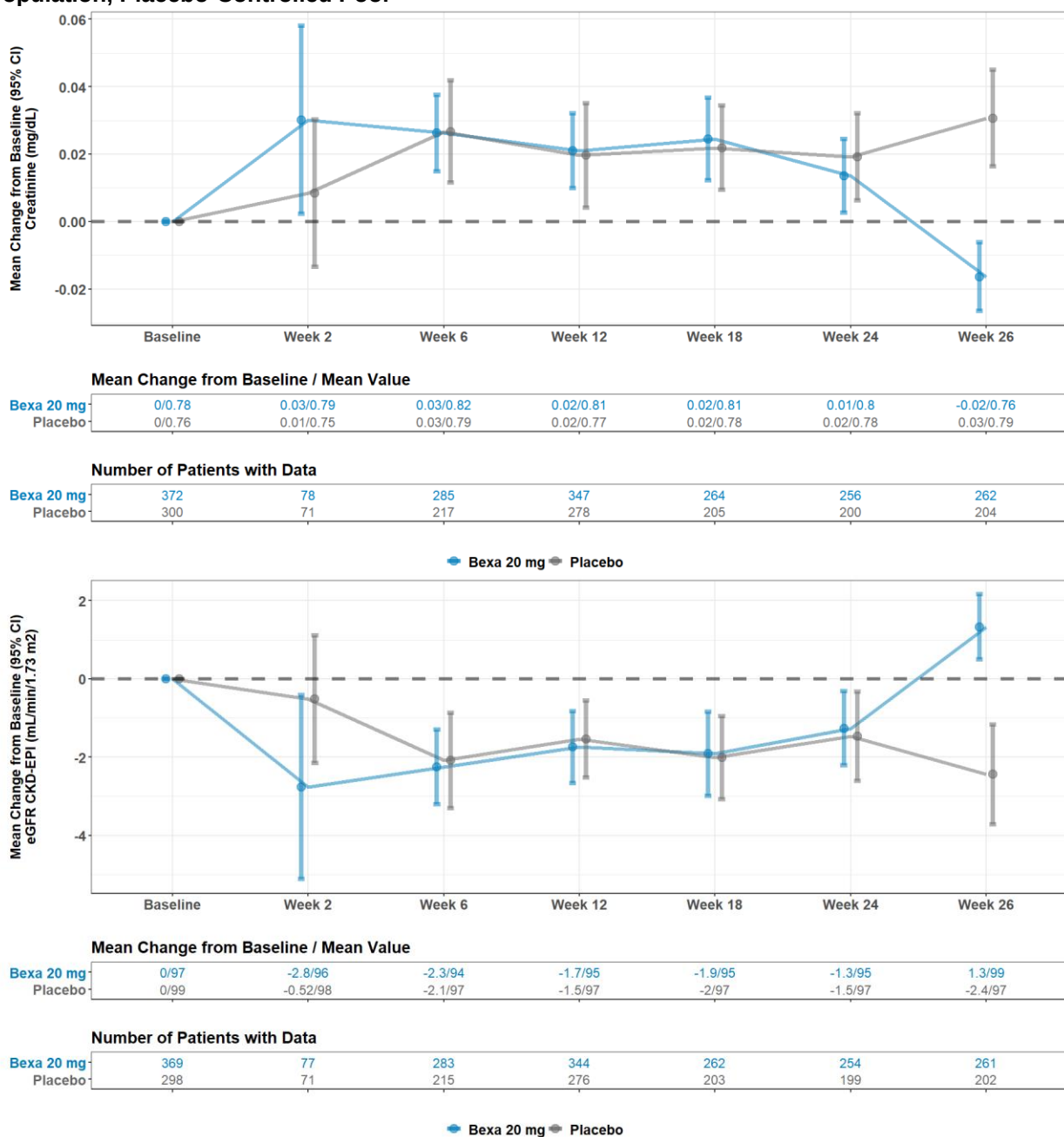
17.3.7. Renal Events

AKI, secondary to volume depletion in the setting of SGLT2 inhibitor treatment, is currently described in the Warnings and Precautions section of the US prescribing information across the class. While postmarketing events of AKI have been observed for approved SGLT2 inhibitors, there is increasing evidence that SGLT2 inhibitor treatment may be renal protective in patients with chronic kidney disease, slowing the decline in eGFR and progression to end-stage renal disease, and reducing renal-related mortality, independent of its effects on glycemic control (Gilbert and Thorpe 2019; Menne et al. 2019; Sridhar et al. 2020). In this section, renal function laboratory data and renal events, including AKI, are reviewed.

Renal Function Tests

Initiation of SGLT2 inhibitor treatment causes modest increases in serum creatinine and decreases in eGFR, an effect that is also observed with bexagliflozin. Maximum changes in serum creatinine and eGFR generally occur within six to twelve weeks of starting therapy and then stabilize. In the placebo-controlled pool, enrolling subjects primarily with normal renal function, changes in serum creatinine and eGFR were generally similar between treatment groups (Figure 74). However, changes in renal function were variable depending on the subject population evaluated. As discussed in Section 7.7.2, in C-448 enrolling subjects with stage 3 CKD, serum creatinine increased 0.14 mg/dL (10.8%) and eGFR decreased -4.6 mL/min/1.73 m² from baseline to Week 6 in the bexagliflozin group, as compared to an increase in serum creatinine of 0.01 mg/dL (0.7%) and a decrease in eGFR of -0.08 mL/min/1.73 m².

Figure 74. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool



Source: adlb.xpt; Software: R; Generated by CDS

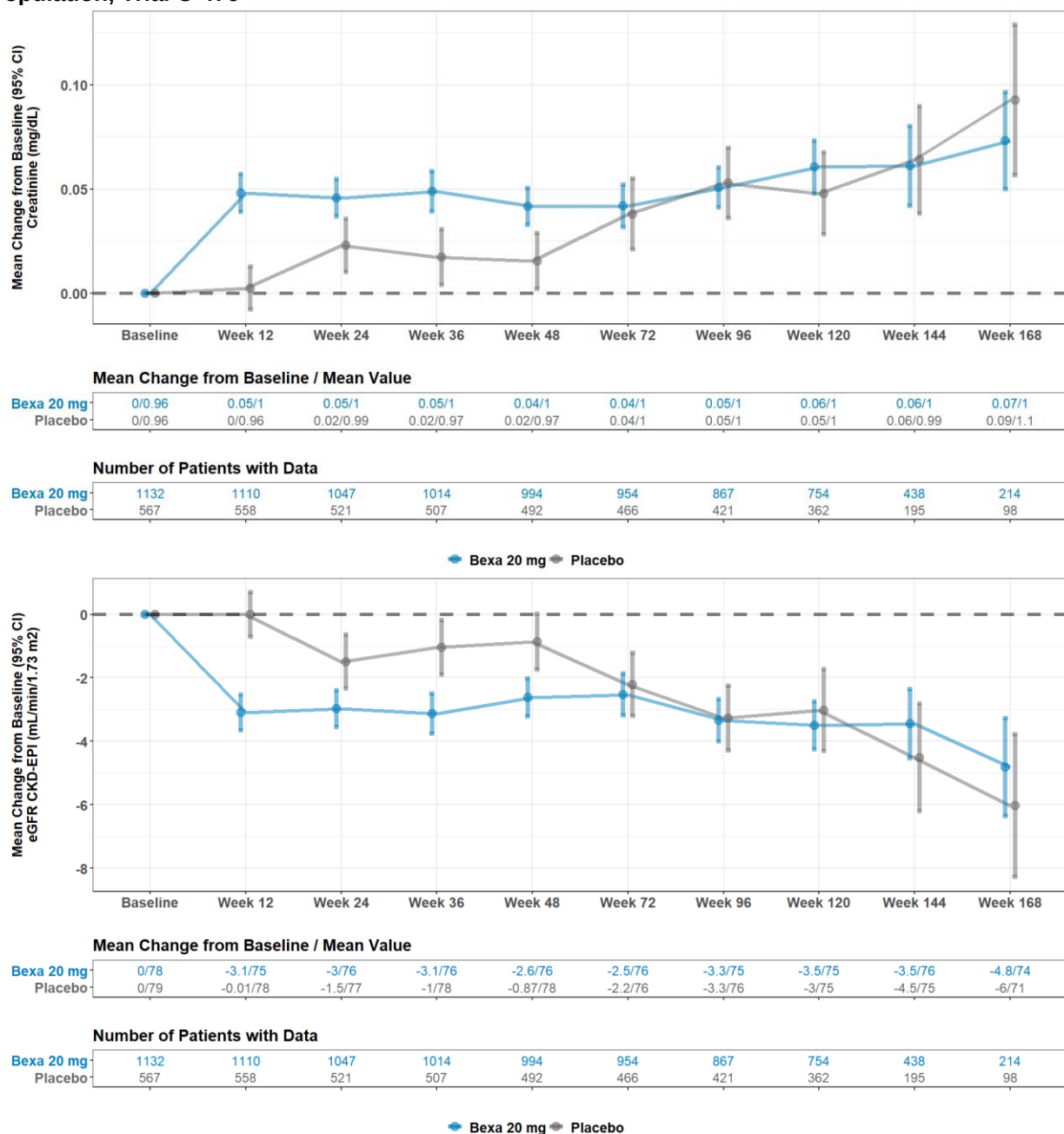
Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Abbreviations: Bexa, bexagliflozin; CI, confidence interval

Longer term impacts of bexagliflozin exposure on renal function tests can be observed in C-476 (Figure 75). Similar to other trials, an initial increase in serum creatinine and decrease in eGFR was observed in the bexagliflozin arm (increases of serum creatinine of 0.05 mg/dL (5.2%) and decreases in eGFR of -3.1 mL/min/1.73 m² from baseline to Week 12), which stabilizes after approximately 12 weeks of treatment. However, with prolonged bexagliflozin exposure, there

was a similar decline in renal function parameters in the bexagliflozin group compared to the placebo group, although this decline appears modest ([Figure 75](#)).

Figure 75. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial C-476



Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Abbreviations: Bexa, bexagliflozin; CI, confidence interval

Regarding kidney parameter outlier values, in all placebo-controlled trials more subjects in the bexagliflozin group met the criteria for level 1 decreases ($\geq 25\%$ decrease) in eGFR compared to the placebo groups; however, there were no meaningful imbalances in level 2 ($\geq 50\%$ decrease)

or 3 ($\geq 75\%$ decrease) outlier values ([Table 215](#)). This is in line with the known effects of initiating SGLT2 inhibitor treatment.

Table 215. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Level	Placebo-Controlled Pool		C-476		C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Creatinine, high (mg/dL)						
Level 1 ($\geq 1.5X$ baseline)	3/363 (0.8)	7/294 (2.4)	61/1111 (5.5)	41/558 (7.3)	3/156 (1.9)	1/154 (0.6)
Level 2 ($\geq 2X$ baseline)	0/363 (0)	2/294 (0.7)	14/1111 (1.3)	9/558 (1.6)	1/156 (0.6)	0/154 (0)
Level 3 ($\geq 3X$ baseline)	0/363 (0)	0/294 (0)	2/1111 (0.2)	1/558 (0.2)	0/156 (0)	0/154 (0)
eGFR, low (ml/min/1.73 m ²)						
Level 1 ($\geq 25\%$ decrease)	23/360 (6.4)	13/292 (4.5)	245/1111 (22.1)	104/558 (18.6)	21/154 (13.6)	10/152 (6.6)
Level 2 ($\geq 50\%$ decrease)	0/360 (0)	3/292 (1.0)	21/1111 (1.9)	11/558 (2.0)	2/154 (1.3)	0/152 (0)
Level 3 ($\geq 75\%$ decrease)	0/360 (0)	0/292 (0)	0/1111 (0)	1/558 (0.2)	0/154 (0)	0/152 (0)

Source: adlb.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; eGFR, estimated glomerular filtration rate.

Renal Events

AKI events, as identified by the AKI FMQ, that occurred in C-476 are shown in [Table 216](#). Renal failure events were prespecified as AESIs in the protocol for this trial, although no special procedures were implemented to identify or appropriately classify or document these events. A higher incidence of AKI events was observed in the bexagliflozin group (2.2% of subjects) than the placebo group (1.6% of subjects). However, there was no imbalance in AKI events between groups when the analysis was limited to serious events, with 0.8% and 0.7% of subjects experiencing events in the bexagliflozin and placebo groups; respectively. Three subjects (0.26%) assigned to the bexagliflozin group and two subjects (0.35%) assigned to the placebo group stopped dosing as a result of an AKI event. A random selection of narratives from serious AKI events were reviewed. While some AKI events occurred in the setting of hypotension/volume depletion, alternative etiologies that could have contributed to or caused the events were also present.

No AKI events occurred in the bexagliflozin groups of the placebo-controlled pool or active-controlled trials. AKI events occurring in C-448 enrolling subjects with moderate renal impairment are reviewed in [Section 7.7.2](#).

FDA Reviewer Comment: As discussed in the next section, SGLT2 inhibitor treatment, including treatment with bexagliflozin, is associated with volume depletion and hypotension, and current labeling for approved SGLT2 inhibitors describes the potential risk of AKI secondary to volume depletion as Warnings and Precautions. Similar labeling appears appropriate for bexagliflozin.

Table 216. AKI Events (FMQ), Safety Population, Trial C-476

FMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Acute Kidney Injury	25 (2.2)	9 (1.6)	0.6 (-0.7, 2.0)
Acute kidney injury	24 (2.1)	9 (1.6)	0.5 (-0.8, 1.9)
Cardiorenal syndrome	1 (<0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Renal Injury	1(<0.1)	0 (0.0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: AKI, acute kidney injury; Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

17.3.8. Volume Depletion/Hypotension Events

SGLT2 inhibitors are associated with osmotic diuresis and thus volume depletion and hypotension events are of concern for this drug class. FMQs for “Volume Depletion,” “Hypotension,” “Dizziness,” and “Syncope” were utilized to characterize the impact of osmotic diuresis in subjects treated with bexagliflozin.

An imbalance unfavorable to drug in hypotension events was observed, with 48 (4.2%) and 15 (2.6%) subjects experiencing a hypotension event in the bexagliflozin and placebo groups of C-476, respectively. All events were nonserious, with one event in a bexagliflozin-treated subject leading to treatment discontinuation. While events of dizziness may be nonspecific to volume depletion events, an excess of these events in the bexagliflozin group was also observed (7.3% versus 5.1% of subjects in the bexagliflozin and placebo groups having an event, respectively). Twelve (1.1%) and four subjects (0.7%) experienced at least one volume depletion event in the bexagliflozin and placebo groups, respectively. All events identified were events of dehydration. One dehydration event in the bexagliflozin group led to treatment discontinuation. There were more serious dehydration events in the placebo group as compared to the bexagliflozin group. AKI is a potentially serious consequence of volume depletion. Three of the 12 subjects who experienced dehydration in the bexagliflozin group had six events of AKI, of which two were SAEs. No events of AKI were observed in the four subjects who experienced dehydration in the placebo group. See Section 17.3.7 for additional discussion regarding AKI events. There were more subjects who experienced a syncope event in the placebo group than the bexagliflozin group. Events related to volume depletion events were limited in other trials, limiting interpretability. Overall, labeling similar to other members of the drug class appears appropriate.

Table 217. Dizziness, Hypotension, Syncope, and Volume Depletion Events (FMQs), Safety Population, Trial C-476

FMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Dizziness	83 (7.3)	29 (5.1)	2.2 (-0.1, 4.6)
Dizziness	55 (4.9)	18 (3.2)	1.7 (-0.2, 3.6)
Vertigo	15 (1.3)	8 (1.4)	-0.1 (-1.3, 1.1)
Presyncope	6 (0.5)	0 (0)	0.5 (0.1, 1.0)
Balance disorder	5 (0.4)	2 (0.4)	0.1 (-0.5, 0.7)
Dizziness postural	4 (0.4)	1 (0.2)	0.2 (-0.3, 0.7)
Vertigo positional	4 (0.4)	1 (0.2)	0.2 (-0.3, 0.7)
Labyrinthitis	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Meniere's disease	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)

FMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Hypotension	48 (4.2)	15 (2.6)	1.6 (-0.2, 3.4)
Hypotension	38 (3.4)	9 (1.6)	1.8 (0.3, 3.2)
Orthostatic hypotension	9 (0.8)	5 (0.9)	-0.1 (-1.0, 0.8)
Blood pressure decreased	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Syncope	12 (1.2)	11 (1.9)	-0.9 (-2.2, 0.4)
Syncope	12 (1.2)	11 (1.9)	-0.9 (-2.2, 0.4)
Volume Depletion	12 (1.1)	4 (0.7)	0.4 (-0.6, 1.3)
Dehydration	12 (1.1)	4 (0.7)	0.4 (-0.6, 1.3)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

17.3.9. UTI Including Pyelonephritis and Urosepsis

Treatment with SGLT2 inhibitors increases the risk for UTIs due to increased glucosuria. Serious UTIs including pyelonephritis and urosepsis requiring hospitalization have been reported in subjects receiving SGLT2 inhibitors, and the risk of pyelonephritis and urosepsis is currently included as a Warnings and Precautions statement in the US prescribing information for approved products. These events were considered AESIs in the bexagliflozin clinical program.

UTI events occurring in the placebo-controlled pool are discussed in Section 7.6.1.3. The FMQ for “Renal and Urinary Tract Infection” was utilized to query for UTI events in C-476. In accordance with data from the placebo-controlled pool, there were more events of UTI in the bexagliflozin group (148 [13.1%] subjects with at least one event) as compared to the placebo group (68 [12.0%]). There was a minor imbalance that was unfavorable to bexagliflozin for UTI-related AEs leading to treatment discontinuation with bexagliflozin (0.8%) as compared to placebo (0.5%). There was no meaningful imbalance in events of pyelonephritis or urosepsis in the bexagliflozin group (11 [1.0%] subjects with at least one event) as compared to the placebo group (6 [1.1%]) as determined by a grouped query of the following PTs: pyelonephritis, pyelonephritis acute, urosepsis, kidney infection. As described in Section 7.6.1.3, upon review of SAE narratives for sepsis events, four events of sepsis in the bexagliflozin group and one event of sepsis in the placebo group appeared secondary to UTI. Addition of sepsis events to the analysis for pyelonephritis and urosepsis did not significantly change the interpretation of results. Regarding the remainder of the phase 3 program, only one other event of pyelonephritis occurred in a bexagliflozin treated subject in C-480.

FDA Reviewer Comment: Overall, the small number of events of pyelonephritis and urosepsis limit interpretability of the data, although it is reassuring that no meaningful imbalances were observed in the available data. As increased risk of pyelonephritis and urosepsis is considered a class effect, labeling similar to other approved products appears appropriate.

Table 218. Subjects With Renal and Urinary Tract Infections (FMQ), Safety Population, Trial C-476

FMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Renal and urinary tract infections	148 (13.1)	68 (12.0)	1.1 (-2.2, 4.4)
Urinary tract infection	134 (11.8)	62 (10.9)	0.9 (-2.3, 4.1)
Urinary tract infection bacterial	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Urinary tract infection fungal	3 (0.3)	0 (0)	0.3 (-0.0, 0.6)
Pyelonephritis	3 (0.3)	1 (0.2)	0.1 (-0.4, 0.5)
Cystitis	7 (0.6)	3 (0.5)	0.1 (-0.7, 0.8)
Kidney infection	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Nitrite urine present	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Urethritis	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Urinary meatitis	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Urinary tract infection staphylococcal	1 (0.09)	0 (0)	0.1 (-0.1, 0.3)
Culture urine positive	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Urosepsis	7 (0.6)	4 (0.7)	-0.1 (-0.9, 0.7)
Pyelonephritis acute	0 (0)	1 (0.2)	-0.2 (-0.5, 0.2)

Source: adlb.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query

17.3.10. GMI

Treatment with SGLT2 inhibitors, including bexagliflozin, increases the risk for GMI. GMI is proposed for inclusion in the labeling by the Applicant, both as an a commonly occurring adverse reaction and as a Warnings and Precautions. GMI in the placebo-controlled pool is discussed in Section 7.6.1.3. The following section focus on clinically meaningful events of GMI in phase 3 trials not included in the placebo-controlled pool.

All phase 3 trials demonstrated a higher incidence of GMI in the bexagliflozin group as compared to comparator groups. In C-476, 9.0% and 2.8% of subjects had at least one event of GMI in the bexagliflozin and placebo groups, respectively, as identified by a customized Medical Dictionary for Regulatory Activities query (CMQ) developed by the Applicant (Table 219). GMIs occurred throughout the study with an onset from 3 to 1129 days after randomization (Applicant's analysis). One subject (476- (b) (6)) in the bexagliflozin group experienced an episode of severe vulvovaginal candidiasis that was not considered an SAE by the investigator. No SAEs of GMI were reported, although 14 subjects (1.2%), all in the bexagliflozin group, ceased dosing due to GMI (Applicant's analysis). The Applicant reports that five male subjects developed phimosis in C-476, four (0.4%) in the bexagliflozin group and one (0.2%) in the placebo group, and surgery/circumcision was performed or planned for all subjects in the bexagliflozin group. Information describing phimosis potentially leading to circumcision should be included in the labeling.

Table 219. Subjects With GMI Events (Applicant CMQ), Safety Population, Trial C-476

CMQ Preferred Term	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
GMI	102 (9.0)	16 (2.8)	6.2 (4.0, 8.3)
Genital infection fungal	30 (2.7)	5 (0.9)	1.8 (0.6, 3.0)
Vulvovaginal mycotic infection	27 (2.4)	9 (1.6)	0.8 (-0.6, 2.2)
Balanoposthitis	23 (2.0)	0 (0.0)	2.0 (1.2, 2.9)
Vulvovaginal candidiasis	9 (0.8)	0 (0.0)	0.8 (0.3, 1.3)
Vulvovaginal pruritus	8 (0.7)	0 (0.0)	0.7 (0.2, 1.3)
Balanitis candida	3 (0.3)	0 (0.0)	0.3 (0, 0.6)
Tinea cruris	3 (0.3)	0 (0.0)	0.3 (0, 0.6)
Genital candidiasis	2 (0.2)	1 (0.2)	0.0 (-0.4, 0.4)
Vulvovaginitis	1 (<0.1)	1 (0.2)	0.1 (-0.1, 0.3)
Fungal balanitis	1 (<0.1)	0 (0.0)	0.1 (-0.1, 0.3)
Vulvovaginal burning sensation	1 (<0.1)	0 (0.0)	0.1 (-0.1, 0.3)

Source: adae.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; CMQ, customized Medical Dictionary for Regulatory Activities query; GMI, genital mycotic infections

17.3.11. Hypoglycemia

Insulin and insulin secretagogues (e.g., sulfonylureas) are known to cause hypoglycemia. The risk of hypoglycemia may be increased when an SGLT2 inhibitor is used in combination with insulin or insulin secretagogues, and this risk is currently labeled as a Warning and Precaution in approved SGLT2 inhibitor drugs and will be similarly included in the bexagliflozin labeling. In all clinical trials, subjects were provided with a glucometer and diary for recording blood glucose measurements and signs and symptoms that may be related to hypoglycemia. Subjects were also advised to perform daily fasting blood glucose measurements and record results. Hypoglycemia was defined in the clinical program into the following five categories: severe hypoglycemia, documented symptomatic hypoglycemia, asymptomatic hypoglycemia, probable symptomatic hypoglycemia, and relative hypoglycemia. Severe hypoglycemia was defined as an event requiring third party assistance for recovery. All other hypoglycemia categories relied on blood glucose cutoff of 70 mg/dL (level 1 hypoglycemia). As 70 mg/dL is generally considered an alert value where action should be taken to prevent further reductions in blood glucose, a re-analysis of the trial data was requested to assess level 2 hypoglycemia using the cutoff of <54 mg/dL (American Diabetes Association Professional Practice et al. 2022a).

Severe hypoglycemia and level 2 hypoglycemia in placebo-controlled studies is presented in [Table 220](#). Events rates for severe hypoglycemia and level 2 hypoglycemia were low in all placebo-controlled trials, generally occurring in trials where background insulin or sulfonylurea use was allowed. While it is reassuring that excess hypoglycemia was not observed with bexagliflozin, limited data impedes meaningful interpretation.

Table 220. Severe and Level 2 Hypoglycemia in Phase 3 Placebo-Controlled Trials, Safety Population, Trials C-419, C-448, C-450, and C-476

Trial	Placebo	Bexa 20 mg
C-419	(N=159)	(N=158)
Overall* [N (%)]	0 (0)	1 (0.6)
Severe† [N (%)]	0 (0)	0 (0)

Trial	Placebo	Bexa 20 mg
C-450	(N=69)	(N=138)
Overall* [N (%)]	0 (0)	0 (0)
Severe† [N (%)]	0 (0)	0 (0)
C-448	(N=155)	(N=157)
Overall* [N (%)]	0 (0)	2 (1.3)
Severe† [N (%)]	0 (0)	1 (0.6)
C-448 subset using insulin or insulin secretagogues	(N=109)	(N=106)
Overall* [N (%)]	0 (0)	2 (1.9)
Severe† [N (%)]	0 (0)	1 (0.9)
C-476	(N=567)	(N=1132)
Overall* [N (%)]	11 (1.9)	23 (2.0)
Severe† [N (%)]	8 (1.4)	10 (0.9)
C-476 subset using insulin or insulin secretagogues	(N=454)	(N=923)
Overall* [N (%)]	10 (2.2)	22 (2.4)
Severe† [N (%)]	8 (1.8)	10 (1.1)

Source: Compiled by Clinical Reviewer from CSRs and SD0028

* Overall hypoglycemic events: plasma or capillary glucose of less than 54 mg/dL.

† Severe hypoglycemic events: required assistance, lost consciousness, or experienced a seizure regardless of blood glucose.

Abbreviations: Bexa, bexagliflozin.

17.3.12. Fournier's Gangrene

Based on postmarketing reports of cases of necrotizing fasciitis of the perineum (Fournier's gangrene) associated with use of SGLT2 inhibitors, a potential safety signal for this adverse event was identified by the Division of Pharmacovigilance-I (DPV-1) and a Tracked Safety Issue was opened (TSI #1844) in 2018. The DPV-I review identified 12 cases of Fournier's gangrene associated with SGLT2 inhibitor use in the FDA Adverse Event Reporting System database and medical literature, prompting a Drug Safety Communication on August 28, 2018 and concurrent Safety Labeling Change that added Fournier's gangrene to the Warnings and Precautions section of the US prescribing information and patient Medication Guide for all products in the SGLT2 inhibitor class.

One case of Fournier's gangrene was reported by the Applicant in a nondiabetic subject in the randomized withdrawal essential hypertension Trial C-603B. Subject 603- (b) (6) was a 63-year-old, white, non-Hispanic male who developed Fournier's gangrene while randomized to bexagliflozin in the run-in period of C-603B. An abdominal/pelvic CT scan showed scrotal wall thickening, subcutaneous emphysema, as well as enlarged retroperitoneal and pelvic sidewall lymph nodes. He was treated with operative scrotal exploration and IV antibiotics. Notably, medical history included HIV infection and prior surgery and prosthesis involving the scrotum. The event was assessed as not likely related to the investigational product by the investigator. Given the noted risk factors and potential alternative etiology, drug causality of the event cannot be determined. Nonetheless, given that Fournier's gangrene cannot be adequately assessed in the premarket program conducted and given that it is considered a class effect, a Warnings and Precautions statement will be included in the labeling.

17.3.13. Revascularization Procedures

As described in Section 7.7.1, the Applicant used a dedicated CRF to capture information on amputation and revascularization procedures. See Section 7.7.1 for a detailed review of amputation events. With regards to revascularization procedures, the CRF prompted the investigator to select one of the following procedure types: cardiac catheterization, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), revascularization for peripheral artery disease (PAD), carotid artery stenosis with revascularization, cardiac transplant, or other (if other was selected, investigators were asked to specify additional information). The revascularization procedures that occurred in C-476 are shown in Table 221. An imbalance was observed for the number of CABG procedures that occurred in C-476 (2.5% versus 0.7% in the bexagliflozin and placebo groups, respectively). The Applicant posits that this imbalance may represent a favorable drug effect, as patients chosen for CABG must be healthy enough to withstand major surgery and a selection bias in which candidates from the active arm were judged to be more fit for surgery may have been present. This seems an unlikely explanation given what is known about bexagliflozin's beneficial effects over the course of the trial. Overall, the meaningfulness of the imbalance in CABG procedures is unclear, but the results from the MACE meta-analysis provide reassurance that bexagliflozin does not increase the risk of major adverse cardiovascular events.

Table 221. Revascularization Procedures, Safety Population, Trial C-476

Procedure	Bexagliflozin N=1132	Placebo N=567
PCI	62 (5.5)	33 (5.8)
CABG	28 (2.5)	4 (0.7)
Revascularization for PAD	28 (2.5)	12 (2.1)
Carotid artery stenosis with revascularization	7 (0.6)	4 (0.7)
Cardiac transplant	1 (0.1)	0 (0)

Source: Adapted from Table 60 in C-476 CSR

Abbreviations: CABG, coronary artery bypass graft; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

17.3.14. Cardiovascular Safety

To show that bexagliflozin was not associated with an excess CV risk, a MACE meta-analysis was performed according to the recommendations in the FDA Guidance titled *Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008). This Guidance document represented the agency's current thinking while the bexagliflozin clinical program was being completed. While this Guidance has since been withdrawn and replaced with the Guidance document titled *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control* (March 2020), the evaluation of cardiovascular safety performed by the Applicant is adequate to evaluate the impact of bexagliflozin on cardiovascular safety.

A detailed review of the MACE meta-analysis is presented in Section 17.1. In short, the upper bound of the 95% confidence interval for the HR for major adverse cardiovascular events defined by a four-point composite endpoint (cardiovascular death, stroke, myocardial infarction, or hospitalization for unstable angina) was less than 1.8 (HR: 0.80 [0.58, 1.09]) and the upper bound of the 95% confidence interval for the hazard ratio defined by a three point composite endpoint (cardiovascular death, stroke, or myocardial infarction) was less than 1.3 (HR: 0.82

[0.59, 1.13]). The upper bound in the latter case was greater than unity and hence superiority to comparator for reduction of risk was not established. The conclusions were corroborated by several sensitivity analyses. HRs favorable to bexagliflozin were observed for all subcomponents with the exception of the risk of nonfatal stroke (HR: 1.2 [0.59, 2.46]), which may be due to few events observed in this category. Subgroup analyses did not identify any meaningful differences in HR by age, sex, race, geographical region, body mass index, disease duration, disease severity, renal function, or systolic blood pressure. Overall, exposure to bexagliflozin is not expected to unacceptably increase the risk of major adverse cardiovascular events in diabetic patients.

17.4. Laboratory Findings

Blood samples for the evaluation of hematology, chemistry, and lipid parameters were collected and assessed in all trials. Sampling timepoints varied by trial, but generally occurred at screening, at the end of treatment (typically Week 24), and at the follow-up safety visit (typically Week 26), as well as at prespecified intervals during each trial, e.g., every 6 to 12 weeks. Urinalysis was also routinely performed, although results of urine glucose in urinalysis reports were suppressed as not to unblind treatment assignment. The placebo-controlled pool was deemed appropriate to characterize changes in laboratory parameters following bexagliflozin exposure. In the analyses utilizing the placebo-controlled pool representing change in laboratory parameters over time, data from the Week 14 follow-up visit from C-449 is excluded, and only Trials C-419 and C-450 contribute to the Week 18, 24, and 26 timepoints. Data from other trials (e.g., C-448 and C-476) are also presented where appropriate.

Hematology

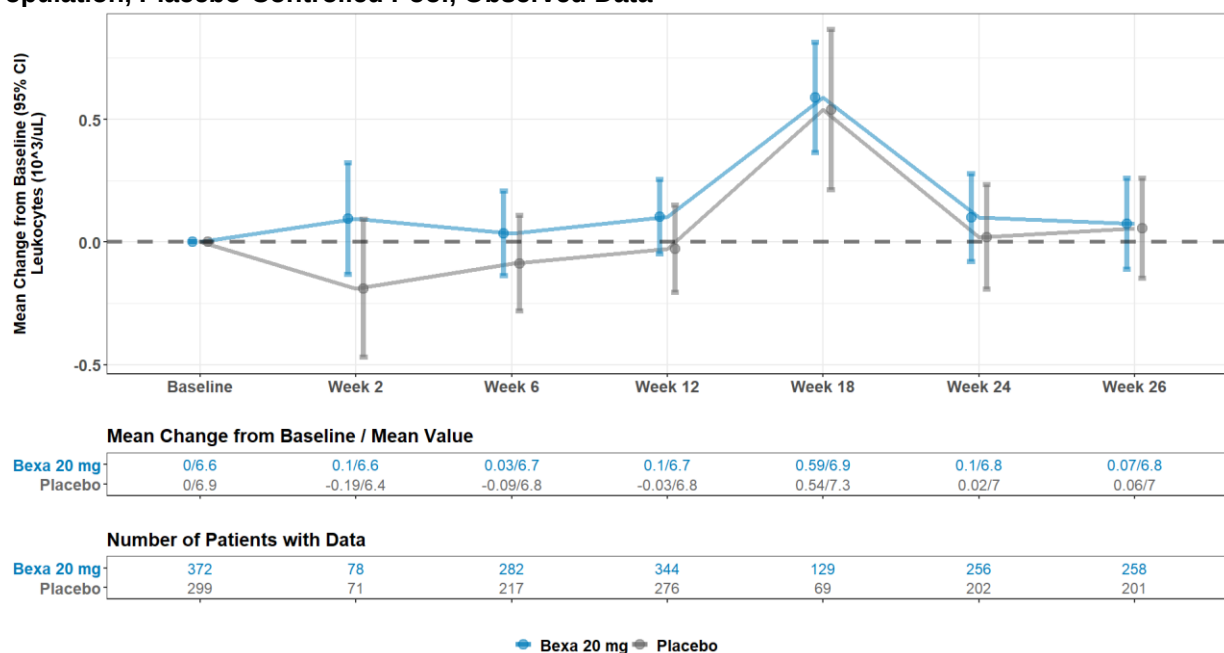
The SGLT2 inhibitor pharmacologic class is associated with small increases in hemoglobin and hematocrit, which may be attributable to osmotic diuresis and hemoconcentration. In the placebo-controlled pool, a mean increase of 0.4 g/dL (2.7%) hemoglobin and 1.3% hematocrit was observed from baseline to Week 24 in the bexagliflozin group, which remained slightly elevated at the Week 26 follow-up visit, as opposed to a slight mean decrease in each parameter in the placebo group ([Figure 76](#)). Increases in these parameters were slightly more pronounced in C-476 and C-448 (data not shown). As shown in [Table 222](#), a higher proportion of subjects had hemoglobin increases >2 g/dL and >3 g/dL from baseline in the bexagliflozin group compared to the placebo group in all trials.

It is clinically plausible that increases in hemoglobin and hematocrit could lead to an increased likelihood of experiencing a thromboembolic event. As discussed in [Section 17.1](#), the results from the MACE+ meta-analysis were overall favorable to bexagliflozin. The nonfatal stroke component of the MACE+ meta-analysis demonstrated a point estimate that was unfavorable to bexagliflozin (HR: 1.2; 95% CI: 0.6, 2.5); however, limited events produced wide confidence intervals that limit the interpretability of this data. Several additional analyses were completed to address this concern utilizing data from C-476, which enrolled a subject population that may be more likely to experience a thromboembolic event as compared to other trials in the clinical program. In addition, approximately 21% of subjects in C-476 had a least one hemoglobin result >2 g/dL above their baseline value ([Table 222](#)). As shown in [Table 222](#), there were proportionally fewer thromboembolic events in the bexagliflozin group compared to the placebo

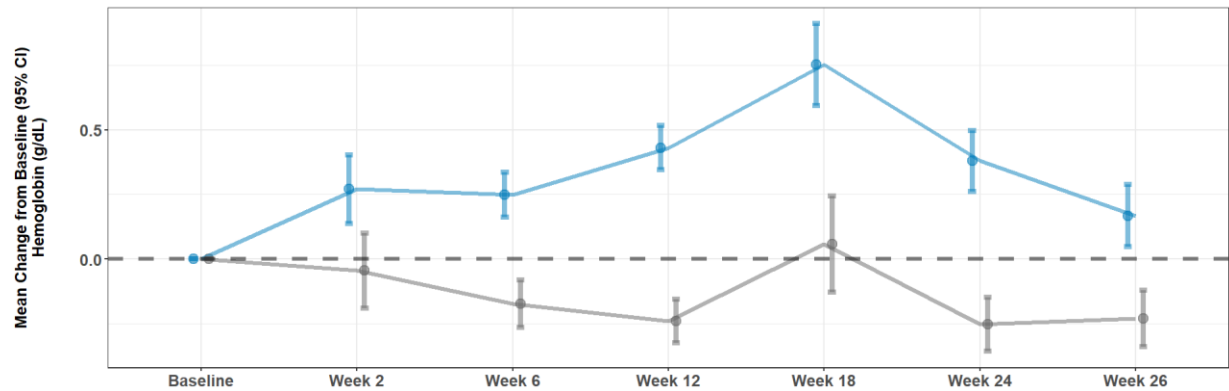
group as assessed by FMQs for “Thrombosis,” “Thrombosis (Arterial),” and “Thrombosis (Venous),” as well as a CMQ that has been previously developed and utilized to assess potentially meaningful thromboembolic events associated with SGLT2 inhibitor treatment. Overall, thromboembolic events do not appear to be a safety issue for bexagliflozin based on the results in this clinical program, but a meta-analysis of events across the class might better inform this potential safety signal, which has a mechanistically plausible basis.

There were no meaningful differences in central tendencies between the bexagliflozin group and the placebo group in the placebo-controlled pool for other hematology parameters, i.e., leukocytes, platelets, eosinophils, lymphocytes, and neutrophils ([Figure 76](#)). Regarding the proportion of subjects with one or more values exceeding specified levels for hematology parameters ([Table 222](#)), a difference was observed in subjects who experienced one or more level 1 (<1000 cells/uL) decreases in lymphocyte values between the bexagliflozin group (5.6%) and the placebo group (1.7%) in the placebo-controlled pool, which was not observed in other trials. The clinical significance of this finding is unclear, although it is notable that an increased incidence in the system organ class of “Infections and Infestations” was not observed in the placebo-controlled pool (16.1% versus 17.7% in the bexagliflozin and placebo groups, respectively).

Figure 76. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool, Observed Data



NDA 214373
Brenzavvy (bexagliflozin)

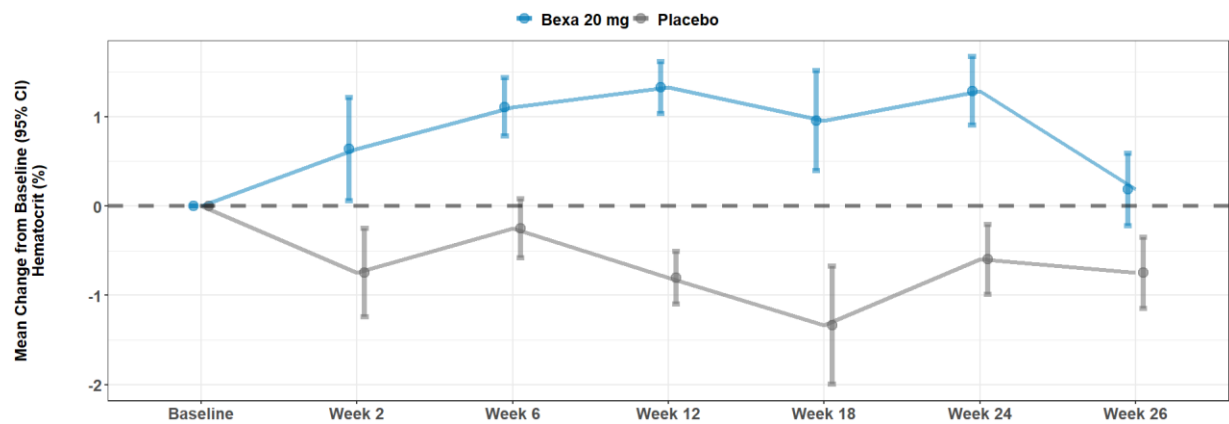


Mean Change from Baseline / Mean Value

Bexa 20 mg	0/14	0.27/14	0.25/14	0.43/14	0.75/14	0.38/14	0.17/14
Placebo	0/14	-0.05/14	-0.17/14	-0.24/14	0.06/14	-0.25/14	-0.23/14

Number of Patients with Data

Bexa 20 mg	372	78	282	344	129	256	258
Placebo	299	71	216	276	69	202	201



Mean Change from Baseline / Mean Value

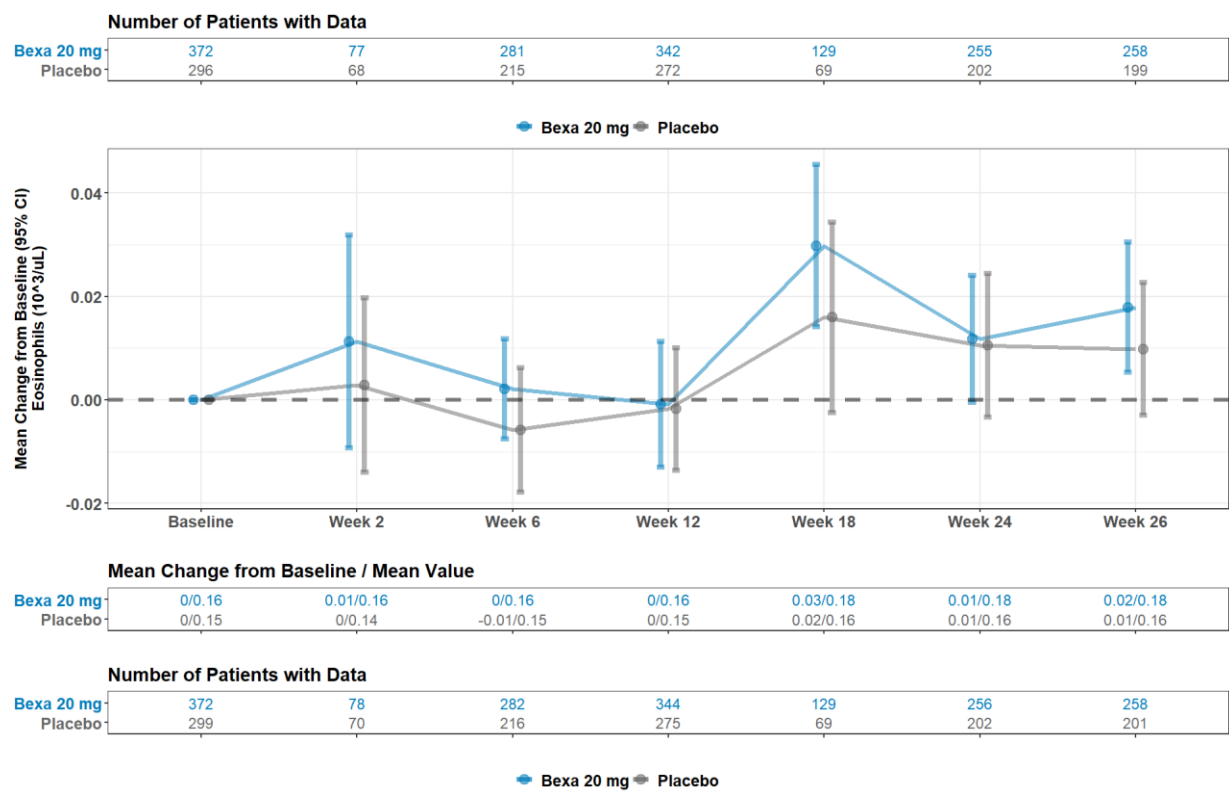
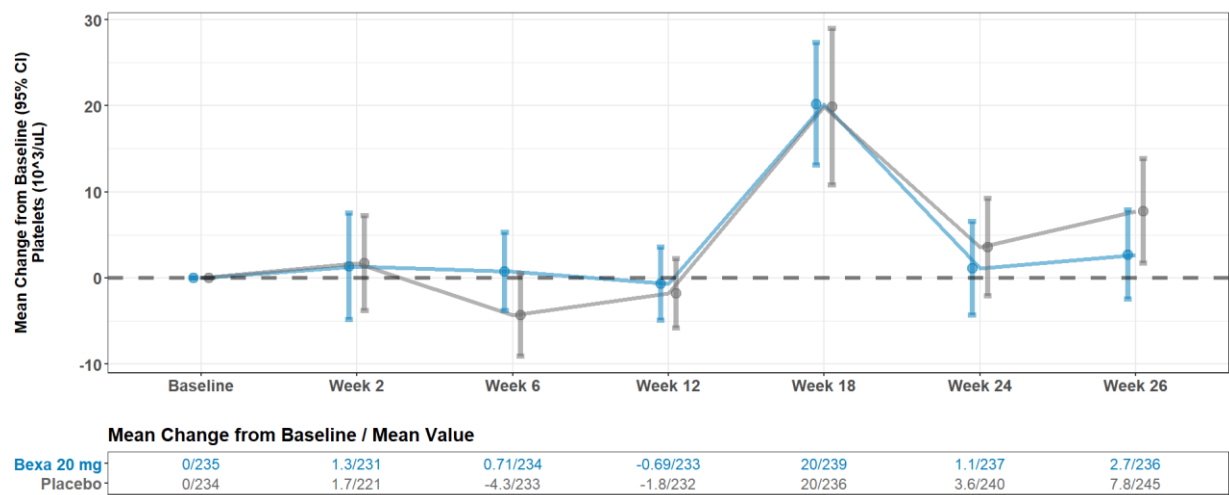
Bexa 20 mg	0/43	0.64/45	1.1/44	1.3/44	0.95/44	1.3/44	0.19/43
Placebo	0/43	-0.75/43	-0.25/43	-0.8/42	-1.3/42	-0.6/42	-0.75/42

Number of Patients with Data

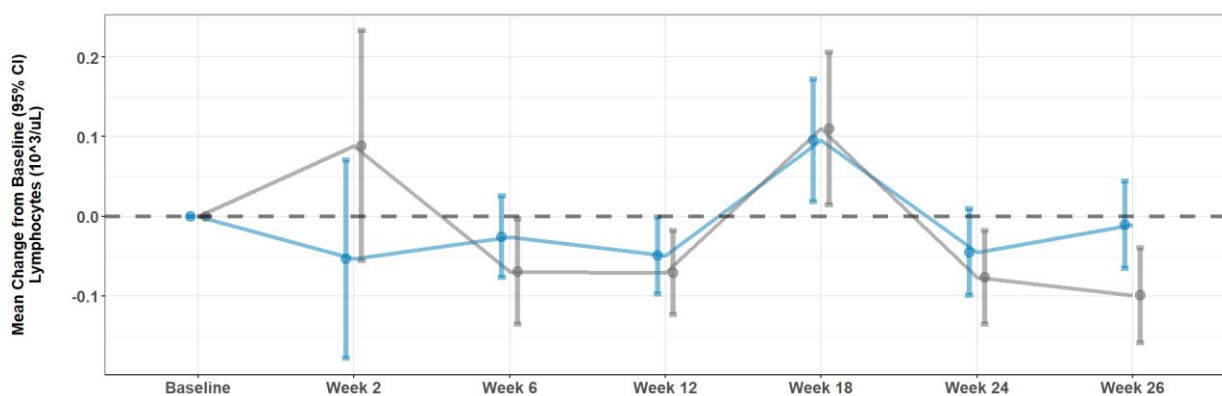
Bexa 20 mg	372	78	281	342	129	255	258
Placebo	299	71	216	274	69	202	201

◆ Bexa 20 mg ● Placebo

NDA 214373
Brenzavvy (bexagliflozin)



NDA 214373
Brenzavvy (bexagliflozin)

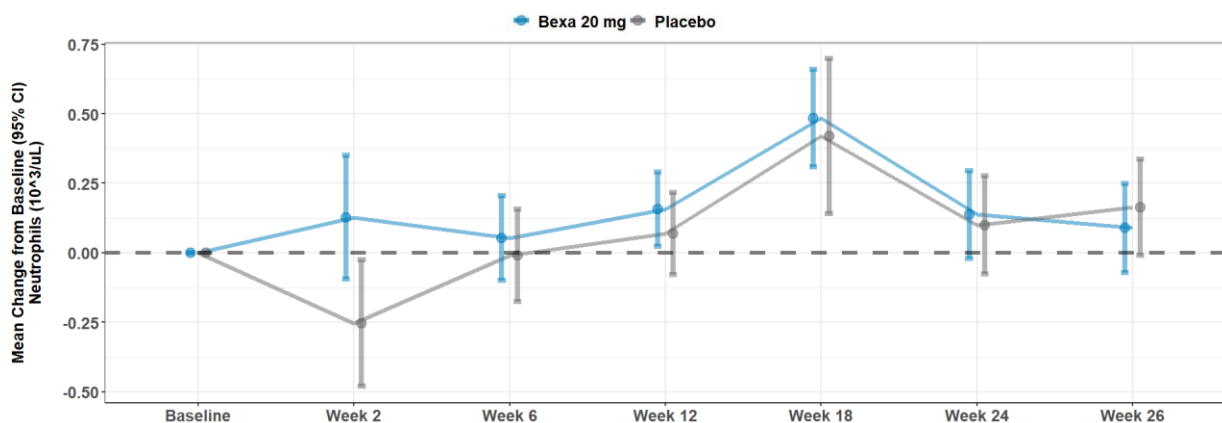


Mean Change from Baseline / Mean Value

Bexa 20 mg	0/2.1	-0.05/2.2	-0.03/2	-0.05/2	0.1/2.1	-0.05/2	-0.01/2
Placebo	0/2.2	0.09/2.1	-0.07/2.1	-0.07/2.1	0.11/2.3	-0.08/2.1	-0.1/2.1

Number of Patients with Data

Bexa 20 mg	372	78	282	344	129	256	258
Placebo	299	70	216	275	69	202	201



Mean Change from Baseline / Mean Value

Bexa 20 mg	0/4	0.13/3.9	0.05/4.1	0.16/4.1	0.48/4.3	0.14/4.2	0.09/4.1
Placebo	0/4.1	-0.25/3.8	-0.01/4.1	0.07/4.1	0.42/4.4	0.1/4.2	0.16/4.3

Number of Patients with Data

Bexa 20 mg	372	78	282	344	129	256	258
Placebo	299	70	216	275	69	202	201

◆ Bexa 20 mg ● Placebo

Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Hematology parameters were measured at the following timepoints: C-419: Screening, 6, 12, 24, and 26 (follow-up) weeks; C-450: Screening, 6, 12, 18, 24, and 26 (follow-up) weeks; C-449: Screening, 2, 12, and 14 (follow-up) weeks (14 week timepoint excluded from analysis).

Abbreviations: Bexa, bexagliflozin.

Table 222. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Level	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Complete Blood Count						
WBC, low (cells/uL)						
Level 1 (<3500)	6/362 (1.7)	4/294 (1.4)	17/1092 (1.6)	12/550 (2.2)	7/156 (4.5)	3/154 (1.9)
Level 2 (<3000)	1/362 (0.3)	1/294 (0.3)	7/1092 (0.6)	3/550 (0.5)	3/156 (1.9)	0/154 (0)
Level 3 (<1000)	0/362 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
WBC, high (cells/uL)						
Level 1 (>10800)	25/362 (6.9)	27/294 (9.2)	190/1092 (17.4)	99/550 (18.0)	17/156 (10.9)	11/154 (7.1)
Level 2 (>13000)	2/362 (0.6)	10/294 (3.4)	64/1092 (5.9)	27/550 (4.9)	6/156 (3.8)	4/154 (2.6)
Level 3 (>15000)	0/362 (0)	3/294 (1.0)	24/1092 (2.2)	7/550 (1.3)	2/156 (1.3)	2/154 (1.3)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 g/dL dec. from baseline)	16/362 (4.4)	24/293 (8.2)	96/1092 (8.8)	90/550 (16.4)	11/156 (7.1)	20/154 (13.0)
Level 3 (>2 g/dL dec. from baseline)	10/362 (2.8)	4/293 (1.4)	50/1092 (4.6)	45/550 (8.2)	7/156 (4.5)	10/154 (6.5)
Hemoglobin, high (g/dL)						
Level 2 (>2 g/dL inc. from baseline)	19/362 (5.2)	3/293 (1.0)	228/1092 (20.9)	22/550 (4.0)	8/156 (5.1)	2/154 (1.3)
Level 3 (>3 g/dL inc. from baseline)	3/362 (0.8)	0/293 (0)	41/1092 (3.8)	5/550 (0.9)	0/156 (0)	1/154 (0.6)
Platelets, low (cells/uL)						
Level 1 (<140000)	26/362 (7.2)	20/293 (6.8)	132/1092 (12.1)	58/550 (10.5)	18/156 (11.5)	24/153 (15.7)
Level 2 (<125000)	14/362 (3.9)	10/293 (3.4)	84/1092 (7.7)	29/550 (5.3)	10/156 (6.4)	13/153 (8.5)
Level 3 (<1e +05)	4/362 (1.1)	3/293 (1.0)	27/1092 (2.5)	7/550 (1.3)	2/156 (1.3)	1/153 (0.7)
WBC Differential						
Lymphocytes, low (cells/uL)						
Level 1 (<1000)	20/362 (5.5)	5/293 (1.7)	80/1092 (7.3)	35/550 (6.4)	17/156 (10.9)	16/154 (10.4)
Level 2 (<750)	6/362 (1.7)	0/293 (0)	20/1092 (1.8)	13/550 (2.4)	4/156 (2.6)	3/154 (1.9)
Level 3 (<500)	0/362 (0)	0/293 (0)	6/1092 (0.5)	3/550 (0.5)	1/156 (0.6)	0/154 (0)
Lymphocytes, high (cells/uL)						
Level 1 (>4000)	11/362 (3.0)	10/293 (3.4)	35/1092 (3.2)	19/550 (3.5)	2/156 (1.3)	6/154 (3.9)
Level 2 (>10000)	0/362 (0)	0/293 (0)	1/1092 (0.09)	0/550 (0)	0/156 (0)	0/154 (0)
Level 3 (>20000)	0/362 (0)	0/293 (0)	1/1092 (0.09)	0/550 (0)	0/156 (0)	0/154 (0)
Neutrophils, low (cells/uL)						
Level 1 (<2000)	32/362 (8.8)	19/293 (6.5)	39/1092 (3.6)	24/550 (4.4)	10/156 (6.4)	5/154 (3.2)
Level 2 (<1000)	1/362 (0.3)	0/293 (0)	2/1092 (0.2)	2/550 (0.4)	0/156 (0)	0/154 (0)
Level 3 (<500)	0/362 (0)	0/293 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Eosinophils, high (cells/uL)						
Level 1 (>650)	9/362 (2.5)	7/293 (2.4)	39/1092 (3.6)	28/550 (5.1)	5/156 (3.2)	4/154 (2.6)
Level 2 (>1500)	1/362 (0.3)	0/293 (0)	3/1092 (0.3)	2/550 (0.4)	1/156 (0.6)	0/154 (0)
Level 3 (>5000)	0/362 (0)	0/293 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)

Source: adlb.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; WBC, white blood cells.

Table 223. Thrombosis Events by FMQ and CMQ, Safety Population, Trial C-476

Query	Bexa 20 mg N=1132 n (%)	Placebo N=567 n (%)	Bexa 20 mg vs. Placebo Risk Difference (%) (95% CI)
Thrombosis FMQ	99 (8.7)	66 (11.6)	-2.9 (-6.2, 0.4)
Thrombosis (arterial) FMQ	92 (8.1)	61 (10.8)	-2.6 (-5.8, 0.6)
Thrombosis (venous) FMQ	4 (0.4)	5 (0.9)	-0.5 (-1.5, 0.4)
Thromboembolic and vascular event CMQ*	5 (0.4)	5 (0.9)	-0.4 (-1.4, 0.5)

Source: adae.xpt; Generated by Clinical Reviewer; Software: SAS

* This CMQ was used for the review of DECALRE for dapagliflozin

Abbreviations: Bexa, bexagliflozin; CMQ, customized Medical Dictionary for Regulatory Activities query; FMQ, Food and Drug Administration Medical Dictionary for Regulatory Activities query.

Lipids

Fasting lipid measurements were completed in all trials, and subjects were queried to assess compliance with an approximately 10 hours fast prior to blood draw to ensure lipid parameters could be accurately assessed. Small increases in low-density lipoprotein cholesterol (LDL-C) have been associated with the SGLT2 inhibitor pharmacologic class, and changes in LDL-C are currently described in the labeling for approved products. In the placebo-controlled pool, mean changes in LDL-C of 1.5 mg/dL (1.4%) and -3.3 mg/dL (-3.1%) were observed from baseline to Week 24 in the bexagliflozin and placebo groups, respectively ([Figure 77](#)). LDL-C was also slightly elevated within the first 24 weeks of treatment of Trial C-476, with mean changes from baseline to Week 24 of 3.1 mg/dL (4.1%) and 2.5 (3.2%) mg/dL in the bexagliflozin and placebo groups, respectively, although these elevations decreased over time with mean changes returning to baseline in both groups by Week 72 (data not shown). No consistent trends were observed in C-476 regarding the proportion of subjects with at least one value exceeding certain LDL-C thresholds; however, there was a greater proportion of subjects who had at least one value that exceeded level 1 (>130 mg/dL) and level 2 (>160 mg/dL) in the bexagliflozin group as compared to the placebo group in the placebo-controlled pool and C-448 ([Table 224](#)). Regarding other lipid parameters, small increases in high-density lipoprotein cholesterol were observed, with mean changes from baseline to Week 24 of 2.2 (4.3%) mg/dL and -0.2 (-0.4%) mg/dL in the bexagliflozin and placebo groups, respectively, of the placebo-controlled pool. There was also a decrease in triglycerides, with mean changes from baseline at Week 24 of -16 mg/dL (-9.3%) and -6.9 (-3.4%) mg/dL in the bexagliflozin and placebo groups, respectively.

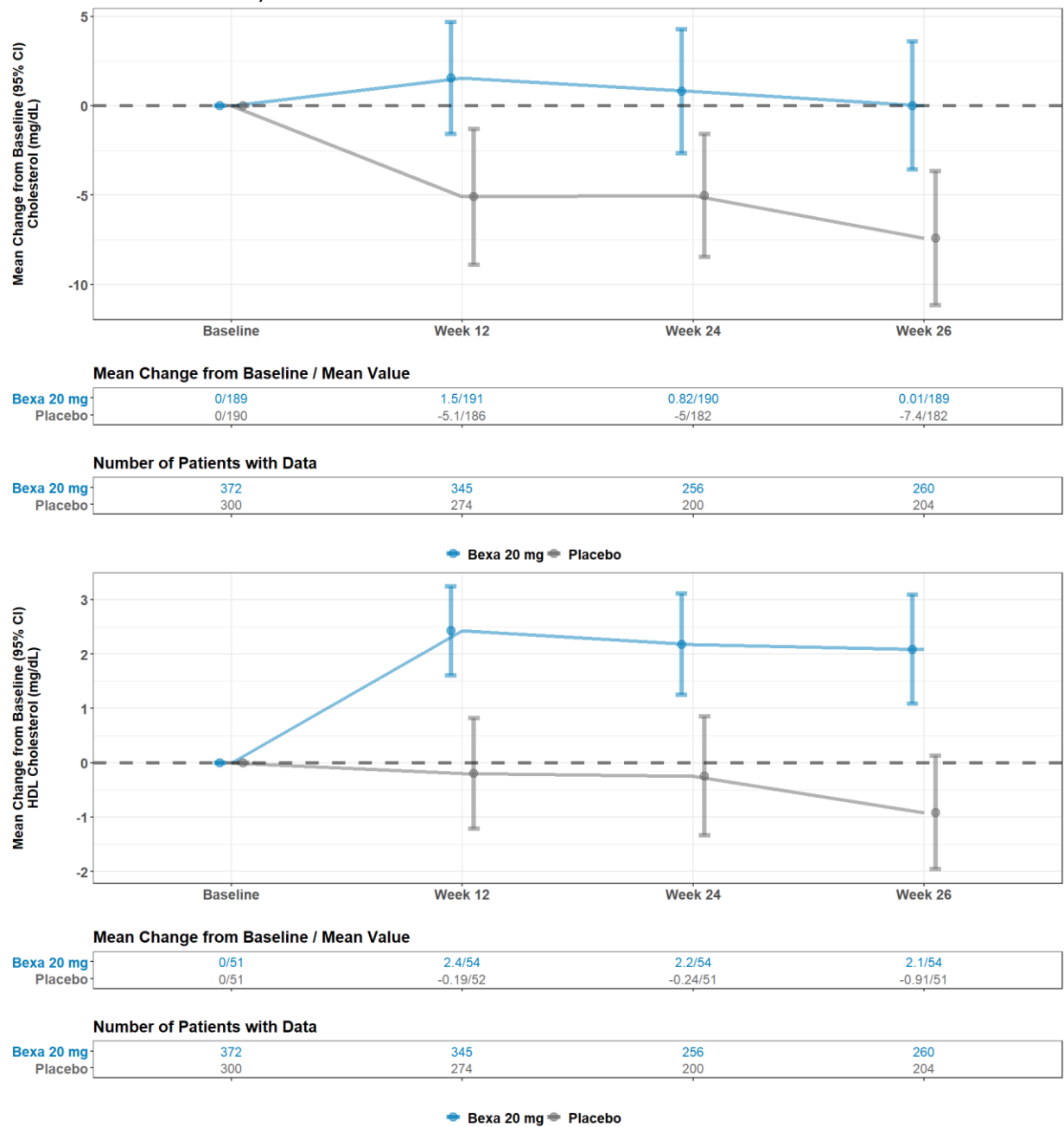
FDA Reviewer Comment: As presented in Section [17.1](#), the MACE+ meta-analysis supports that bexagliflozin is not associated with increased risk for MACE, providing reassuring evidence that the small changes in lipid parameters described herein do not adversely impact cardiac safety.

(b) (4)

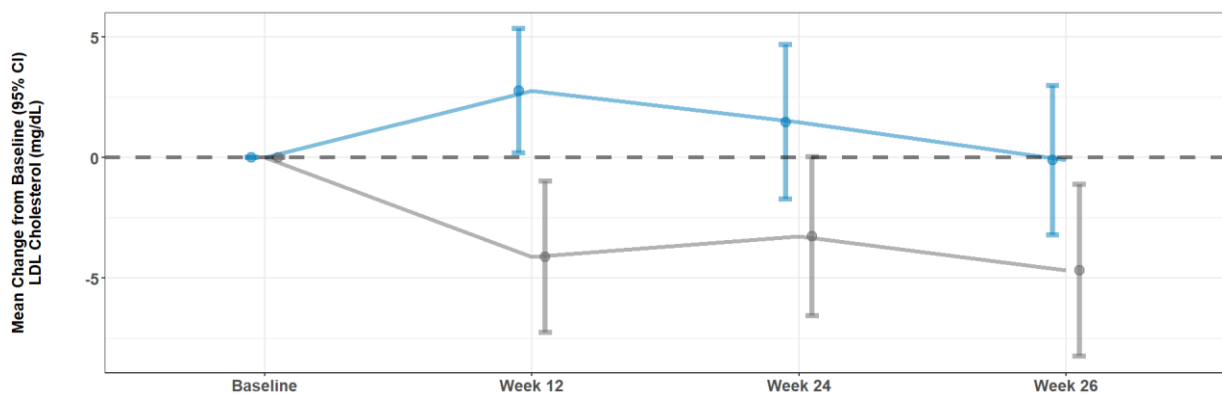
(b) (4)

per current FDA Guidance *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011), and labeling similar to other members of the class, wherein information is provided in Section 6, is recommended.

Figure 77. Mean Laboratory (Lipids) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data



NDA 214373
Brenzavvy (bexagliflozin)

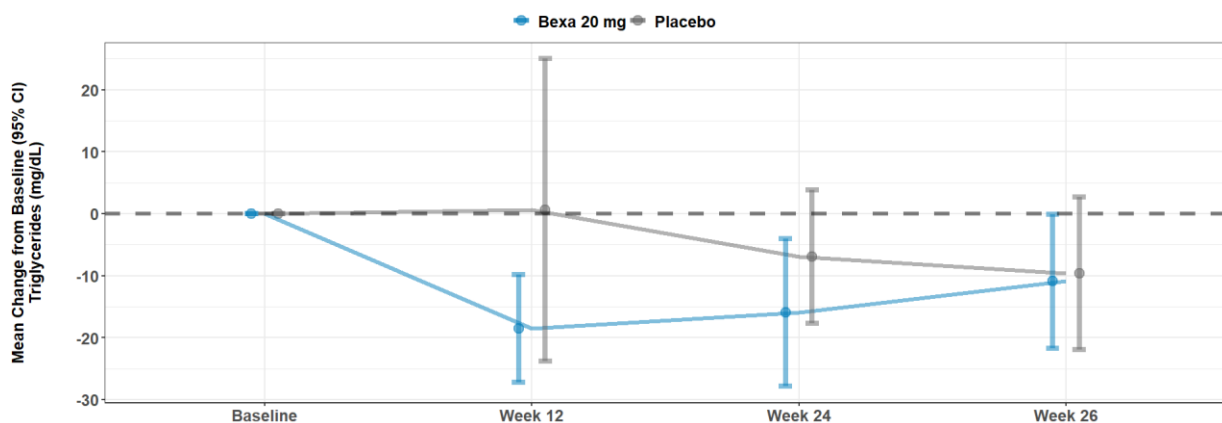


Mean Change from Baseline / Mean Value

Bexa 20 mg	0/105	2.8/107	1.5/105	-0.11/102
Placebo	0/106	-4.1/102	-3.3/100	-4.7/101

Number of Patients with Data

Bexa 20 mg	362	339	251	253
Placebo	294	268	196	199



Mean Change from Baseline / Mean Value

Bexa 20 mg	0/172	-19/155	-16/164	-11/169
Placebo	0/177	0.58/179	-6.9/169	-9.6/163

Number of Patients with Data

Bexa 20 mg	372	345	256	260
Placebo	300	274	200	204

◆ Bexa 20 mg ● Placebo

Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Lipid parameters were measured at the following timepoints: C-419: Screening, 12, 24, and 26 (follow-up) weeks; C-450: Screening, 6, 12, 18, 24, and 26 (follow-up) weeks; C-449: Screening, 12, and 14 (follow-up) weeks (14 week timepoint excluded from analysis).

Abbreviations: Bexa, bexagliflozin.

Table 224. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Level	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Cholesterol, total, high (mg/dL)						
Level 1 (>200)	168/356 (47.2)	115/280 (41.1)	350/1090 (32.1)	186/550 (33.8)	55/155 (35.5)	39/152 (25.7)
Level 2 (>210)	145/356 (40.7)	91/280 (32.5)	284/1090 (26.1)	149/550 (27.1)	44/155 (28.4)	27/152 (17.8)
Level 3 (>225)	85/356 (23.9)	59/280 (21.1)	209/1090 (19.2)	107/550 (19.5)	29/155 (18.7)	19/152 (12.5)
HDL, males, low (mg/dL)						
Level 1 (<40)	61/209 (29.2)	47/156 (30.1)	471/765 (61.6)	253/379 (66.8)	37/92 (40.2)	52/101 (51.5)
Level 2 (<30)	8/209 (3.8)	6/156 (3.8)	140/765 (18.3)	66/379 (17.4)	10/92 (10.9)	13/101 (12.9)
Level 3 (<20)	0/209 (0)	0/156 (0)	16/765 (2.1)	3/379 (0.8)	1/92 (1.1)	0/101 (0)
HDL, females, low (mg/dL)						
Level 1 (<50)	66/147 (44.9)	66/124 (53.2)	244/326 (74.8)	136/171 (79.5)	30/63 (47.6)	34/51 (66.7)
Level 2 (<40)	26/147 (17.7)	21/124 (16.9)	128/326 (39.3)	66/171 (38.6)	12/63 (19.0)	14/51 (27.5)
Level 3 (<20)	0/147 (0)	0/124 (0)	2/326 (0.6)	0/171 (0)	0/63 (0)	0/51 (0)
LDL, high (mg/dL)						
Level 1 (>130)	116/352 (33.0)	72/279 (25.8)	220/1092 (20.1)	118/549 (21.5)	31/155 (20.0)	23/152 (15.1)
Level 2 (>160)	39/352 (11.1)	27/279 (9.7)	82/1092 (7.5)	53/549 (9.7)	11/155 (7.1)	7/152 (4.6)
Level 3 (>190)	7/352 (2.0)	8/279 (2.9)	34/1092 (3.1)	13/549 (2.4)	4/155 (2.6)	1/152 (0.7)
Triglycerides, high (mg/dL)						
Level 1 (>150)	183/356 (51.4)	157/280 (56.1)	831/1090 (76.2)	402/550 (73.1)	98/155 (63.2)	102/152 (67.1)
Level 2 (>300)	48/356 (13.5)	46/280 (16.4)	268/1090 (24.6)	130/550 (23.6)	22/155 (14.2)	20/152 (13.2)
Level 3 (>500)	7/356 (2.0)	7/280 (2.5)	65/1090 (6.0)	36/550 (6.5)	5/155 (3.2)	3/152 (2.0)

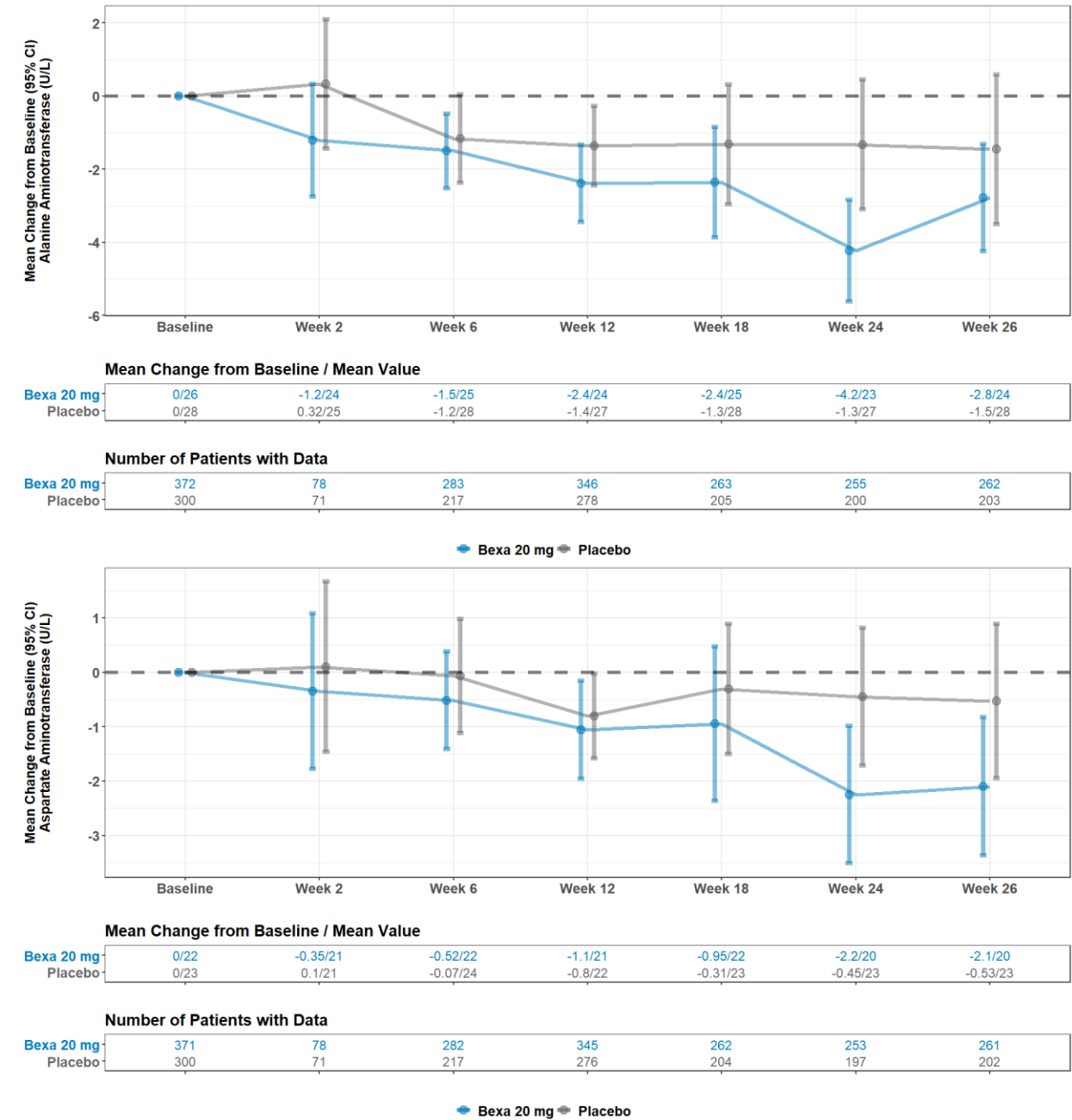
Source: adlb.xpt; Software: R; Generated by CDS

Abbreviations: Bexa, bexagliflozin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

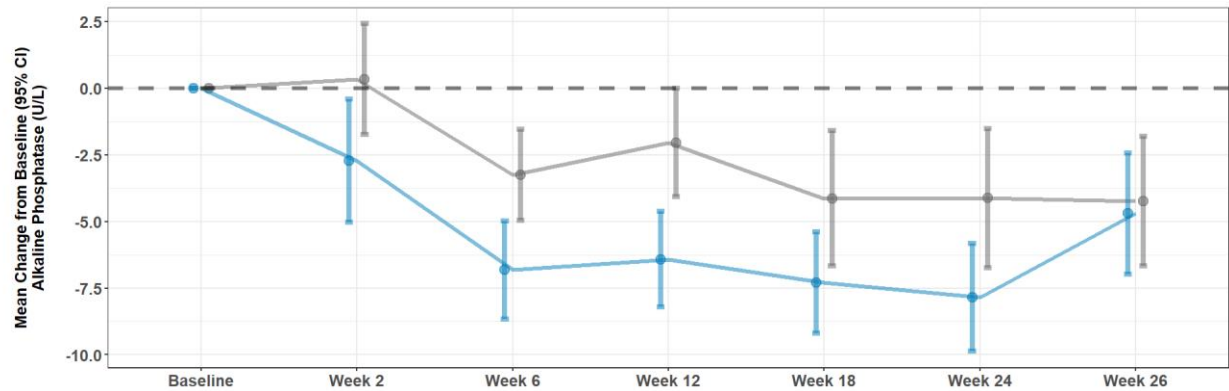
Liver Chemistry

ALT, AST, and total and direct bilirubin were measured in all trials. Alkaline phosphatase was also measured in all trials with the exception of C-448 and in C-450. In the placebo-controlled pool, there were no meaningful changes in central tendencies in liver chemistry parameters, with minor decreases in ALT, AST, and alkaline phosphatase between baseline and Week 24 ([Figure 78](#)). Results were comparable in Trials C-476 and C-448 (data not shown). Outlier enzyme elevations were generally balanced between treatment groups. See Section [17.3.5](#) Hepatic Injury for additional analysis of potential DILI events.

Figure 78. Mean Laboratory (Liver Biochemistry) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data

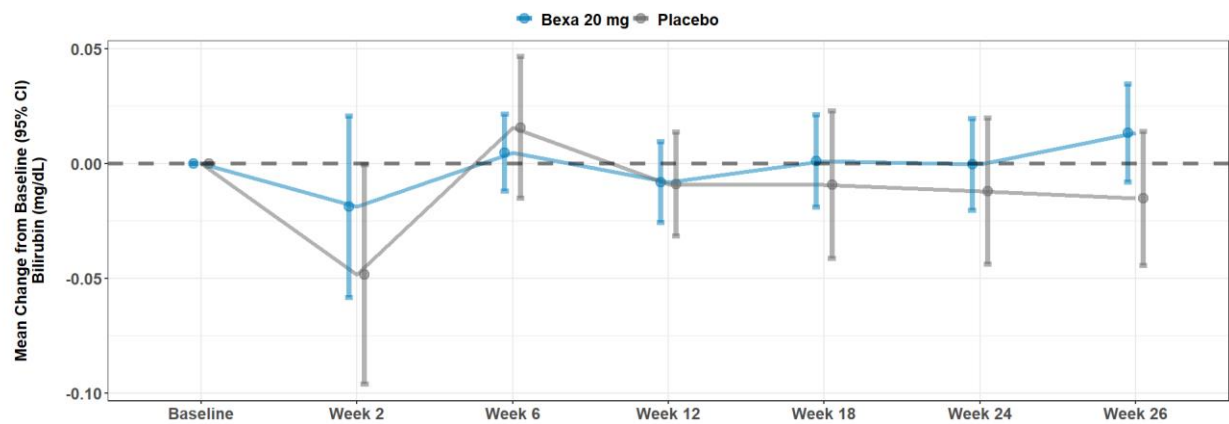


NDA 214373
Brexavvy (bexagliflozin)



Mean Change from Baseline / Mean Value							
Bexa 20 mg	0/81	-2.7/79	-6.8/75	-6.4/75	-7.3/74	-7.8/73	-4.7/75
Placebo	0/76	0.34/77	-3.3/72	-2/74	-4.1/70	-4.1/69	-4.2/70

Number of Patients with Data							
Bexa 20 mg	233	71	154	217	139	138	137
Placebo	231	65	152	210	142	139	141



Mean Change from Baseline / Mean Value							
Bexa 20 mg	0/0.49	-0.02/0.54	0/0.48	-0.01/0.48	0/0.48	0/0.48	0.01/0.48
Placebo	0/0.52	-0.05/0.5	0.02/0.54	-0.01/0.51	-0.01/0.51	-0.01/0.5	-0.02/0.5

Number of Patients with Data							
Bexa 20 mg	372	78	283	346	263	255	262
Placebo	300	71	217	278	205	200	203

NDA 214373
Brenzavvy (bexagliflozin)



Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline. Liver biochemistry parameters were measured at the following timepoints: C-419: Screening, 6, 12, 24, and 26 (follow-up) weeks; C-450: Screening, 6, 12, 18, 24, and 26 (follow-up) weeks; C-449: Screening, 2, 12, and 14 (follow-up) weeks (14 week timepoint excluded from analysis).

Abbreviations: Bexa, bexagliflozin.

Table 225. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Level	Placebo-Controlled Pool*		Trial C-476		Trial C-448*	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	2/229 (0.9)	3/224 (1.3)	11/1092 (1.0)	10/551 (1.8)	N/A	N/A
Level 2 (>2X ULN)	0/229 (0)	1/224 (0.4)	4/1092 (0.4)	2/551 (0.4)	N/A	N/A
Level 3 (>3X ULN)	0/229 (0)	0/224 (0)	1/1092 (0.09)	0/551 (0)	N/A	N/A
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	3/363 (0.8)	1/294 (0.3)	19/1093 (1.7)	9/551 (1.6)	1/156 (0.6)	1/154 (0.6)
Level 2 (>5X ULN)	0/363 (0)	0/294 (0)	4/1093 (0.4)	3/551 (0.5)	1/156 (0.6)	0/154 (0)
Level 3 (>10X ULN)	0/363 (0)	0/294 (0)	1/1093 (0.09)	1/551 (0.2)	0/156 (0)	0/154 (0)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	2/363 (0.6)	1/294 (0.3)	11/1093 (1.0)	5/551 (0.9)	1/156 (0.6)	2/154 (1.3)
Level 2 (>5X ULN)	0/363 (0)	0/294 (0)	6/1093 (0.5)	1/551 (0.2)	0/156 (0)	0/154 (0)
Level 3 (>10X ULN)	0/363 (0)	0/294 (0)	1/1093 (0.09)	0/551 (0)	0/156 (0)	0/154 (0)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	2/363 (0.6)	2/294 (0.7)	11/1093 (1.0)	7/551 (1.3)	0/156 (0)	0/154 (0)
Level 2 (>2X ULN)	0/363 (0)	0/294 (0)	3/1093 (0.3)	1/551 (0.2)	0/156 (0)	0/154 (0)
Level 3 (>3X ULN)	0/363 (0)	0/294 (0)	1/1093 (0.09)	0/551 (0)	0/156 (0)	0/154 (0)

Source: adlb.xpt; Software: R; Generated by CDS

*Alkaline phosphatase was not measured in C-450 in the Placebo-Controlled Pool or C-448

Abbreviations: Bexa, bexagliflozin; ULN, upper limit of normal.

Chemistry

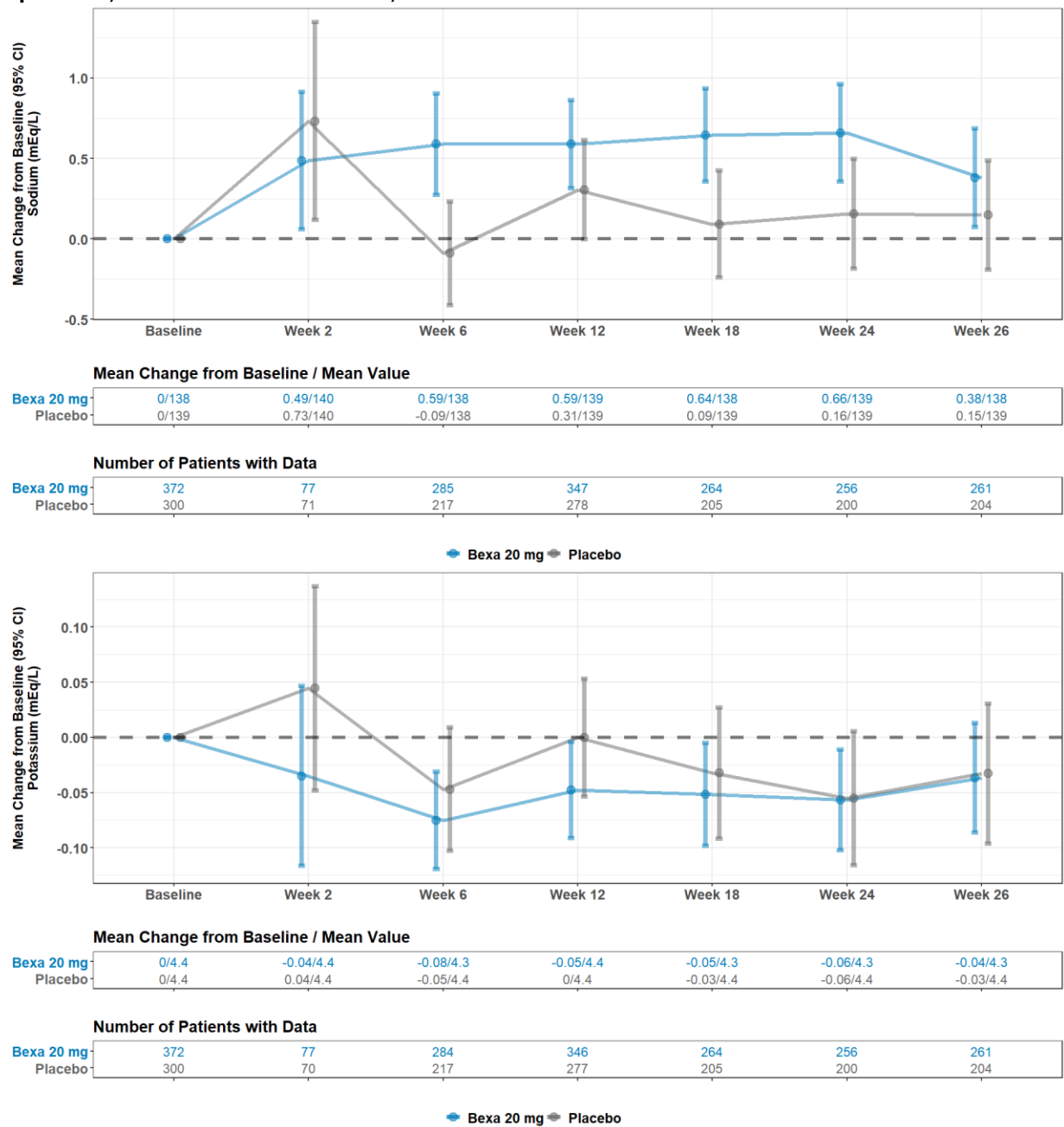
In the placebo-controlled pool, no meaningful changes were observed from baseline to Week 24 in mean sodium, potassium, chloride, calcium, protein, and albumin ([Figure 79](#)).

Magnesium is regulated by the urinary system and hypermagnesemia is most often associated with renal impairment in the absence of overdose scenarios, making this laboratory marker relevant in assessing the impact of bexagliflozin on renal function. Clinical symptoms such as nausea, lethargy, and headache may be seen when plasma levels exceed 4.8 mg/dL, while concentrations higher than 7.2 mg/dL are associated with hypocalcemia, hypotension, bradycardia, and EKG changes. There was an increase of 0.13 mg/dL (6.8%) in magnesium levels in the bexagliflozin group compared to a -0.01 mg/dL (0.5%) decrease in the placebo group in the placebo-controlled pool at week 24, which returned approximately to baseline levels after drug withdrawal at the follow-up visit. Increases of approximately 0.32 mg/dL (18%) and 0.21 mg/dL (10%) from baseline to Week 24 were also observed in the bexagliflozin groups of C-476 and C-448, respectively, as compared to an increase of 0.1 mg/dL (5%) and a decrease of -0.02 mg/dL (1%) in the respective placebo groups. In line with these results, the placebo-controlled pool, C-476, and C-448 had a higher proportion of subjects with level 1 (>2.3 mg/dL) increases in magnesium in the bexagliflozin group compared to the placebo group in each trial, although it is reassuring that no subjects had magnesium values meeting the criteria for level 2 (>4 mg/dL) or Level 3 (>7 mg/dL) ([Table 226](#)). In addition, a search for AEs indicative of elevated magnesium levels (i.e., PTs of “hypermagnesemia” or “blood magnesium increased”) in bexagliflozin-exposed subjects did not reveal any events in any trial. While not currently described in the labeling for approved SGLT2 inhibitors, increases in serum magnesium associated with SGLT2 inhibitor treatment have been noted in prior clinical reviews (see Dr. Hyon’s review for canagliflozin in DARRTS dated August 10, 2012) and reported in the literature (Tang et al. 2016; Sasaki et al. 2017; Ray et al. 2020). The magnitude of serum magnesium elevations observed in the clinical program do not appear clinically concerning.

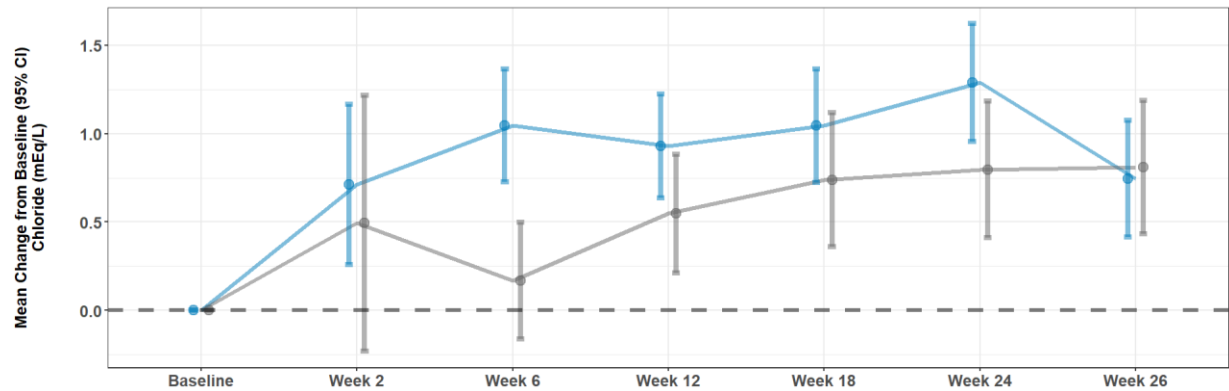
Transient decreases in mean serum bicarbonate occurred in the placebo-controlled pool, with a maximum mean decrease of -1.4 mEq/L in the bexagliflozin group compared to -0.5 mEq/L in the placebo group at Week 6. Transient decreases were also observed in C-476 and C-448 although to a lesser extent (data not shown). In line with these results, there were also more subjects who experienced at least one level 1 (<20 mEq/L), 2 (<18 mEq/L), and 3 (<15 mEq/L) low bicarbonate values in the bexagliflozin groups of the placebo-controlled pool and C-476 compared to the placebo groups ([Table 226](#)). Similar trends were also observed for the proportion of subjects with values exceeding level 1 and 2 low bicarbonate values for C-448. The clinical meaningfulness of these findings is unclear. As discussed in [Section 17.3.6](#), there was no signal for DKA observed in the bexagliflozin clinical program; however, the event rate of DKA may be too low to adequately assess in a premarket setting.

Serum phosphate increased 0.23 mg/dL (6.6%) in the bexagliflozin group as compared to 0.02 mg/dL (0.6%) in the placebo group from baseline to Week 24 in the placebo-controlled pool. Similar trends were observed in C-476 and C-448 (data not shown). Minor increases in serum phosphate levels have been previously characterized (e.g., see US prescribing information for ertugliflozin).

Figure 79. Mean Laboratory (Chemistry) Data Change From Baseline Over Time, Safety Population, Placebo-Controlled Pool; Observed Data



NDA 214373
Brenzavvy (bexagliflozin)

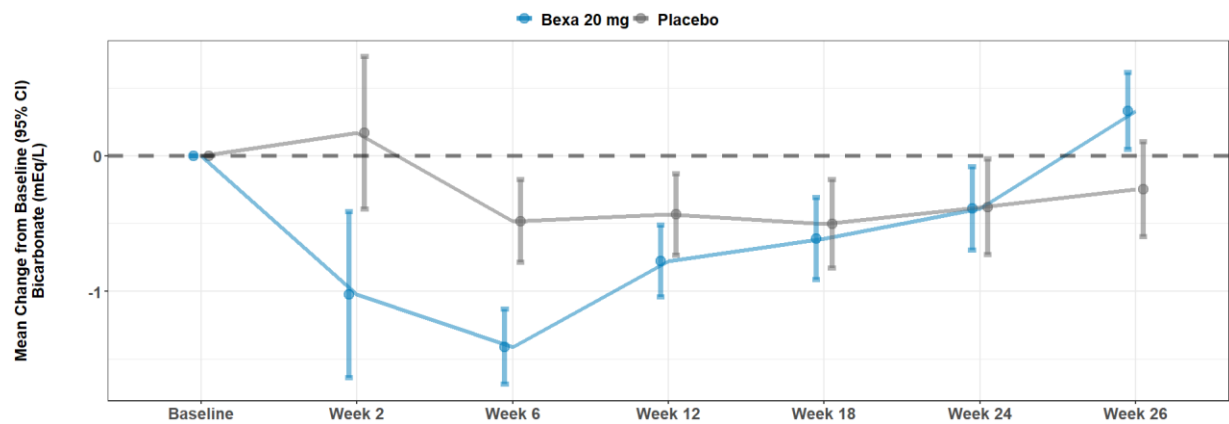


Mean Change from Baseline / Mean Value

Bexa 20 mg	0/99	0.71/101	1/100	0.93/100	1/100	1.3/100	0.74/100
Placebo	0/99	0.49/100	0.17/99	0.55/100	0.74/100	0.8/100	0.81/100

Number of Patients with Data

Bexa 20 mg	372	77	285	347	264	256	261
Placebo	300	71	217	278	205	200	204



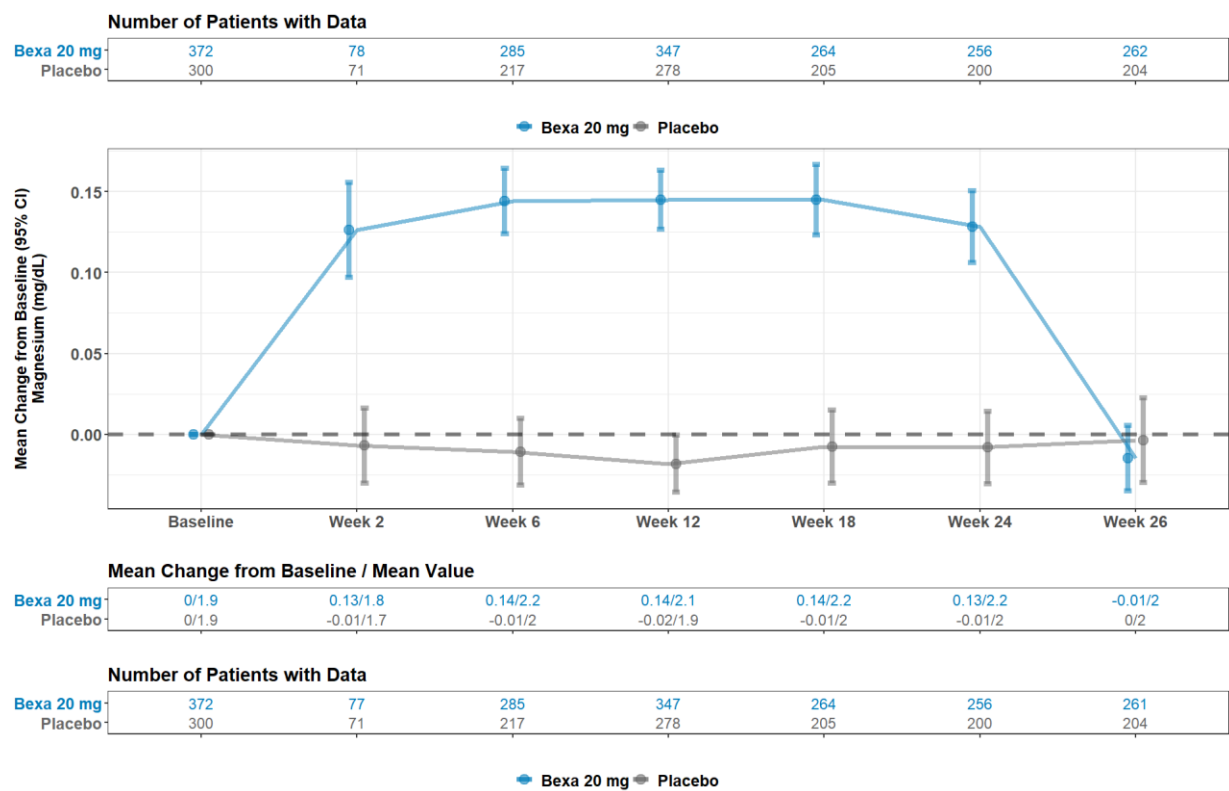
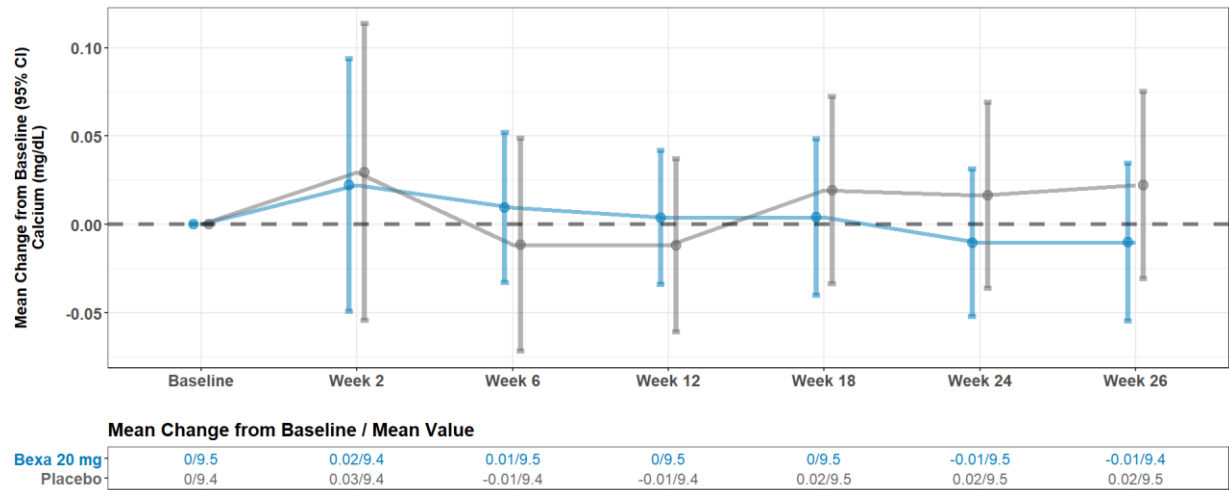
Mean Change from Baseline / Mean Value

Bexa 20 mg	0/24	-1/24	-1.4/22	-0.78/23	-0.61/23	-0.39/23	0.33/23
Placebo	0/24	0.17/25	-0.48/23	-0.43/23	-0.5/23	-0.38/23	-0.25/23

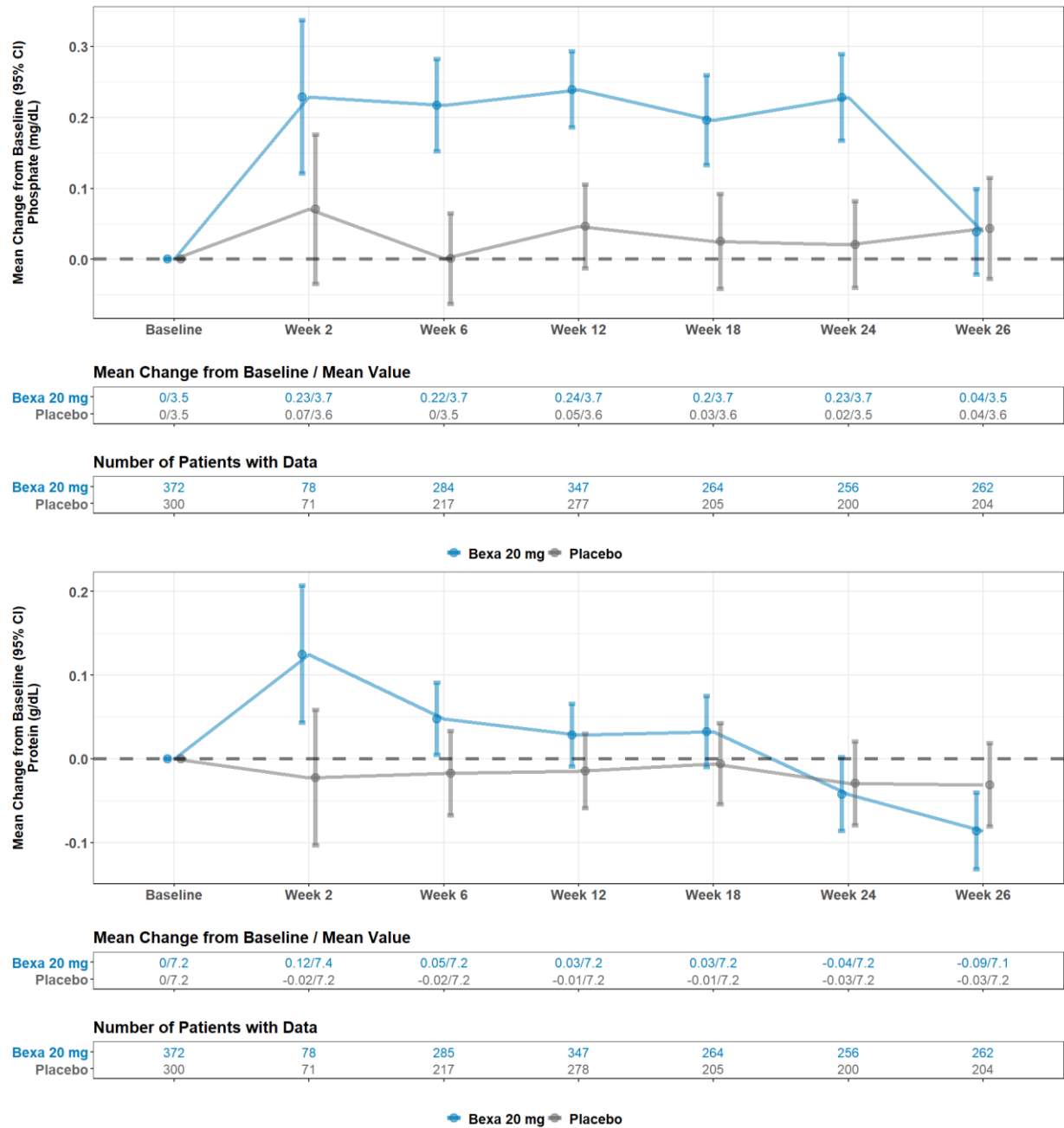
Number of Patients with Data

Bexa 20 mg	372	77	283	346	263	255	261
Placebo	299	71	216	278	204	200	203

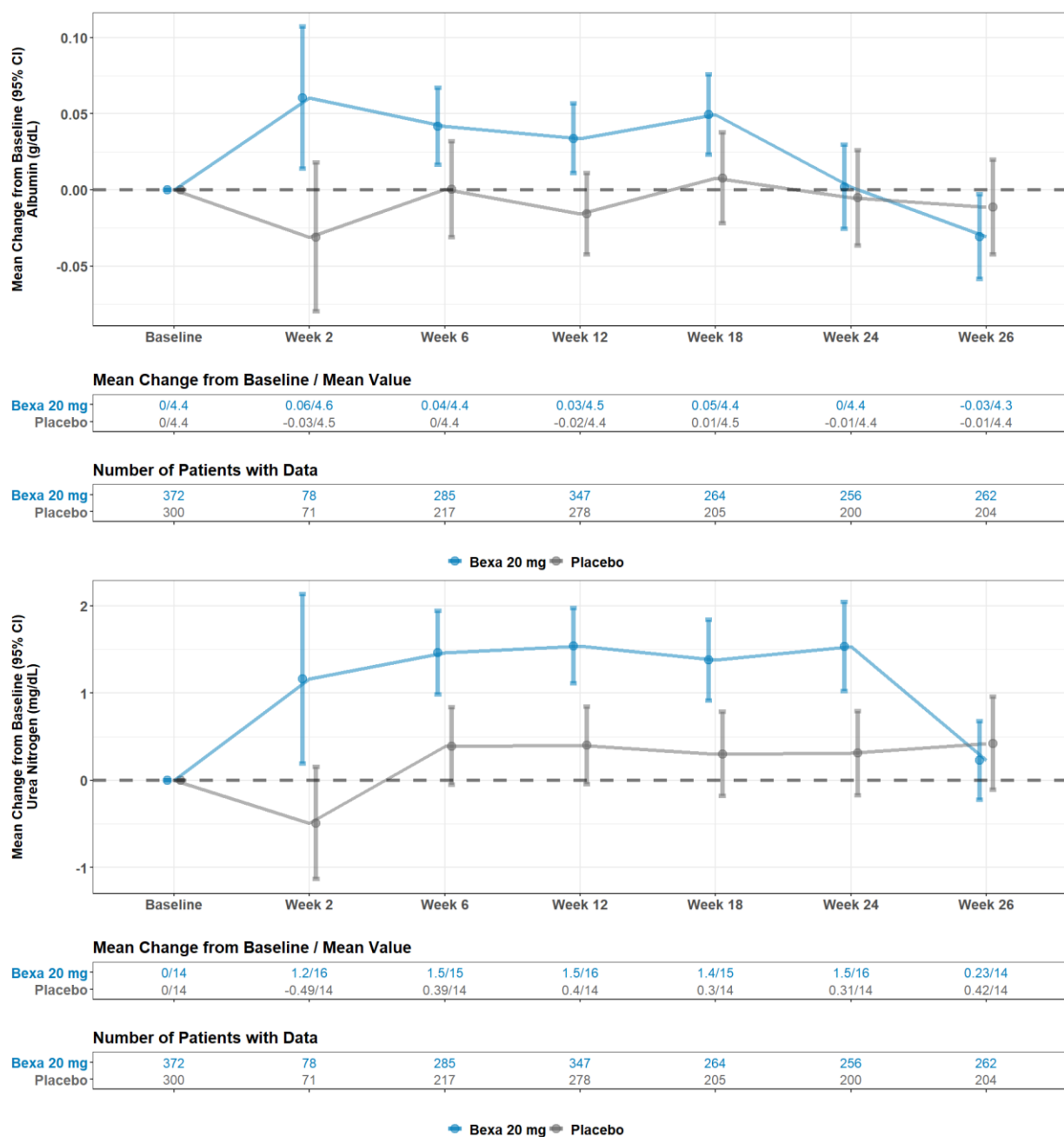
NDA 214373
Brenzavvy (bexagliflozin)



NDA 214373
Brenzavvy (bexagliflozin)



NDA 214373
Brenzavvy (bexagliflozin)



Source: adlb.xpt; Software: R; Generated by CDS

Mean change from baseline calculated as the mean of the per-subject differences between the specific time point and baseline.

Abbreviations: Bexa, bexagliflozin.

Table 226. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Placebo-Controlled Pool, Trials C-476 and C-448

Level	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Sodium, low (mEq/L)						
Level 1 (<132)	9/363 (2.5)	6/294 (2.0)	14/1092 (1.3)	7/550 (1.3)	1/156 (0.6)	2/154 (1.3)
Level 2 (<130)	3/363 (0.8)	1/294 (0.3)	1/1092 (0.09)	3/550 (0.5)	0/156 (0)	0/154 (0)
Level 3 (<125)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)

NDA 214373
Brenzavvy (bexagliflozin)

Level	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Sodium, high (mEq/L)						
Level 1 (>150)	0/363 (0)	0/294 (0)	1/1092 (0.09)	0/550 (0)	0/156 (0)	0/154 (0)
Level 2 (>155)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Level 3 (>160)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Potassium, low (mEq/L)						
Level 1 (<3.6)	22/363 (6.1)	17/294 (5.8)	79/1093 (7.2)	42/550 (7.6)	9/156 (5.8)	8/154 (5.2)
Level 2 (<3.4)	8/363 (2.2)	9/294 (3.1)	31/1093 (2.8)	21/550 (3.8)	3/156 (1.9)	4/154 (2.6)
Level 3 (<3)	0/363 (0)	0/294 (0)	5/1093 (0.5)	2/550 (0.4)	0/156 (0)	1/154 (0.6)
Potassium, high (mEq/L)						
Level 1 (>5.5)	11/363 (3.0)	13/294 (4.4)	126/1093 (11.5)	56/550 (10.2)	15/156 (9.6)	8/154 (5.2)
Level 2 (>6)	1/363 (0.3)	1/294 (0.3)	13/1093 (1.2)	11/550 (2.0)	0/156 (0)	1/154 (0.6)
Level 3 (>6.5)	0/363 (0)	1/294 (0.3)	3/1093 (0.3)	4/550 (0.7)	0/156 (0)	0/154 (0)
Chloride, low (mEq/L)						
Level 1 (<95)	25/363 (6.9)	16/294 (5.4)	90/1092 (8.2)	45/550 (8.2)	10/156 (6.4)	10/154 (6.5)
Level 2 (<88)	3/363 (0.8)	1/294 (0.3)	3/1092 (0.3)	1/550 (0.2)	0/156 (0)	0/154 (0)
Level 3 (<80)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Chloride, high (mEq/L)						
Level 1 (>108)	0/363 (0)	0/294 (0)	35/1092 (3.2)	19/550 (3.5)	3/156 (1.9)	4/154 (2.6)
Level 2 (>112)	0/363 (0)	0/294 (0)	2/1092 (0.2)	2/550 (0.4)	0/156 (0)	0/154 (0)
Level 3 (>115)	0/363 (0)	0/294 (0)	0/1092 (0)	1/550 (0.2)	0/156 (0)	0/154 (0)
Bicarbonate, low (mEq/L)						
Level 1 (<20)	99/363 (27.3)	51/294 (17.3)	520/1092 (47.6)	221/550 (40.2)	67/156 (42.9)	46/154 (29.9)
Level 2 (<18)	28/363 (7.7)	13/294 (4.4)	211/1092 (19.3)	82/550 (14.9)	28/156 (17.9)	16/154 (10.4)
Level 3 (<15)	4/363 (1.1)	2/294 (0.7)	24/1092 (2.2)	11/550 (2.0)	2/156 (1.3)	4/154 (2.6)
Bicarbonate, high (mEq/L)						
Level 3 (>30)	2/363 (0.6)	4/294 (1.4)	20/1092 (1.8)	9/550 (1.6)	0/156 (0)	3/154 (1.9)
Calcium, low (mg/dL)						
Level 1 (<8.4)	0/363 (0)	6/294 (2.0)	41/1093 (3.8)	26/551 (4.7)	4/156 (2.6)	3/154 (1.9)
Level 2 (<8)	0/363 (0)	2/294 (0.7)	25/1093 (2.3)	12/551 (2.2)	1/156 (0.6)	3/154 (1.9)
Level 3 (<7.5)	0/363 (0)	2/294 (0.7)	14/1093 (1.3)	4/551 (0.7)	1/156 (0.6)	1/154 (0.6)
Calcium, high (mg/dL)						
Level 1 (>10.5)	8/363 (2.2)	5/294 (1.7)	60/1093 (5.5)	32/551 (5.8)	7/156 (4.5)	3/154 (1.9)
Level 2 (>11)	2/363 (0.6)	0/294 (0)	10/1093 (0.9)	8/551 (1.5)	1/156 (0.6)	1/154 (0.6)
Level 3 (>12)	0/363 (0)	0/294 (0)	1/1093 (0.09)	0/551 (0)	0/156 (0)	0/154 (0)
Magnesium, low (mg/dL)						
Level 1 (<1.5)	2/363 (0.6)	20/294 (6.8)	24/1092 (2.2)	58/550 (10.5)	0/156 (0)	7/154 (4.5)
Level 2 (<1.2)	0/363 (0)	1/294 (0.3)	2/1092 (0.2)	7/550 (1.3)	0/156 (0)	1/154 (0.6)
Level 3 (<0.9)	0/363 (0)	1/294 (0.3)	0/1092 (0)	0/550 (0)	0/156 (0)	1/154 (0.6)
Magnesium, high (mg/dL)						
Level 1 (>2.3)	95/363 (26.2)	25/294 (8.5)	428/1092 (39.2)	73/550 (13.3)	84/156 (53.8)	38/154 (24.7)
Level 2 (>4)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Level 3 (>7)	0/363 (0)	0/294 (0)	0/1092 (0)	0/550 (0)	0/156 (0)	0/154 (0)
Phosphate, low (mg/dL)						
Level 1 (<2.5)	10/363 (2.8)	5/294 (1.7)	37/1094 (3.4)	45/551 (8.2)	3/156 (1.9)	15/154 (9.7)
Level 2 (<2)	1/363 (0.3)	0/294 (0)	3/1094 (0.3)	4/551 (0.7)	0/156 (0)	1/154 (0.6)
Level 3 (<1.4)	0/363 (0)	0/294 (0)	0/1094 (0)	1/551 (0.2)	0/156 (0)	0/154 (0)
Protein, total, low (g/dL)						
Level 1 (<6)	0/363 (0)	4/294 (1.4)	21/1093 (1.9)	17/551 (3.1)	4/156 (2.6)	2/154 (1.3)
Level 2 (<5.4)	0/363 (0)	0/294 (0)	2/1093 (0.2)	1/551 (0.2)	0/156 (0)	0/154 (0)
Level 3 (<5)	0/363 (0)	0/294 (0)	0/1093 (0)	0/551 (0)	0/156 (0)	0/154 (0)

Level	Placebo-Controlled Pool		Trial C-476		Trial C-448	
	Bexa 20 mg N=372	Placebo N=300	Bexa 20 mg N=1132	Placebo N=567	Bexa 20 mg N=157	Placebo N=155
Albumin, low (g/dL)						
Level 1 (<3.1)	0/363 (0)	0/294 (0)	2/1093 (0.2)	2/551 (0.4)	0/156 (0)	1/154 (0.6)
Level 2 (<2.5)	0/363 (0)	0/294 (0)	1/1093 (0.09)	0/551 (0)	0/156 (0)	0/154 (0)
Level 3 (<2)	0/363 (0)	0/294 (0)	0/1093 (0)	0/551 (0)	0/156 (0)	0/154 (0)
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	39/363 (10.7)	21/294 (7.1)	547/1093 (50.0)	228/551 (41.4)	120/156 (76.9)	103/154 (66.9)
Level 2 (>27)	10/363 (2.8)	8/294 (2.7)	336/1093 (30.7)	136/551 (24.7)	87/156 (55.8)	79/154 (51.3)
Level 3 (>31)	4/363 (1.1)	3/294 (1.0)	194/1093 (17.7)	81/551 (14.7)	63/156 (40.4)	55/154 (35.7)

Source: adlb.xpt; Software: R; Generated by CDS
Abbreviations: Bexa, bexagliflozin.

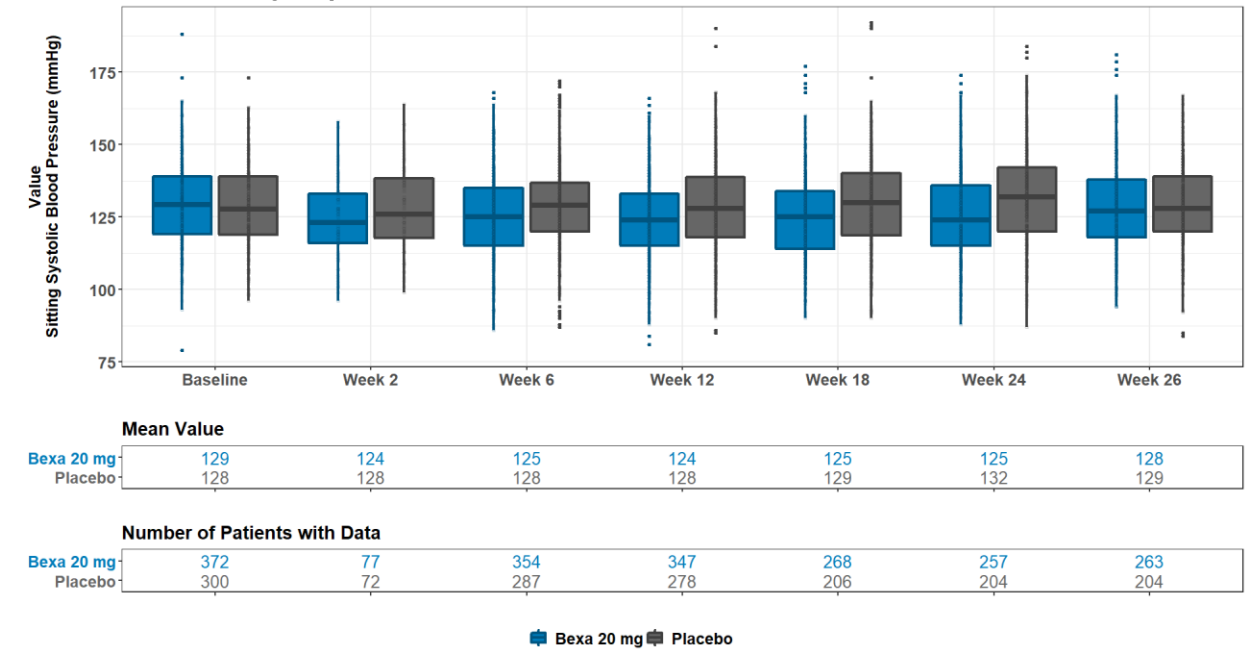
Renal Function

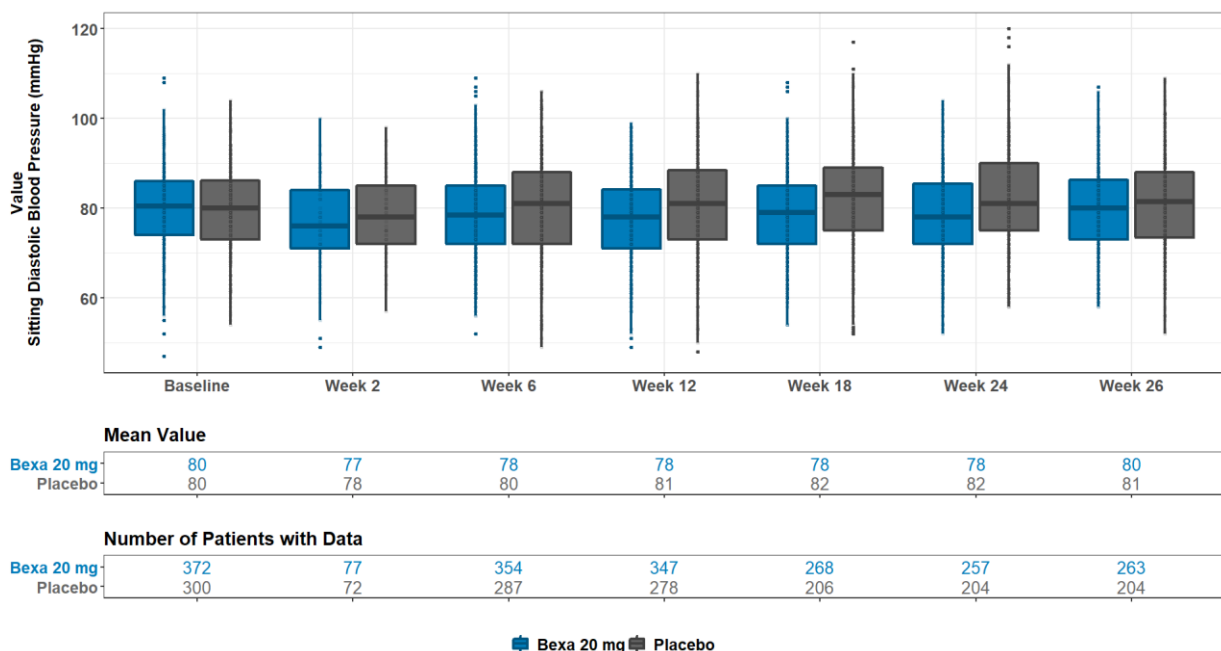
See Sections 7.7.2 and 17.3.7 for a detailed discussion regarding drug-induced changes in renal function.

17.5. Vital Signs

The Applicant assessed changes in blood pressure and heart rate in the clinical program. In the placebo-controlled pool, a small mean reduction in SBP from baseline to Week 24 occurred in the bexagliflozin group as opposed to a small mean increase in the placebo group (Figure 80). Blood pressure changes were evaluated as secondary efficacy endpoints in the clinical program and additional information characterizing the drug effect on blood pressure can be found in Section 6.2.3.3. In addition, refer to Section 17.3.8 for additional information regarding an assessment of hypotension in the clinical program. There were no noteworthy changes in heart rate between treatment groups (data not shown).

Figure 80. Median and Interquartile Range of Systolic and Diastolic Blood Pressure Over Time by Treatment Arm, Safety Population, Placebo-Controlled Pool; Observed Data





Source: advs.xpt; Software: R; Generated by CDS
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual points are those beyond this range.
Abbreviations: Bexa, bexagliflozin.

17.6. QT

The Applicant conducted a thorough QT (TQT) study (C-428) to assess the proarrhythmic potential of bexagliflozin. The protocol for this study was reviewed by the Agency prior to its initiation under IND 103822. In this randomized, partially-blinded, three-period crossover study, 37 healthy subjects received bexagliflozin 100 mg (capsule formulation), placebo, and a single oral dose of moxifloxacin 400 mg. The Applicant's TQT study results were reviewed by the Interdisciplinary Review Team for Cardiac Safety Studies (IRT-CS), and their independent analysis yielded similar results to those reported by the Applicant. The IRT-CS states that the studied dose of 100 mg meets the recommendation for exposure coverage in a TQT study. The IRT-CS confirmed that C-428, conducted using the capsule formulation of bexagliflozin, is adequate to support the QT assessment for the to-be-marketed tablet formulation. The largest upper bound of the 2-sided 90% CI for the mean difference between bexagliflozin and placebo was below 10 ms, which is the threshold for regulatory concern as described in ICH E14 guidelines ([Table 227](#)). The IRT-CS concluded that a single dose of 100 mg bexagliflozin does not cause drug-related QT prolongation (DARRTS review under NDA 214373 dated December 6, 2021 and under IND 103822 dated November 4, 2013). These findings are in accordance with nonclinical studies, which indicated a low potential for QT prolongation.

Table 227. The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Bexagliflozin and the Largest Lower Bound for Moxifloxacin, Trial C-428

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Bexagliflozin 100 mg	10	2.4	(0.6, 4.2)
Moxifloxacin 400 mg*	3	13.5	(10.5, 16.5)

Source: IRT-CS Review under IND 103822 dated November 4, 2013 in DARRTS

*Bonferroni adjustment of 3 time points was applied

Regarding other safety findings from C-428, there were no deaths, SAEs, or AEs of clinical importance per ICH E14 guidelines (e.g., syncope, seizures, significant ventricular arrhythmias, sudden cardiac death) that occurred in this study. Subjects who experienced a PR interval >200 ms or a QRS interval >100 ms were generally balanced between bexagliflozin and placebo treatment periods (data not shown).

17.7. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroup utilizing the placebo-controlled pool and C-476 were performed to evaluate whether commonly occurring events and AESIs differed importantly between subgroups ([Table 228](#) and [Table 229](#)). For the placebo-controlled pool, grouped queries (GQs) were utilized to align with analyses of this data pool presented in Section 6 and in the labeling, and commonly occurring AEs (i.e., >2% and greater in the bexagliflozin group than the placebo group) are presented. For C-476, CMQs derived by the Applicant were utilized to examine AESIs by subgroup, and selected AESIs are presented. A trend between increased BMI quartile and female GMI events in subjects treated with bexagliflozin was observed in both the placebo-controlled pool and C-476. There were no concerning trends regarding age >65 years and increased incidence of adverse reactions in either analysis. More females had UTI events in both bexagliflozin and placebo groups.

Table 228. Safety Analyses by Demographic Subgroups, Safety Population, Placebo-Controlled Pool

Characteristic	n (% of pop)	Male GMI		Female GMI		UTI		Increased Urination		Thirst		Vaginal Pruritus	
		Bexa N=216 n/Ns (%)	Placebo N=170 n/Ns (%)	Bexa N=156 n/Ns (%)	Placebo N=130 n/Ns (%)	Bexa N=372 n/Ns (%)	Placebo N=300 n/Ns (%)	Bexa N=372 n/Ns (%)	Placebo N=300 n/Ns (%)	Bexa N=372 n/Ns (%)	Placebo N=300 n/Ns (%)	Bexa N=156 n/Ns (%)	Placebo N=130 n/Ns (%)
Sex, (n%)													
Female	286 (43)	NA	NA	9/156 (6)	0/130 (0)	14/156 (9)	9/130 (7)	6/156 (4)	7/130 (5)	6/156 (4)	4/130 (3)	4/156 (3)	0/130 (0)
Male	386 (57)	5/216 (2)	2/170 (1)	NA	NA	9/216 (4)	3/170 (2)	19/216 (9)	2/170 (1)	6/216 (3)	1/170 (0.6)	NA	NA
Race, (n%)													
American Indian or Alaska Native	2 (0.3)	0/1 (0)	0/1 (0)	NA	NA	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/1 (0)	NA	NA
Asian	255 (38)	0/92 (0)	0/82 (0)	1/42 (2)	0/39 (0)	3/134 (2)	3/121 (3)	2/134 (2)	0/121 (0)	0/134 (0)	0/121 (0)	2/42 (5)	0/39 (0)
Black or African American	102 (15)	0/27 (0)	0/19 (0)	2/32 (6)	0/24 (0)	0/59 (0)	3/43 (7)	9/59 (15)	0/43 (0)	4/59 (7)	1/43 (2.3)	1/32 (3)	0/24 (0)
Multiple	4 (0.6)	0/2 (0)	0/0 (NA)	0/0 (NA)	0/2 (0)	0/2 (0)	0/2 (0)	0/2 (0)	1/2 (50)	0/2 (0)	1/2 (50)	0/0 (NA)	0/2 (0)
Native Hawaiian or Other Pacific Islander	2 (0.3)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/2 (0)	0/0 (NA)	1/2 (5)	0/0 (NA)	1/2 (50)	0/0 (NA)	0/1 (0)	0/0 (NA)
Other	1 (0.1)	NA	NA	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)
White	306 (46)	5/93 (5)	2/68 (3)	6/80 (8)	0/65 (0)	20/173 (12)	6/133 (5)	13/173 (8)	8/133 (6)	7/173 (4)	3/133 (2)	1/80 (1)	0/65 (0)
Age group, years, (n%)													
Age <65 years	519 (77)	5/167 (3)	2/129 (2)	9/121 (7)	0/102 (0)	18/288 (6)	11/231 (5)	19/288 (7)	7/231 (3)	11/288 (4)	4/231 (2)	4/121 (3)	0/102 (0)
Age ≥65 years	153 (23)	0/49 (0)	0/41 (0)	0/35 (0)	0/28 (0)	5/84 (6)	1/69 (1)	6/84 (7)	2/69 (3)	1/84 (1)	1/69 (1)	0/35 (0)	0/28 (0)
Ethnicity, (n%)													
Hispanic/Latino	203 (30)	3/57 (5)	1/38 (3)	4/60 (7)	0/48 (0)	13/117 (11)	3/86 (4)	8/117 (7)	3/86 (4)	4/117 (3)	1/86 (1)	1/60 (2)	0/48 (0)
Not Hispanic/Latino	468 (70)	2/159 (1)	1/131 (1)	5/96 (5)	0/82 (0)	10/255 (4)	9/213 (4)	17/255 (7)	6/213 (3)	8/255 (3)	4/213 (2)	3/96 (3)	0/82 (0)
Unknown	1 (0.1)	0/0 (NA)	0/1 (0)	NA	NA	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	NA	NA
BMI, quartile													
Missing	1 (0.1)	NA	NA	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/1 (0)	0/0 (NA)
Quartile 1	167 (25)	0/58 (0)	0/56 (0)	0/23 (0)	0/30 (0)	1/81 (1)	0/86 (0)	4/81 (5)	1/86 (1)	0/81 (0)	0/86 (0)	0/23 (0)	0/30 (0)
Quartile 2	167 (25)	0/66 (0)	0/38 (0)	2/28 (7)	0/35 (0)	6/94 (6)	5/73 (7)	3/94 (3)	0/73 (0)	5/94 (5)	0/73 (0)	2/28 (7)	0/35 (0)
Quartile 3	167 (25)	2/44 (5)	1/44 (2)	2/50 (4)	0/29 (0)	6/94 (6)	3/73 (4)	9/94 (10)	4/73 (6)	2/94 (2)	2/73 (3)	2/50 (4)	0/29 (0)
Quartile 4	170 (25)	3/48 (6)	1/32 (3)	5/54 (9)	0/36 (0)	10/102 (10)	4/68 (6)	9/102 (9)	4/68 (6)	5/102 (5)	3/68 (4)	0/54 (0)	0/36 (0)

Source: adlb.xpt; Software: R; Generated by CDS

GQs developed by the Clinical Reviewer were utilized in this analysis

Abbreviations: Bexa, bexagliflozin; BMI, body mass index; GMI, genital mycotic infections; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; UTI, urinary tract infection.

NDA 214373
Brenzavvy (bexagliflozin)

Table 229. Safety Analyses by Demographic Subgroups, Safety Population, Trial C-476

Characteristic	n (% of pop)	Male GMI		Female GMI		UTI		Fracture		Hypotension		Rash	
		Bexa N=791	Placebo N=390	Bexa N=341	Placebo N=177	Bexa N=1132	Placebo N=567	Bexa N=1132	Placebo N=567	Bexa N=1132	Placebo N=567	Bexa N=1132	Placebo N=567
Sex, (n%)													
Female	518 (30)	NA	NA	55/341 (16)	13/177 (7)	94/341 (28)	48/177 (27)	17/341 (5)	8/177 (5)	21/341 (6)	12/177 (7)	12/341 (4)	8/177 (5)
Male	1181 (70)	47/791 (6)	3/390 (<1)	NA	NA	70/791 (9)	23/390 (6)	24/791 (3)	13/390 (3)	40/791 (5)	15/390 (4)	27/791 (3)	18/390 (5)
Race, (n%)													
American Indian or Alaska Native	152 (9)	3/57 (5)	0/31 (0)	2/41 (5)	0/23 (0)	16/98 (16)	12/54 (22)	3/98 (3)	2/54 (4)	3/98 (3)	1/54 (2)	0/98 (0)	0/54 (0)
Asian	162 (10)	0/84 (0)	0/42 (0)	0/23 (0)	0/13 (0)	6/107 (6)	2/55 (4)	6/107 (6)	2/55 (4)	3/107 (3)	3/55 (6)	9/107 (8)	5/55 (9)
Black or African American	74 (4)	4/25 (16)	0/13 (0)	6/21 (29)	2/15 (13)	10/46 (22)	3/28 (11)	3/46 (7)	1/28 (4)	2/46 (4)	1/28 (3.6)	3/46 (7)	1/28 (4)
Native Hawaiian or Other Pacific Islander	2 (<1)	0/2 (0)	0/0 (NA)	NA	NA	0/2 (0)	0/0 (NA)	0/2 (0)	0/0 (NA)	2/2 (100)	0/0 (NA)	0/2 (0)	0/0 (NA)
White	1309 (77)	40/623 (6)	3/304 (1)	47/256 (18)	11/126 (9)	132/879 (15)	54/430 (13)	29/879 (3)	16/430 (4)	51/879 (6)	22/430 (5)	27/879 (3)	20/430 (5)
Age group, years, (n%)													
Age <65 years	837 (49)	24/385 (6)	0/193 (0)	33/176 (19)	7/83 (8)	74/561 (13)	31/276 (11)	12/561 (2)	11/276 (4)	25/561 (5)	7/276 (3)	23/561 (4)	8/276 (3)
Age ≥ 65 years	862 (51)	23/406 (6)	3/197 (2)	22/165 (13)	6/94 (6)	90/571 (16)	40/291 (14)	29/571 (5)	10/291 (3)	36/571 (6)	20/291 (7)	16/571 (3)	18/291 (6)
Ethnicity, (n%)													
Hispanic/Latino	259 (15)	4/96 (4)	0/54 (0)	3/70 (4)	2/39 (5)	34/166 (21)	23/93 (25)	5/166 (3)	3/93 (3)	4/166 (2)	3/93 (3)	1/166 (<1)	1/93 (1)
Not Hispanic/Latino	1440 (85)	43/695 (6)	3/336 (1)	52/271 (19)	11/138 (8)	130/966 (14)	48/474 (10)	36/966 (4)	18/474 (4)	57/966 (6)	24/474 (5)	38/966 (4)	25/474 (5)
Unknown													
BMI, quartile													
Quartile 1	418 (25)	10/186 (5)	1/109 (1)	4/77 (5)	1/46 (2)	27/263 (10)	21/155 (14)	8/263 (3)	5/155 (3)	12/263 (5)	11/155 (7)	7/263 (3)	6/155 (3.9)
Quartile 2	425 (25)	15/215 (7)	0/98 (0)	9/76 (12)	2/36 (6)	39/291 (13)	18/134 (13)	12/291 (4)	3/134 (2)	11/291 (4)	7/134 (5)	10/291 (3)	1/134 (<1)
Quartile 3	427 (25)	15/208 (7)	1/99 (1)	14/74 (19)	2/46 (4)	42/282 (15)	15/145 (10)	8/282 (3)	8/145 (6)	18/282 (6)	4/145 (3)	9/282 (3)	7/145 (5)
Quartile 4	429 (25)	7/182 (4)	1/84 (1)	28/114 (24)	8/49 (16)	56/296 (19)	17/133 (13)	13/296 (4)	5/133 (6)	20/296 (7)	5/133 (4)	13/296 (4)	12/133 (9)

Source: adlb.xpt; Software: R; Generated by CDS

GQs developed by the Clinical Reviewer were utilized in this analysis

Abbreviations: Bexa, bexagliflozin; BMI, body mass index; GMI, genital mycotic infections; N, number of subjects in treatment arm; n, number of subjects with adverse event; Ns, total number of subjects for each specific subgroup and were assigned to that specific arm; UTI, urinary tract infection.

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Not applicable.

19. Other Drug Development Considerations: Additional Information and Assessment

Not applicable.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Eight domestic clinical investigators were inspected. Investigators/study sites were selected based on the ability of data from their site to potentially impact the overall benefit risk assessment. Office of Scientific Investigations (OSI) concludes that no significant regulatory violations were found upon inspection and that, based on the results of inspections and regulatory assessments, C-419, C-423, C-448, C-450, C-476 and C-480 appear to have been conducted adequately. See OSI's review dated July 13, 2022 in DARRTS for additional information.

21. Labeling Summary of Considerations and Key Additional Information

The Applicant has submitted proposed labeling for bexagliflozin. The proposed labeling was reviewed to ensure that the labeling is reflective of the data submitted in this Application. The labeling was also reviewed for consistency with approved labeling for other SGLT2 inhibitor products including JARDIANCE (empagliflozin), FARXIGA (dapagliflozin), STEGLATRO (ertugliflozin), and INVOKANA (canagliflozin), as it relates to events considered to be class effects. Significant labeling negotiations are summarized below.

(b) (4)

22. Postmarketing Requirements and Commitments

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](#). For further information see the action letter for this application.

23. Financial Disclosure

Table 230. Covered Clinical Studies: C-418, C-419, C-423, C-449, C-450, C-476, C-480, C-603

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 516		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

Literature

American Diabetes Association Professional Practice, C, 2022, 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022, Diabetes Care, 45(Suppl 1):S144-S174.

American Diabetes Association Professional Practice, C, B Draznin, VR Aroda, G Bakris, G Benson, FM Brown, R Freeman, J Green, E Huang, D Isaacs, S Kahan, J Leon, SK Lyons, AL Peters, P Prahalad, JEB Reusch, and D Young-Hyman, 2022a, 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022, Diabetes Care, 45(Suppl 1):S83-S96.

American Diabetes Association Professional Practice, C, B Draznin, VR Aroda, G Bakris, G Benson, FM Brown, R Freeman, J Green, E Huang, D Isaacs, S Kahan, J Leon, SK Lyons, AL Peters, P Prahalad, JEB Reusch, and D Young-Hyman, 2022b, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022, Diabetes Care, 45(Suppl 1):S125-S143.

American Diabetes Association Professional Practice, C, B Draznin, VR Aroda, G Bakris, G Benson, FM Brown, R Freeman, J Green, E Huang, D Isaacs, S Kahan, J Leon, SK Lyons, AL Peters, P Prahalad, JEB Reusch, and D Young-Hyman, 2022c, 11. Chronic Kidney Disease and Risk Management: Standards of Medical Care in Diabetes-2022, Diabetes Care, 45(Suppl 1):S175-S184.

American Diabetes Association Professional Practice, C, B Draznin, VR Aroda, G Bakris, G Benson, FM Brown, R Freeman, J Green, E Huang, D Isaacs, S Kahan, J Leon, SK Lyons, AL Peters, P Prahalad, JEB Reusch, and D Young-Hyman, 2022d, 12. Retinopathy, Neuropathy, and Foot Care: Standards of Medical Care in Diabetes-2022, *Diabetes Care*, 45(Suppl 1):S185-S194.

Avramidis, I, A Apsemidou, AZ Lalia, N Petridis, E Tourtouras, G Kalopitas, and G Piliandis, 2020, Lessons From a Diabetes Clinic: Achieving Glycemic Goals and Clinical Use of Antidiabetic Agents in Patients With Type 2 Diabetes, *Clin Diabetes*, 38(3):248-255.

Bilezikian, JP, NB Watts, K Usiskin, D Polidori, A Fung, D Sullivan, and N Rosenthal, 2016, Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2 Diabetes Treated With Canagliflozin, *J Clin Endocrinol Metab*, 101(1):44-51.

Bolon, B, 2017, Mini-Review: Toxic Tendinopathy, *Toxicol Pathol*, 45(7):834-837.

Carls, G, J Huynh, E Tuttle, J Yee, and SV Edelman, 2017, Achievement of Glycated Hemoglobin Goals in the US Remains Unchanged Through 2014, *Diabetes Ther*, 8(4):863-873.

Charbonnel, B, A Karasik, J Liu, M Wu, G Meininger, and G Sitagliptin Study, 2006, Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone, *Diabetes Care*, 29(12):2638-2643.

Charpentier, G, L Vaur, S Halimi, F Fleury, E Derobert, A Grimaldi, V Oriol, S Etienne, JJ Altman, and Diametre, 2001, Predictors of response to glimepiride in patients with type 2 diabetes mellitus, *Diabetes Metab*, 27(5 Pt 1):563-571.

Chong, WH, LB Yanoff, E Andraca-Carrera, and M Thanh Hai, 2020, Assessing the Safety of Glucose-Lowering Drugs - A New Focus for the FDA, *N Engl J Med*, 383(13):1199-1202.

Control, D, G Complications Trial Research, DM Nathan, S Genuth, J Lachin, P Cleary, O Crofford, M Davis, L Rand, and C Siebert, 1993, The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus, *N Engl J Med*, 329(14):977-986.

Damiani, G, U Loite, S Ramoni, and AV Marzano, 2016, Possible new inflammatory side-effect of SGLT2-inhibitors: Fixed drug eruption, *J Diabetes Complications*, 30(8):1530-1531.

Fioretto, P, A Giaccari, and G Sesti, 2015, Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus, *Cardiovasc Diabetol*, 14:142.

Gilbert, RE and KE Thorpe, 2019, Acute kidney injury with sodium-glucose co-transporter-2 inhibitors: A meta-analysis of cardiovascular outcome trials, *Diabetes Obes Metab*, 21(8):1996-2000.

Khunti, K, A Cieriello, X Cos, and C De Block, 2018, Achievement of guideline targets for blood pressure, lipid, and glycaemic control in type 2 diabetes: A meta-analysis, *Diabetes Res Clin Pract*, 137:137-148.

Khwaja, A, 2012, KDIGO clinical practice guidelines for acute kidney injury, *Nephron Clin Pract*, 120(4):c179-184.

Kirchgesner, T, A Larbi, P Omoumi, J Malghem, N Zamali, J Manelfe, F Lecouvet, B Vande Berg, S Djebbar, and B Dallaudiere, 2014, Drug-induced tendinopathy: from physiology to clinical applications, *Joint Bone Spine*, 81(6):485-492.

- Knobloch, K, 2016, Drug-Induced Tendon Disorders, *Adv Exp Med Biol*, 920:229-238.
- Menne, J, E Dumann, H Haller, and BMW Schmidt, 2019, Acute kidney injury and adverse renal events in patients receiving SGLT2-inhibitors: A systematic review and meta-analysis, *PLoS Med*, 16(12):e1002983.
- Ohkubo, Y, H Kishikawa, E Araki, T Miyata, S Isami, S Motoyoshi, Y Kojima, N Furuyoshi, and M Shichiri, 1995, Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study, *Diabetes Res Clin Pract*, 28(2):103-117.
- Raschi, E, M Parisotto, E Forcesi, M La Placa, G Marchesini, F De Ponti, and E Poluzzi, 2017, Adverse events with sodium-glucose co-transporter-2 inhibitors: A global analysis of international spontaneous reporting systems, *Nutr Metab Cardiovasc Dis*, 27(12):1098-1107.
- Ray, EC, CR Boyd-Shiwerski, P Liu, D Novacic, and D Cassiman, 2020, SGLT2 Inhibitors for Treatment of Refractory Hypomagnesemia: A Case Report of 3 Patients, *Kidney Med*, 2(3):359-364.
- Sakaeda, T, S Kobuchi, R Yoshioka, M Haruna, N Takahata, Y Ito, A Sugano, K Fukuzawa, T Hayase, T Hayakawa, H Nakayama, Y Takaoka, and M Tohkin, 2018, Susceptibility to serious skin and subcutaneous tissue disorders and skin tissue distribution of sodium-dependent glucose co-transporter type 2 (SGLT2) inhibitors, *Int J Med Sci*, 15(9):937-943.
- Sasaki, Y, K Koyano, S Iida, and T Yanagawa, 2017, Mechanism Underlying Increase of the Serum Magnesium Concentration Observed Following Treatment with Sodium-Glucose Cotransporter 2 Inhibitors, *Journal of Diabetes Mellitus*, 7.
- Sridhar, VS, KR Tuttle, and DZI Cherney, 2020, We Can Finally Stop Worrying About SGLT2 Inhibitors and Acute Kidney Injury, *Am J Kidney Dis*, 76(4):454-456.
- Stratton, IM, AI Adler, HA Neil, DR Matthews, SE Manley, CA Cull, D Hadden, RC Turner, and RR Holman, 2000, Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study, *BMJ*, 321(7258):405-412.
- Tang, H, K Yang, Y Song, and J Han, 2018, Meta-analysis of the association between sodium-glucose co-transporter-2 inhibitors and risk of skin cancer among patients with type 2 diabetes, *Diabetes Obes Metab*, 20(12):2919-2924.
- Tang, H, X Zhang, J Zhang, Y Li, LC Del Gobbo, S Zhai, and Y Song, 2016, Elevated serum magnesium associated with SGLT2 inhibitor use in type 2 diabetes patients: a meta-analysis of randomised controlled trials, *Diabetologia*, 59(12):2546-2551.
- UKPDS, 1998, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group, *Lancet*, 352(9131):837-853.

Guidances

Guidance for Industry *Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008)

Guidance for Industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)

NDA 214373
Brenzavvy (bexagliflozin)

Guidance for Industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995)

Draft Guidance for Industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention* (March 2008)

Guidance for Industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018)

Guidance for Industry *Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control* (March 2020)

Guidance for Industry *Computerized Systems Used in Clinical Investigations* (May 2007)

Guidance for Industry *Non-Inferiority Clinical Trials* (November 2016)

Guidance for Industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011)

Prescribing Information

AstraZeneca, 2021, FARXIGA prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202293s024lbl.pdf.

Ingelheim, B, 2022, JARDIANCE prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/204629s034lbl.pdf.

Janssen, 2020, INVOKANA prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204042s034lbl.pdf.

Lilly, 2022, TRULICITY prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125469s046s052lbl.pdf.

Merck, 2021, STEGLATRO prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209803s004lbl.pdf.

Nordisk, N, 2022a, OZEMPIC prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209637Orig1s009lbl.pdf.

Nordisk, N, 2022b, VICTOZA prescribing information, accessed,
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf.

Other

Bornkamp, B, J Pinheiro, F Bretz, and L Sandig, 2021, DoseFinding: Planning and Analyzing Dose Finding Experiments. R package version 1.0-2.

CDC, 2022a, Leading Causes of Death, accessed October 19, 2022,
<https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm>.

CDC, 2022b, National Diabetes Statistics Report, accessed August 4, 2022,
<https://www.cdc.gov/diabetes/data/statistics-report/index.html>.

FDA, 2022, Table of Surrogate Endpoints That Were the Basis of Drug Approval or Licensure, accessed, <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure>.

25. Review Team

Table 231. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Supendeeep Dosanjh
Nonclinical Reviewer	Karen Hao
Nonclinical Team Leader	Federica Basso
Office of Clinical Pharmacology Reviewer(s)	Li Li, Jiajun Liu
Office of Clinical Pharmacology Team Leader(s)	Jaya Vaidyanathan
Clinical Reviewer	Kristen Pluchino
Clinical Team Leader	Michael Nguyen
Statistical Reviewer	Jade (Yu) Wang
Statistical Team Leader	Yoonhee Kim
Cross-Disciplinary Team Leader	Michael Nguyen
Division Director (pharm/tox)	C. Lee Elmore
Division Director (OCP)	Shirley Seo
Division Director (OB)	Mark Rothmann
Division Director (clinical)	John Sharretts
Office Director (or designated signatory authority)	Hylton Joffe

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 232. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Muthukumar Ramaswamy
Microbiology	
OPDP	Ankur Kalola/Meena Savani
OSI	Ling Yang/Min Lu
OSE/DEPI	Po-Yin Chang/Yandong Qiang
OSE/DMEPA	Ariane Conrad/Idalia Rychlik
OSE/DRISK	Till Olickal
Other	

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Table 233. Signatures of Reviewers

See appended pages.

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Hylton Joffe, M.D.	OND/OCHEN	☐ Authored ☒ Approved: All sections
Signatory Authority	Signature: {See appended electronic signature page}		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	John Sharretts, M.D.	OND/OCHEN/ DDLO	☒ Authored: Sections 1, 2.2 ☒ Approved: All sections
Division Director	Signature: John M. Sharretts -S Digitally signed by John M. Sharretts -S Date: 2023.01.18 12:14:34 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Michael Nguyen, M.D.	OND/OCHEN/ DDLO	☐ Authored ☒ Approved: All sections
Cross-Disciplinary Team Lead	Signature: Michael D. Nguyen -S Digitally signed by Michael D. Nguyen -S Date: 2023.01.18 11:28:33 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical	Kristen Pluchino, Ph.D., MPH	OND/OCHEN/DDLO	☒ Authored: Sections 2.1, 3, 4, 6, 7, 9, 10, 11, 12.1, 15, 17, 20, 21, 22, 23 ☒ Approved: All Sections
Primary Reviewer	Signature: Kristen M. Pluchino -S Digitally signed by Kristen M. Pluchino -S Date: 2023.01.13 13:17:31 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	C. Lee Elmore, Ph.D.	OND/DPTCHEN	☐ Authored ☒ Approved: Section 5, 7.1, 8.4, 13
Deputy Director	Signature: Calvin L. Elmore -S Digitally signed by Calvin L. Elmore -S Date: 2023.01.17 17:11:58 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Federica Basso, Ph.D.	OND/DPTCHEN	☐ Authored ☒ Approved: Section 5, 7.1, 8.4, 13
Supervisor	Signature: Federica Basso -S Digitally signed by Federica Basso -S Date: 2023.01.17 14:21:03 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Pharmacology/Toxicology	Karen Hao, Ph.D.	OND/DPTCHEN	☒ Authored: Section 5, 7.1, 8.4, 13 ☐ Approved:
Primary Reviewer	Signature: Karen H. Hao -S Digitally signed by Karen H. Hao -S Date: 2023.01.13 15:59:22 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Doanh Tran, Ph.D.	OTS/OCP/DCEP	☐ Authored ☒ Approved: Sections 5, 6.1, 6.3, 8.1, 8.2, 8.3, 14.1, 14.2, 14.3, 14.4
Deputy Director	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S Date: 2023.01.18 11:03:50 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Jayabharathi Vaidyanathan, Ph.D.	OTS/OCP/DCEP	☐ Authored ☒ Approved: Sections 5, 6.1, 6.3, 8.1, 8.2, 8.3, 14.1, 14.2, 14.3, 14.4
Team Leader	Signature: Jayabharath Vaidyanathan -S Digitally signed by Jayabharath Vaidyanathan -S Date: 2023.01.17 12:33:01 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology/Pharmacometrics	Justin C Earp, Ph.D.	OND/OCP/DCEP	☐ Authored ☒ Approved: Sections 5, 6.1, 6.3, 8.1, 8.2, 14.3
Team Leader	Signature: Justin C. Earp -S Digitally signed by Justin C. Earp -S Date: 2023.01.17 16:09:01 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology/Pharmacometrics	Jiajun Liu, Pharm.D., MSc	OND/OCP/DCEP	☒ Authored: Sections 5, 6.1, 6.3, 8.1, 8.2, 14.3 ☐ Approved:
Primary Reviewer	Signature: Jiajun Liu -S Digitally signed by Jiajun Liu -S Date: 2023.01.13 14:07:31 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Clinical Pharmacology	Li Li, Ph.D.	OND/OCP/DCEP	☒ Authored: Sections 5, 6.1, 6.3, 8.1, 8.2, 8.3, 14.1, 14.2, 14.4 ☐ Approved:
Primary Reviewer	Signature: Li Li -S Digitally signed by Li Li -S Date: 2023.01.13 14:20:16 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Mark Rothmann, Ph.D.	OTS/OB/DB II	☐ Authored ☒ Approved: Sections 6.2., 12.2, 16
Division Director	Signature: Mark D. Rothmann -S Digitally signed by Mark D. Rothmann -S Date: 2023.01.17 21:26:57 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Yoonhee Kim, Ph.D.	OTS/OB/DB II	☒ Authored: Sections 6.2, 12.2, 16 ☐ Approved:
Team Leader	Signature: Yoonhee Kim -S Digitally signed by Yoonhee Kim -S Date: 2023.01.17 11:40:48 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Bo Li, Ph.D.	OTS/OB/DB7	☒ Authored: Sections 7.7.1, 17.1 ☐ Approved:
Primary Reviewer	Signature: Bo Li -S Digitally signed by Bo Li -S Date: 2023.01.13 13:44:50 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Biometrics	Eugenio Andraca-Carrera, Ph.D.	OTS/OB/DB7	☐ Authored: ☒ Approved: Sections 7.7.1, 17.1
Team Leader	Signature: Eugenio Andraca-carrera -S Digitally signed by Eugenio Andraca-carrera -S Date: 2023.01.17 11:33:46 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Labeling	Melinda Wilson, Pharm.D., MPH	OND/OCHEN/DDLO	☒ Authored: Section 21 ☐ Approved:
Associate Director for Labeling	Signature: Melinda M. Wilson -S Digitally signed by Melinda M. Wilson -S Date: 2023.01.13 15:19:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved
Product Quality	Muthukumar Ramaswamy Ph.D.	OPQ/ONDP/ DNDPIII/NDPB5	☒ Authored Section 9 ☒ Approved: Section 9
Application Technical Lead	Signature: Muthukumar Ramaswamy -S  Digitally signed by Muthukumar Ramaswamy -S Date: 2023.01.17 12:39:11 -05'00'		

Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MICHAEL D NGUYEN
01/19/2023 03:19:22 PM

JOHN M SHARRETTS
01/19/2023 10:21:17 PM

HYLTON V JOFFE
01/20/2023 02:03:11 PM