CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202293Orig1s018

Trade Name: **FARXIGA**

Generic Name: Dapagliflozin

Sponsor: AstraZeneca AB

Approval Date: 10/18/19

Indications: FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated:

• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

• to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

APPROVAL LETTER

NDA 202293/S-018
NDA 205649/S-011

SUPPLEMENT APPROVAL
FULFILLMENT OF POST MARKETING REQUIREMENTS

AstraZeneca AB
C/O AstraZeneca Pharmaceuticals LP
Attention: Sally Walsh
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Walsh:

Please refer to your supplemental new drug applications (sNDAs) dated and received December 18, 2018, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Farxiga (dapagliflozin) tablets and Xigduo XR (dapagliflozin and metformin HCL) extended release tablets.

These Prior Approval supplemental new drug applications provide for revisions to labeling based on the results of Study D1693C0001, Dapagliflozin Effect on Cardiovascular Events (DECLARE), which was conducted to assess cardiovascular outcomes and to assess the risk of bladder cancer associated with dapagliflozin.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable since the disease is rare in children. For a meaningful study to be conducted, the population would require a diagnosis of type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. The number of pediatric patients fitting these criteria is small, and a clinical trial for the new indication is therefore not feasible.

FULFILLMENT OF POSTMARKETING REQUIREMENTS

The supplemental application for NDA 202293 contained the final reports for the following postmarketing requirements listed in the January 8, 2014, approval letter for NDA 202293.

2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/ urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.

2121-6 To assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

We have reviewed your submission and conclude that the above requirements were fulfilled.

We remind you that there are postmarketing requirements listed in the December 4, 2015, supplement approval letter, and the April 24, 2017, post-approval postmarketing requirement letter that are still open for NDA 202293.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and*

Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Richard Whitehead, M.S., Regulatory Project Manager, at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guides

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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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/

PATRICK ARCHDEACON
10/18/2019 04:48:51 PM
signing as associate director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

OTHER ACTION LETTERS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FARXIGA safely and effectively. See full prescribing information for FARXIGA.

FARXIGA® (dapagliflozin) tablets, for oral use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	10/2019
Dosage and Administration (2)	10/2019
Warnings and Precautions (5.2, 5.3, 5.5)	10/2019
Warnings and Precautions (5.6)	10/2018
Warnings and Precautions, (5.8, 5.9, 5.10))	Removed 10/2019

---------- INDICATIONS AND USAGE ----------

FARXIGA is a sodium-glucose cotransporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1)
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. (1)

Limitations of use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Assess renal function before initiating and periodically thereafter. (2.1)
- To improve glycemic control the recommended starting dose is 5 mg once daily, taken in the morning. Increase dose to 10 mg once daily in patients tolerating 5 mg who require additional glycemic control. (2.2)
- To reduce the risk of hospitalization for heart failure, the recommended dose is 10 mg once daily. (2.2)
- FARXIGA is not recommended when the eGFR is less than 45 mL/min/1.73 m^2. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tablets: 5 mg and 10 mg (3)

---------- CONTRAINDICATIONS ----------

- History of serious hypersensitivity reaction to FARXIGA. (4)
- Severe renal impairment (eGFR less than 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- *Hypotension* Before initiating FARXIGA, assess and correct volume status in the elderly, patients with renal impairment or low systolic blood pressure, and in patients on diuretics. Monitor for signs and symptoms during therapy. (5.1, 6.1)
- *Ketoacidosis* Assess patients who present with signs and symptoms of metabolic acidosis for ketoacidosis regardless of blood glucose level. If suspected, discontinue FARXIGA, evaluate and treat promptly. Before initiating FARXIGA, consider risk factors for ketoacidosis. Patients on FARXIGA may require monitoring and temporary discontinuation of therapy in clinical situations known to predispose to ketoacidosis. (5.2)
- *Acute Kidney Injury* Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy. (5.3)
- *Urosepsis and Pyelonephritis* Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.4)
- *Hypoglycemia* Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with FARXIGA. (5.5)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)* Serious, life-threatening cases have occurred in both females and males. Assess patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise. If suspected, institute prompt treatment. (5.6)
- *Genital Mycotic Infections* Monitor and treat if indicated. (5.7)

---------- ADVERSE REACTIONS ----------

- The most common adverse reactions associated with FARXIGA (5% or greater incidence) were female genital mycotic infections, nasopharyngitis, and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy* Advise females of the potential risk to a fetus especially during the second and third trimesters. (8.1)
- *Lactation* FARXIGA is not recommended when breastfeeding. (8.2)
- *Geriatrics* Higher incidence of adverse reactions related to reduced intravascular volume. (5.1, 8.5)
- *Renal Impairment* Higher incidence of adverse reactions related to reduced intravascular volume and renal function. (5.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FARXIGA (dapagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.

Limitations of Use

FARXIGA is not recommended for patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of FARXIGA

Assess renal function prior to initiation of FARXIGA therapy and periodically thereafter *[see Warnings and Precautions (5.3)]*.

In patients with volume depletion, correct this condition prior to initiation of FARXIGA *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.5, 8.6)]*.

2.2 Recommended Dosage

To improve glycemic control, the recommended starting dose of FARXIGA is 5 mg once daily, taken in the morning, with or without food. In patients tolerating FARXIGA 5 mg once daily who require additional glycemic control, the dose can be increased to 10 mg once daily.

To reduce the risk of hospitalization for heart failure, the recommended dose of FARXIGA is 10 mg once daily.

2.3 Patients with Renal Impairment

No dose adjustment is needed in patients with an eGFR greater than or equal to 45 mL/min/1.73 m^2.

Use of FARXIGA is not recommended when the eGFR is less than 45 mL/min/1.73 m^2 *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.6)]*.

FARXIGA is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Contraindications (4)]*.

3 DOSAGE FORMS AND STRENGTHS

- FARXIGA 5 mg tablets are yellow, biconvex, round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side.
- FARXIGA 10 mg tablets are yellow, biconvex, diamond-shaped, film-coated tablets with “10” engraved on one side and “1428” engraved on the other side.

4 CONTRAINDICATIONS

- History of a serious hypersensitivity reaction to FARXIGA, such as anaphylactic reactions or angioedema *[see Adverse Reactions (6.1)]*.
- Severe renal impairment, (eGFR less than 30 mL/min/1.73 m^2) end-stage renal disease (ESRD), or patients on dialysis *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension

FARXIGA causes intravascular volume contraction. Symptomatic hypotension can occur after initiating FARXIGA *[see Adverse Reactions (6.1)]* particularly in patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics. Before initiating FARXIGA in patients with one or more of these characteristics, volume status should be assessed and corrected. Monitor for signs and symptoms of hypotension after initiating therapy.

5.2 Ketoacidosis

Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in patients with type 1 and type 2 diabetes mellitus receiving sodium-glucose cotransporter 2 (SGLT2) inhibitors, including FARXIGA *[see Adverse Reactions (6.1)]*. Fatal cases of ketoacidosis have been reported in patients taking FARXIGA. FARXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage (1)]*.

Patients treated with FARXIGA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels as ketoacidosis associated with FARXIGA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, FARXIGA should be discontinued, the patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid, and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized, and the institution of treatment was delayed because the presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis, such as insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating FARXIGA, consider factors in the patient history that may predispose to ketoacidosis, including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse. In patients treated with FARXIGA consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA in clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or surgery).

5.3 Acute Kidney Injury

FARXIGA causes intravascular volume contraction *[see Warning and Precautions (5.1)]*, and can cause acute kidney injury. There have been postmarketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients receiving FARXIGA.

Increases in serum creatinine and decreases in estimated GFR may also be observed with initiation of FARXIGA. Elderly patients and patients with impaired renal function may be more susceptible to these changes. Before initiating FARXIGA, consider factors that may predispose patients to acute kidney injury including hypovolemia, chronic renal insufficiency, congestive heart failure and concomitant medications (diuretics, ACE inhibitors, ARBs, NSAIDs). Consider temporarily discontinuing FARXIGA in the setting of reduced oral intake (such as acute illness or fasting) or fluid losses (such as gastrointestinal illness or excessive heat exposure); monitor patients for signs and symptoms of acute kidney injury. If acute kidney injury occurs, discontinue FARXIGA promptly and institute treatment.

Renal function should be evaluated prior to initiation of FARXIGA and monitored periodically thereafter. Use of FARXIGA is not recommended when the eGFR is less than 45 mL/min/1.73 m^2 and is contraindicated in patients with an eGFR less than 30 mL/min/1.73 m^2 *[see Dosage and Administration (2.3), Contraindications (4) and Use in Specific Populations (8.6)]*.

5.4 Urosepsis and Pyelonephritis

There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including FARXIGA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions (6)]*.

5.5 Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. FARXIGA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions (6.1)]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when these agents are used in combination with FARXIGA.

5.6 Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Reports of necrotizing fasciitis of the perineum (Fournier's Gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with FARXIGA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue FARXIGA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

5.7 Genital Mycotic Infections

FARXIGA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections *[see Adverse Reactions (6.1)]*. Monitor and treat appropriately.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Hypotension *[see Warnings and Precautions (5.1)]*
- Ketoacidosis *[see Warnings and Precautions (5.2)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.3)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.4)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.5)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.6)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Pool of 12 Placebo-Controlled Studies for FARXIGA 5 and 10 mg for Glycemic Control

The data in Table 1 is derived from 12 placebo-controlled studies ranging from 12 to 24 weeks. In 4 studies FARXIGA was used as monotherapy, and in 8 studies FARXIGA was used as add-on to background antidiabetic therapy or as combination therapy with metformin *[see Clinical Studies (14.1)]*.

These data reflect exposure of 2338 patients to FARXIGA with a mean exposure duration of 21 weeks. Patients received placebo (N=1393), FARXIGA 5 mg (N=1145), or FARXIGA 10 mg (N=1193) once daily. The mean age of the population was 55 years and 2% were older than 75 years of age. Fifty percent (50%) of the population were male; 81% were White, 14% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 6 years, had a mean hemoglobin A1c (HbA1c) of 8.3%, and 21% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired in 92% of patients and moderately impaired in 8% of patients (mean eGFR 86 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of FARXIGA. These adverse reactions were not present at baseline, occurred more commonly on FARXIGA than on placebo, and occurred in at least 2% of patients treated with either FARXIGA 5 mg or FARXIGA 10 mg.

Table 1: Adverse Reactions in Placebo-Controlled Studies Reported in ≥2% of Patients Treated with FARXIGA

Adverse Reaction	% of Patients		
	Pool of 12 Placebo-Controlled Studies		
	Placebo N=1393	FARXIGA 5 mg N=1145	FARXIGA 10 mg N=1193
Female genital mycotic infections*	1.5	8.4	6.9
Nasopharyngitis	6.2	6.6	6.3
Urinary tract infections†	3.7	5.7	4.3
Back pain	3.2	3.1	4.2
Increased urination‡	1.7	2.9	3.8
Male genital mycotic infections§	0.3	2.8	2.7
Nausea	2.4	2.8	2.5
Influenza	2.3	2.7	2.3
Dyslipidemia	1.5	2.1	2.5
Constipation	1.5	2.2	1.9
Discomfort with urination	0.7	1.6	2.1
Pain in extremity	1.4	2.0	1.7

* Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for females: vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial. (N for females: Placebo=677, FARXIGA 5 mg=581, FARXIGA 10 mg=598).

† Urinary tract infections include the following adverse reactions, listed in order of frequency reported: urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

‡ Increased urination includes the following adverse reactions, listed in order of frequency reported: pollakiuria, polyuria, and urine output increased.

§ Genital mycotic infections include the following adverse reactions, listed in order of frequency reported for males: balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis. (N for males: Placebo=716, FARXIGA 5 mg=564, FARXIGA 10 mg=595).

Pool of 13 Placebo-Controlled Studies for FARXIGA 10 mg for Glycemic Control

FARXIGA 10 mg was also evaluated in a larger placebo-controlled study pool. This pool combined 13 placebo-controlled studies, including 3 monotherapy studies, 9 add-on to background antidiabetic therapy studies, and an initial combination with metformin study. Across these 13 studies, 2360 patients were treated once daily with FARXIGA 10 mg for a mean duration of exposure of 22 weeks. The mean age of the population was 59 years and 4% were older than 75 years. Fifty-eight percent (58%) of the population were male; 84% were White, 9% were Asian, and 3% were Black or African American. At baseline, the population had diabetes for an average of 9 years, had a mean HbA1c of 8.2%, and 30% had established microvascular disease. Baseline renal function was normal or mildly impaired in 88% of patients and moderately impaired in 11% of patients (mean eGFR 82 mL/min/1.73 m^2).

Volume Depletion

FARXIGA causes an osmotic diuresis, which may lead to reductions in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension) for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 2 *[see Warnings and Precautions (5.1)]*.

Table 2: Adverse Reactions of Volume Depletion* in Clinical Studies with FARXIGA

	Pool of 12 Placebo-Controlled Studies			Pool of 13 Placebo-Controlled Studies		DECLARE Study	
	Placebo	**FARXIGA 5 mg**	**FARXIGA 10 mg**	**Placebo**	**FARXIGA 10 mg**	**Placebo**	**FARXIGA 10 mg**
Overall population N (%)	N=1393 5 (0.4%)	N=1145 7 (0.6%)	N=1193 9 (0.8%)	N=2295 17 (0.7%)	N=2360 27 (1.1%)	N=8569 207 (2.4%)	N=8574 213 (2.5%)
Patient Subgroup n (%)							
Patients on loop diuretics	n=55 1 (1.8%)	n=40 0	n=31 3 (9.7%)	n=267 4 (1.5%)	n=236 6 (2.5%)	n=934 57 (6.1%)	n=866 57 (6.6%)
Patients with moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m^2	n=107 2 (1.9%)	n=107 1 (0.9%)	n=89 1 (1.1%)	n=268 4 (1.5%)	n=265 5 (1.9%)	n=658 30 (4.6%)	n=604 35 (5.8%)
Patients ≥65 years of age	n=276 1 (0.4%)	n=216 1 (0.5%)	n=204 3 (1.5%)	n=711 6 (0.8%)	n=665 11 (1.7%)	n=3950 121 (3.1%)	n=3948 117 (3.0%)

* Volume depletion includes reports of dehydration, hypovolemia, orthostatic hypotension, or hypotension.

Hypoglycemia

The frequency of hypoglycemia by study *[see Clinical Studies (14.1)]* is shown in Table 3. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.5)]*.

Table 3: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Clinical Studies

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
Monotherapy (24 weeks)	**N=75**	**N=64**	**N=70**
Severe [n (%)]	0	0	0
Glucose < 54 mg/dL [n (%)]	0	0	0
Add-on to Metformin (24 weeks)	**N=137**	**N=137**	**N=135**
Severe [n (%)]	0	0	0
Glucose < 54 mg/dL [n (%)]	0	0	0
Add-on to Glimepiride (24 weeks)	**N=146**	**N=145**	**N=151**
Severe [n (%)]	0	0	0
Glucose < 54 mg/dL [n (%)]	1 (0.7)	3 (2.1)	5 (3.3)
Add-on to Metformin and a Sulfonylurea (24 Weeks)	**N=109**	**-**	**N=109**
Severe [n (%)]	0	-	0
Glucose < 54 mg/dL [n (%)]	3 (2.8)	-	7 (6.4)
Add-on to Pioglitazone (24 weeks)	**N=139**	**N=141**	**N=140**
Severe [n (%)]	0	0	0
Glucose < 54 mg/dL [n (%)]	0	1 (0.7)	0
Add-on to DPP4 inhibitor (24 weeks)	**N=226**	**–**	**N=225**
Severe [n (%)]	0	–	1 (0.4)
Glucose < 54 mg/dL [n (%)]	1 (0.4)	–	1 (0.4)
Add-on to Insulin with or without other OADs‡ (24 weeks)	**N=197**	**N=212**	**N=196**
Severe [n (%)]	1 (0.5)	2 (0.9)	2 (1.0)
Glucose < 54 mg/dL [n (%)]	43 (21.8)	55 (25.9)	45 (23.0)

* Severe episodes of hypoglycemia were defined as episodes of severe impairment in consciousness or behavior, requiring external (third party) assistance, and with prompt recovery after intervention regardless of glucose level.

† Episodes of hypoglycemia with glucose < 54 mg/dL (3 mmol/L) were defined as reported episodes of hypoglycemia meeting the glucose criteria that did not also qualify as a severe episode.

‡ OAD = oral antidiabetic therapy.

In the DECLARE study *[see Clinical Studies (14.2)]*, severe events of hypoglycemia were reported in 58 (0.7%) out of 8574 patients treated with FARXIGA and 83 (1.0%) out of 8569 patients treated with placebo.

Genital Mycotic Infections

Genital mycotic infections were more frequent with FARXIGA treatment. Genital mycotic infections were reported in 0.9% of patients on placebo, 5.7% on FARXIGA 5 mg, and 4.8% on FARXIGA 10 mg, in the 12-study placebo-controlled pool. Discontinuation from study due to genital infection occurred in 0% of placebo-treated patients and 0.2% of patients treated with FARXIGA 10 mg. Infections were more frequently reported in females than in males (see Table 1). The most frequently reported genital mycotic infections were vulvovaginal mycotic infections in females and balanitis in males. Patients with a history of genital mycotic infections were more likely to have a genital mycotic infection during the study than those with no prior history (10.0%, 23.1%, and 25.0% versus 0.8%, 5.9%, and 5.0% on placebo,

FARXIGA 5 mg, and FARXIGA 10 mg, respectively). In the DECLARE study *[see Clinical Studies (14.2)]*, serious genital mycotic infections were reported in <0.1% of patients treated with FARXIGA and <0.1% of patients treated with placebo. Genital mycotic infections that caused study drug discontinuation were reported in 0.9% of patients treated with FARXIGA and <0.1% of patients treated with placebo.

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., angioedema, urticaria, hypersensitivity) were reported with FARXIGA treatment. Across the clinical program, serious anaphylactic reactions and severe cutaneous adverse reactions and angioedema were reported in 0.2% of comparator-treated patients and 0.3% of FARXIGA-treated patients. If hypersensitivity reactions occur, discontinue use of FARXIGA; treat per standard of care and monitor until signs and symptoms resolve.

Ketoacidosis

In the DECLARE study *[see Clinical Studies (14.2)]*, events of diabetic ketoacidosis (DKA) were reported in 27 out of 8574 patients in the FARXIGA-treated group and 12 out of 8569 patients in the placebo group. The events were evenly distributed over the study period.

Laboratory Tests

Increases in Serum Creatinine and Decreases in eGFR

Initiation of FARXIGA causes an increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, serum creatinine and eGFR returned to baseline at Week 24. Sustained decreases in eGFR were seen in patients with moderate renal impairment (eGFR 30 to less than 60 ml/min/1.73 m^2) *[see Warnings and Precautions (5.3) and Mechanism of Action (12.1)]*.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies, increases from baseline in mean hematocrit values were observed in FARXIGA-treated patients starting at Week 1 and continuing up to Week 16, when the maximum mean difference from baseline was observed. At Week 24, the mean changes from baseline in hematocrit were −0.33% in the placebo group and 2.30% in the FARXIGA 10 mg group. By Week 24, hematocrit values >55% were reported in 0.4% of placebo-treated patients and 1.3% of FARXIGA 10 mg-treated patients.

Increase in Low-Density Lipoprotein Cholesterol

In the pool of 13 placebo-controlled studies, changes from baseline in mean lipid values were reported in FARXIGA-treated patients compared to placebo-treated patients. Mean percent changes from baseline at Week 24 were 0.0% versus 2.5% for total cholesterol, and -1.0% versus 2.9% for LDL cholesterol in the placebo and FARXIGA 10 mg groups, respectively. In the DECLARE study *[see Clinical Studies (14.2)]*, mean changes from baseline after 4 years were 0.4 mg/dL versus -4.1 mg/dL for total cholesterol, and -2.5 mg/dL versus -4.4 mg/dL for LDL cholesterol, in FARXIGA-treated and the placebo groups, respectively.

Decrease in Serum Bicarbonate

In a study of concomitant therapy of FARXIGA 10 mg with exenatide extended-release (on a background of metformin), four patients (1.7%) on concomitant therapy had a serum bicarbonate value of less than or equal to 13 mEq/L compared to one each (0.4%) in the FARXIGA and exenatide-extended release treatment groups *[see Warnings and Precautions (5.2)]*.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Ketoacidosis
- Acute Kidney Injury
- Urosepsis and Pyelonephritis
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)
- Rash

7 DRUG INTERACTIONS

7.1 Positive Urine Glucose Test

Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

7.2 Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data showing adverse renal effects, FARXIGA is not recommended during the second and third trimesters of pregnancy.

Limited data with FARXIGA in pregnant women are not sufficient to determine drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *(see Clinical Considerations)*.

In animal studies, adverse renal pelvic and tubule dilatations, that were not fully reversible, were observed in rats when dapagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at all doses tested; the lowest of which provided an exposure 15-times the 10 mg clinical dose *(see Data)*.

The estimated background risk of major birth defects is 6 to 10% in women with pre-gestational diabetes with a HbA1c greater than 7% and has been reported to be as high as 20 to 25% in women with HbA1c greater than 10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

Dapagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 1, 15, or 75 mg/kg/day, increased kidney weights and increased the incidence of renal pelvic and tubular dilatations at all dose levels. Exposure at the lowest dose tested was 15-times the 10 mg clinical dose (based on AUC). The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In a prenatal and postnatal development study, dapagliflozin was administered to maternal rats from gestation day 6 through lactation day 21 at doses of 1, 15, or 75 mg/kg/day, and pups were indirectly exposed *in utero* and throughout lactation. Increased incidence or severity of renal pelvic dilatation was observed in 21-day-old pups offspring of treated dams at 75 mg/kg/day (maternal and pup dapagliflozin exposures were 1415-times and 137-times, respectively, the human values at the 10 mg clinical dose, based on AUC). Dose-related reductions in pup body weights were observed at greater or equal to

29-times the 10 mg clinical dose (based on AUC). No adverse effects on developmental endpoints were noted at 1 mg/kg/day (19-times the 10 mg clinical dose, based on AUC). These outcomes occurred with drug exposure during periods of renal development in rats that corresponds to the late second and third trimester of human development.

In embryofetal development studies in rats and rabbits, dapagliflozin was administered throughout organogenesis, corresponding to the first trimester of human pregnancy. In rats, dapagliflozin was neither embryolethal nor teratogenic at doses up to 75 mg/kg/day (1441-times the 10 mg clinical dose, based on AUC). Dose related effects on the rat fetus (structural abnormalities and reduced body weight) occurred only at higher dosages, equal to or greater than 150 mg/kg (more than 2344-times the 10 mg clinical dose, based on AUC), which were associated with maternal toxicity. No developmental toxicities were observed in rabbits at doses up to 180 mg/kg/day (1191-times the 10 mg clinical dose, based on AUC).

8.2 Lactation

Risk Summary

There is no information regarding the presence of dapagliflozin in human milk, the effects on the breastfed infant, or the effects on milk production. Dapagliflozin is present in the milk of lactating rats *(see Data)*. However, due to species specific differences in lactation physiology, the clinical relevance of these data are not clear. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in breastfed infants, advise women that use of FARXIGA is not recommended while breastfeeding.

Data

Dapagliflozin was present in rat milk at a milk/plasma ratio of 0.49, indicating that dapagliflozin and its metabolites are transferred into milk at a concentration that is approximately 50% of that in maternal plasma. Juvenile rats directly exposed to dapagliflozin showed risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

8.4 Pediatric Use

Safety and effectiveness of FARXIGA in pediatric patients under 18 years of age have not been established.

8.5 Geriatric Use

No FARXIGA dosage change is recommended based on age. A total of 1424 (24%) of the 5936 FARXIGA-treated patients were 65 years and older and 207 (3.5%) patients were 75 years and older in a pool of 21 double-blind, controlled, clinical studies assessing the efficacy of FARXIGA in improving glycemic control. After controlling for level of renal function (eGFR), efficacy was similar for patients under age 65 years and those 65 years and older. In patients ≥65 years of age, a higher proportion of patients treated with FARXIGA had adverse reactions of hypotension *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

8.6 Renal Impairment

Use of FARXIGA is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.3) and Warnings and Precautions (5.3)]* and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or ESRD *[see Contraindications (4)]*.

FARXIGA was evaluated in two glycemic control studies that included patients with moderate renal impairment (an eGFR of 45 to less than 60 mL/min/1.73 m^2 *[see Clinical Studies (14.1)]*, and an eGFR of 30 to less than 60 mL/min/1.73 m^2, respectively). The safety profile of FARXIGA in the study of patients with an eGFR of 45 to less than 60 mL/min/1.73 m^2 was similar to the general population of patients with type 2 diabetes. Although patients in the FARXIGA arm had reduction in eGFR compared to the placebo arm, eGFR generally returned towards baseline after treatment discontinuation. Patients with renal impairment using FARXIGA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury. In the study of patients with an eGFR 30 to less than 60 mL/min/1.73 m^2, 13 patients receiving FARXIGA experienced bone fractures compared to none receiving placebo.

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild, moderate, or severe hepatic impairment. However, the benefit-risk for the use of dapagliflozin in patients with severe hepatic impairment should be individually assessed since the safety and efficacy of dapagliflozin have not been specifically studied in this population *[see Clinical Pharmacology (12.3)]*.

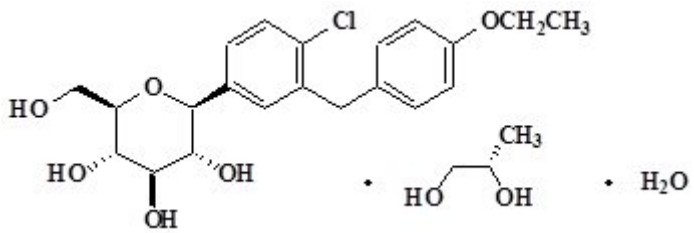
10 OVERDOSAGE

There were no reports of overdose during the clinical development program for FARXIGA.

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ supportive measures as dictated by the patient's clinical status. The removal of dapagliflozin by hemodialysis has not been studied.

11 DESCRIPTION

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-*C*-[4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \cdot C_3H_8O_2 \cdot H_2O$ and the molecular weight is 502.98. The structural formula is:



FARXIGA is available as a film-coated tablet for oral administration containing the equivalent of 5 mg dapagliflozin as dapagliflozin propanediol or the equivalent of 10 mg dapagliflozin as dapagliflozin

propanediol, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

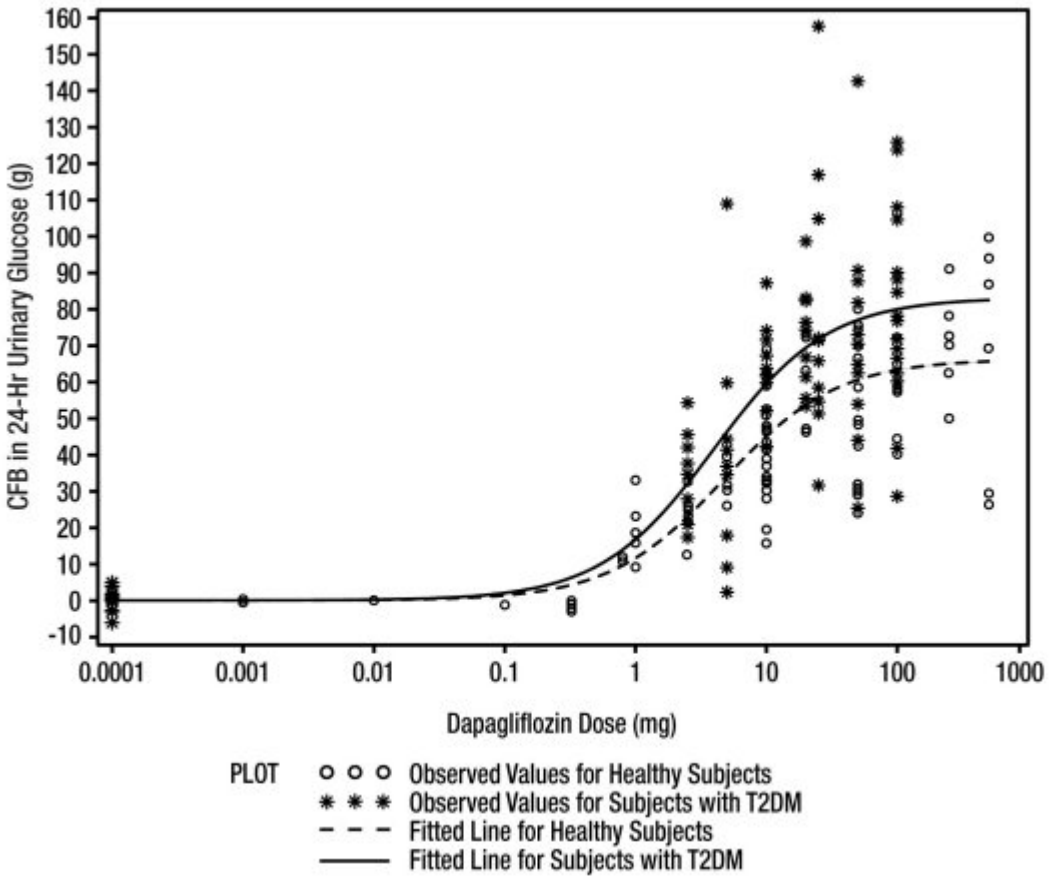
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre- and afterload of the heart and downregulation of sympathetic activity.

12.2 Pharmacodynamics

General

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in patients with type 2 diabetes mellitus following the administration of dapagliflozin (see Figure 1). Dapagliflozin doses of 5 or 10 mg per day in patients with type 2 diabetes mellitus for 12 weeks resulted in excretion of approximately 70 grams of glucose in the urine per day at Week 12. A near maximum glucose excretion was observed at the dapagliflozin daily dose of 20 mg. This urinary glucose excretion with dapagliflozin also results in increases in urinary volume *[see Adverse Reactions (6.1)]*.

Figure 1: Scatter Plot and Fitted Line of Change from Baseline in 24-Hour Urinary Glucose Amount versus Dapagliflozin Dose in Healthy Subjects and Subjects with Type 2 Diabetes Mellitus (T2DM) (Semi-Log Plot)



Cardiac Electrophysiology

Dapagliflozin was not associated with clinically meaningful prolongation of QTc interval at daily doses up to 150 mg (15-times the recommended maximum dose) in a study of healthy subjects. In addition, no clinically meaningful effect on QTc interval was observed following single doses of up to 500 mg (50-times the recommended maximum dose) of dapagliflozin in healthy subjects.

12.3 Pharmacokinetics

Absorption

Following oral administration of dapagliflozin, the maximum plasma concentration (C_{max}) is usually attained within 2 hours under fasting state. The C_{max} and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its C_{max} by up to 50% and prolongs T_{max} by approximately 1 hour, but does not

alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding is not altered in patients with renal or hepatic impairment.

Metabolism

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Elimination

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of FARXIGA 10 mg.

Specific Populations

Renal Impairment

At steady-state (20 mg once daily dapagliflozin for 7 days), patients with type 2 diabetes with mild, moderate, or severe renal impairment (as determined by eGFR) had geometric mean systemic exposures of dapagliflozin that were 45%, 2.04-fold, and 3.03-fold higher, respectively, as compared to patients with type 2 diabetes with normal renal function. Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment did not result in a correspondingly higher 24-hour urinary glucose excretion. The steady-state 24-hour urinary glucose excretion in patients with type 2 diabetes and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than patients with type 2 diabetes with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.6), and Clinical Studies (14)]*.

Hepatic Impairment

In subjects with mild and moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, as compared to healthy matched control subjects following single-dose administration of 10 mg dapagliflozin. These differences were not considered to be clinically meaningful. In patients with severe hepatic impairment (Child-Pugh class C), mean C_{max} and AUC of dapagliflozin were up to 40% and 67% higher, respectively, as compared to healthy matched controls *[see Use in Specific Populations (8.7)]*.

Effects of Age, Gender, Race, and Body Weight on Pharmacokinetics

Based on a population pharmacokinetic analysis, age, gender, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of dapagliflozin and thus, no dose adjustment is recommended.

Pediatric

Pharmacokinetics in the pediatric population has not been studied.

Drug Interactions

In Vitro Assessment of Drug Interactions

In *in vitro* studies, dapagliflozin and dapagliflozin 3-O-glucuronide neither inhibited CYP 1A2, 2C9, 2C19, 2D6, or 3A4, nor induced CYP 1A2, 2B6, or 3A4. Dapagliflozin is a weak substrate of the P-glycoprotein (P-gp) active transporter, and dapagliflozin 3-O-glucuronide is a substrate for the OAT3 active transporter. Dapagliflozin or dapagliflozin 3-O-glucuronide did not meaningfully inhibit P-gp, OCT2, OAT1, or OAT3 active transporters. Overall, dapagliflozin is unlikely to affect the pharmacokinetics of concurrently administered medications that are P-gp, OCT2, OAT1, or OAT3 substrates.

Effects of Other Drugs on Dapagliflozin

Table 4 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Table 4: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	**Dapagliflozin (Dose Regimen)***	**Effect on Dapagliflozin Exposure (% Change [90% CI])**	
		C_{max}	**AUC†**
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↔	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↔
Voglibose (0.2 mg three times daily)	10 mg	↔	↔
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↔	↔
Valsartan (320 mg)	20 mg	↓12% [↓3%, ↓20%]	↔
Simvastatin (40 mg)	20 mg	↔	↔
Anti-infective Agent			
Rifampin (600 mg once daily for 6 days)	10 mg	↓7%	↓22%

Table 4: Effects of Coadministered Drugs on Dapagliflozin Systemic Exposure

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Dapagliflozin Exposure (% Change [90% CI])	
		C_{max}	AUC†
		[↓22%, ↑11%]	[↓27%, ↓17%]
Nonsteroidal Anti-inflammatory Agent			
Mefenamic Acid (loading dose of 500 mg followed by 14 doses of 250 mg every 6 hours)	10 mg	↑13% [↑3%, ↑24%]	↑51% [↑44%, ↑58%]

↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher, respectively, with coadministration compared to dapagliflozin administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25)

* Single dose unless otherwise noted.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

Effects of Dapagliflozin on Other Drugs

Table 5 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 5: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure (% Change [90% CI])	
		C_{max}	AUC†
No dosing adjustments required for the following:			
Oral Antidiabetic Agents			
Metformin (1000 mg)	20 mg	↔	↔
Pioglitazone (45 mg)	50 mg	↓7% [↓25%, ↑15%]	↔
Sitagliptin (100 mg)	20 mg	↔	↔
Glimepiride (4 mg)	20 mg	↔	↑13% [0%, ↑29%]
Other Medications			
Hydrochlorothiazide (25 mg)	50 mg	↔	↔
Bumetanide (1 mg)	10 mg once daily for 7 days	↑13% [↓2%, ↑31%]	↑13% [↓1%, ↑30%]
Valsartan (320 mg)	20 mg	↓6% [↓24%, ↑16%]	↑5% [↓15%, ↑29%]
Simvastatin (40 mg)	20 mg	↔	↑19%
Digoxin (0.25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔
Warfarin (25 mg)	20 mg loading dose then 10 mg once daily for 7 days	↔	↔

↔ = no change (geometric mean ratio of test: reference within 0.80 to 1.25); ↓ or ↑ = parameter was lower or higher,

Table 5: Effects of Dapagliflozin on the Systemic Exposures of Coadministered Drugs

Coadministered Drug (Dose Regimen)*	Dapagliflozin (Dose Regimen)*	Effect on Coadministered Drug Exposure (% Change [90% CI])	
		C_{max}	AUC†

respectively, with coadministration compared to the other medicine administered alone (geometric mean ratio of test: reference was lower than 0.80 or higher than 1.25).

* Single dose unless otherwise noted.

† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Dapagliflozin did not induce tumors in either mice or rats at any of the doses evaluated in 2-year carcinogenicity studies. Oral doses in mice consisted of 5, 15, and 40 mg/kg/day in males and 2, 10 and 20 mg/kg/day in females, and oral doses in rats were 0.5, 2, and 10 mg/kg/day for both males and females. The highest doses evaluated in mice were approximately 72-times (males) and 105-times (females) the clinical dose of 10 mg per day, based on AUC exposure. In rats, the highest dose was approximately 131-times (males) and 186-times (females) the clinical dose of 10 mg per day, based on AUC exposure.

Dapagliflozin was negative in the Ames mutagenicity assay and was positive in a series of *in vitro* clastogenicity assays in the presence of S9 activation and at concentrations greater than or equal to 100 µg/mL. Dapagliflozin was negative for clastogenicity in a series of *in vivo* studies evaluating micronuclei or DNA repair in rats at exposure multiples greater than 2100-times the clinical dose.

There was no carcinogenicity or mutagenicity signal in animal studies, suggesting that dapagliflozin does not represent a genotoxic risk to humans.

Dapagliflozin had no effects on mating, fertility, or early embryonic development in treated male or female rats at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.

14 CLINICAL STUDIES

14.1 Glycemic Control

Overview of Clinical Studies of FARXIGA for Type 2 Diabetes

FARXIGA has been studied as monotherapy, in combination with metformin, pioglitazone, sulfonylurea (glimepiride), sitagliptin (with or without metformin), metformin plus a sulfonylurea, or insulin (with or without other oral antidiabetic therapy), compared to a sulfonylurea (glipizide), and in combination with a GLP-1 receptor agonist (exenatide extended-release) added-on to metformin. FARXIGA has also been studied in patients with type 2 diabetes and moderate renal impairment.

Treatment with FARXIGA as monotherapy and in combination with metformin, glimepiride, pioglitazone, sitagliptin, or insulin produced statistically significant improvements in mean change from

baseline at Week 24 in HbA1c compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, duration of disease, and baseline body mass index (BMI).

Monotherapy

A total of 840 treatment-naive patients with inadequately controlled type 2 diabetes participated in 2 placebo-controlled studies to evaluate the safety and efficacy of monotherapy with FARXIGA.

In 1 monotherapy study, a total of 558 treatment-naive patients with inadequately controlled diabetes participated in a 24-week study (NCT00528372). Following a 2-week diet and exercise placebo lead-in period, 485 patients with HbA1c ≥7% and ≤10% were randomized to FARXIGA 5 mg or FARXIGA 10 mg once daily in either the morning (QAM, main cohort) or evening (QPM), or placebo.

At Week 24, treatment with FARXIGA 10 mg QAM provided significant improvements in HbA1c and the fasting plasma glucose (FPG) compared with placebo (see Table 6).

Table 6: Results at Week 24 (LOCF[*]) in a Placebo-Controlled Study of FARXIGA Monotherapy in Patients with Type 2 Diabetes (Main Cohort AM Doses)

Efficacy Parameter	FARXIGA 10 mg N=70[†]	FARXIGA 5 mg N=64[†]	Placebo N=75[†]
HbA1c (%)			
Baseline (mean)	8.0	7.8	7.8
Change from baseline (adjusted mean[‡])	−0.9	−0.8	−0.2
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.7[§] (−1.0, −0.4)	−0.5 (−0.8, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	50.8%[¶]	44.2%[¶]	31.6%
FPG (mg/dL)			
Baseline (mean)	166.6	157.2	159.9
Change from baseline (adjusted mean[‡])	−28.8	−24.1	−4.1
Difference from placebo (adjusted mean[‡]) (95% CI)	−24.7[§] (−35.7, −13.6)	−19.9 (−31.3, −8.5)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo. Sensitivity analyses yielded smaller estimates of treatment difference with placebo.

¶ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.

Initial Combination Therapy with Metformin XR

A total of 1236 treatment-naive patients with inadequately controlled type 2 diabetes (HbA1c ≥7.5% and ≤12%) participated in 2 active-controlled studies of 24-week duration to evaluate initial therapy with FARXIGA 5 mg (NCT00643851) or 10 mg (NCT00859898) in combination with metformin extended-release (XR) formulation.

In 1 study, 638 patients randomized to 1 of 3 treatment arms following a 1-week lead-in period received: FARXIGA 10 mg plus metformin XR (up to 2000 mg per day), FARXIGA 10 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of FARXIGA 10 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 7 and Figure 2). FARXIGA 10 mg as monotherapy also provided statistically significant improvements in FPG and statistically significant reduction in body weight compared with metformin alone and was noninferior to metformin XR monotherapy in lowering HbA1c.

Table 7: Results at Week 24 (LOCF[*]) in an Active-Controlled Study of FARXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	**FARXIGA 10 mg + Metformin XR N=211[†]**	**FARXIGA 10 mg N=219[†]**	**Metformin XR N=208[†]**
HbA1c (%)			
Baseline (mean)	9.1	9.0	9.0
Change from baseline (adjusted mean[‡])	−2.0	−1.5	−1.4
Difference from FARXIGA (adjusted mean[‡]) (95% CI)	−0.5[§] (−0.7, −0.3)		
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−0.5[§] (−0.8, −0.3)	0.0[¶] (−0.2, 0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	46.6%[#]	31.7%	35.2%
FPG (mg/dL)			
Baseline (mean)	189.6	197.5	189.9
Change from baseline (adjusted mean[‡])	−60.4	−46.4	−34.8
Difference from FARXIGA (adjusted mean[‡]) (95% CI)	−13.9[§] (−20.9, −7.0)		
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−25.5[§] (−32.6, −18.5)	−11.6[#] (−18.6, −4.6)	
Body Weight (kg)			
Baseline (mean)	88.6	88.5	87.2
Change from baseline (adjusted mean[‡])	−3.3	−2.7	−1.4
Difference from metformin XR (adjusted mean[‡]) (95% CI)	−2.0[§] (−2.6, −1.3)	−1.4[§] (−2.0, −0.7)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

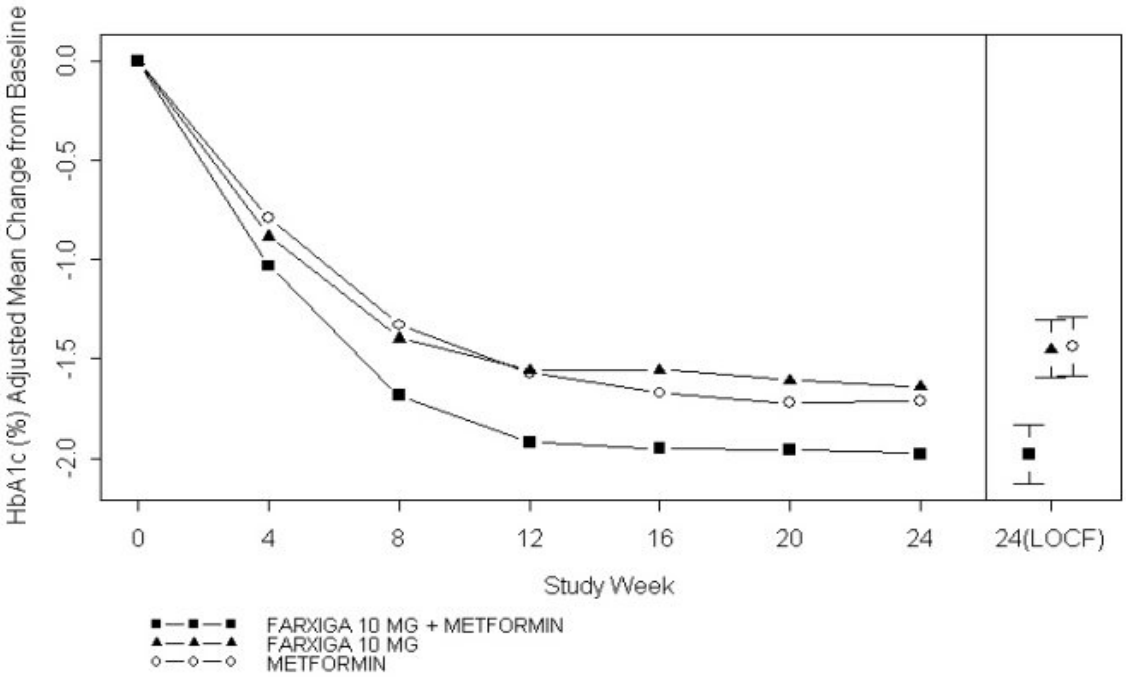
‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ Noninferior versus metformin XR.

\# p-value <0.05.

Figure 2: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Active-Controlled Study of FARXIGA Initial Combination Therapy with Metformin XR



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed the study with both baseline and Week 24 HbA1c values without rescue.
Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

In a second study, 603 patients were randomized to 1 of 3 treatment arms following a 1-week lead-in period: FARXIGA 5 mg plus metformin XR (up to 2000 mg per day), FARXIGA 5 mg plus placebo, or metformin XR (up to 2000 mg per day) plus placebo. Metformin XR dose was up-titrated weekly in 500 mg increments, as tolerated, with a median dose achieved of 2000 mg.

The combination treatment of FARXIGA 5 mg plus metformin XR provided statistically significant improvements in HbA1c and FPG compared with either of the monotherapy treatments and statistically significant reduction in body weight compared with metformin XR alone (see Table 8).

Table 8: Results at Week 24 (LOCF[*]) in an Active-Controlled Study of FARXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	**FARXIGA 5 mg + Metformin XR N=194[†]**	**FARXIGA 5 mg N=203[†]**	**Metformin XR N=201[†]**
HbA1c (%)			
Baseline (mean)	9.2	9.1	9.1
Change from baseline (adjusted mean[‡])	−2.1	−1.2	−1.4
Difference from FARXIGA (adjusted mean[‡])	−0.9[§]		

Table 8: Results at Week 24 (LOCF*) in an Active-Controlled Study of FARXIGA Initial Combination Therapy with Metformin XR

Efficacy Parameter	FARXIGA 5 mg + Metformin XR N=194†	FARXIGA 5 mg N=203†	Metformin XR N=201†
(95% CI)	(−1.1, −0.6)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−0.7§ (−0.9, −0.5)		
Percent of patients achieving HbA1c <7% adjusted for baseline	52.4%¶	22.5%	34.6%
FPG (mg/dL)			
Baseline (mean)	193.4	190.8	196.7
Change from baseline (adjusted mean‡)	−61.0	−42.0	−33.6
Difference from FARXIGA (adjusted mean‡) (95% CI)	−19.1§ (−26.7, −11.4)		
Difference from metformin XR (adjusted mean‡) (95% CI)	−27.5§ (−35.1, −19.8)		
Body Weight (kg)			
Baseline (mean)	84.2	86.2	85.8
Change from baseline (adjusted mean‡)	−2.7	−2.6	−1.3
Difference from metformin XR (adjusted mean‡) (95% CI)	−1.4§ (−2.0, −0.7)		

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001.

¶ p-value <0.05.

Add-On to Metformin

A total of 546 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10%) participated in a 24-week, placebo-controlled study to evaluate FARXIGA in combination with metformin (NCT00528879). Patients on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week, single-blind, placebo lead-in period. Following the lead-in period, eligible patients were randomized to FARXIGA 5 mg, FARXIGA 10 mg, or placebo in addition to their current dose of metformin.

As add-on treatment to metformin, FARXIGA 10 mg provided statistically significant improvements in HbA1c and FPG, and statistically significant reduction in body weight compared with placebo at Week 24 (see Table 9 and Figure 3). Statistically significant ($p < 0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus metformin were −4.5 mmHg and −5.3 mmHg with FARXIGA 5 mg and 10 mg plus metformin, respectively.

Table 9: Results of a 24-Week (LOCF*) Placebo-Controlled Study of FARXIGA in Add-On Combination with Metformin

Efficacy Parameter	FARXIGA 10 mg+ Metformin N=135†	FARXIGA 5 mg + Metformin N=137†	Placebo + Metformin N=137†
HbA1c (%)			
Baseline (mean)	7.9	8.2	8.1
Change from baseline (adjusted mean‡)	−0.8	−0.7	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−0.5§ (−0.7, −0.3)	−0.4§ (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	40.6%¶	37.5%¶	25.9%
FPG (mg/dL)			
Baseline (mean)	156.0	169.2	165.6
Change from baseline at Week 24 (adjusted mean‡)	−23.5	−21.5	−6.0
Difference from placebo (adjusted mean‡) (95% CI)	−17.5§ (−25.0, −10.0)	−15.5§ (−22.9, −8.1)	
Change from baseline at Week 1 (adjusted mean‡)	−16.5§ (N=115)	−12.0§ (N=121)	1.2 (N=126)
Body Weight (kg)			
Baseline (mean)	86.3	84.7	87.7
Change from baseline (adjusted mean‡)	−2.9	−3.0	−0.9
Difference from placebo (adjusted mean‡) (95% CI)	−2.0§ (−2.6, −1.3)	−2.2§ (−2.8, −1.5)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

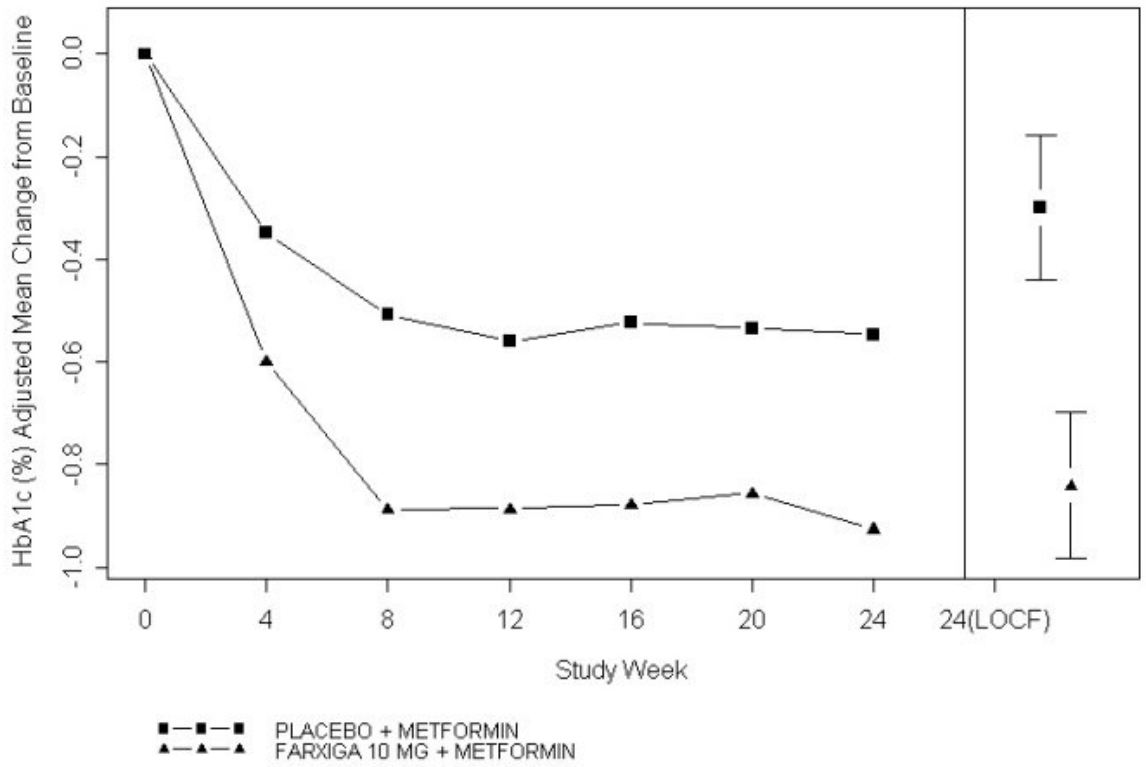
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ Least squares mean adjusted for baseline value.

§ p-value <0.0001 versus placebo + metformin.

¶ p-value <0.05 versus placebo + metformin.

Figure 3: Adjusted Mean Change from Baseline Over Time in HbA1c (%) in a 24-Week Placebo-Controlled Study of FARXIGA in Combination with Metformin



Left side graph: Values for adjusted mean change from baseline based on a longitudinal repeated measures model, including randomized subjects who completed Short-Term Period with both baseline and Week 24 HbA1c values without rescue. Right side graph for Week 24 (LOCF): Values for adjusted mean change from baseline and 95% CIs based on an ANCOVA model, including randomized subjects with a baseline and at least one post baseline HbA1c before rescue.

Active Glipizide-Controlled Study Add-On to Metformin

A total of 816 patients with type 2 diabetes with inadequate glycemic control (HbA1c >6.5% and ≤10%) were randomized in a 52-week, glipizide-controlled, noninferiority study to evaluate FARXIGA as add-on therapy to metformin (NCT00660907). Patients on metformin at a dose of at least 1500 mg per day were randomized following a 2-week placebo lead-in period to glipizide or dapagliflozin (5 mg or 2.5 mg, respectively) and were up-titrated over 18 weeks to optimal glycemic effect (FPG <110 mg/dL, <6.1 mmol/L) or to the highest dose level (up to glipizide 20 mg and FARXIGA 10 mg) as tolerated by patients. Thereafter, doses were kept constant, except for down-titration to prevent hypoglycemia.

At the end of the titration period, 87% of patients treated with FARXIGA had been titrated to the maximum study dose (10 mg) versus 73% treated with glipizide (20 mg). FARXIGA led to a similar mean reduction in HbA1c from baseline at Week 52 (LOCF), compared with glipizide, thus demonstrating noninferiority (see Table 10). FARXIGA treatment led to a statistically significant mean reduction in body weight from baseline at Week 52 (LOCF) compared with a mean increase in body weight in the glipizide group. Statistically significant ($p<0.0001$) mean change from baseline in systolic blood pressure relative to glipizide plus metformin was −5.0 mmHg with FARXIGA plus metformin.

Table 10: Results at Week 52 (LOCF*) in an Active-Controlled Study Comparing FARXIGA to Glipizide as Add-On to Metformin

Efficacy Parameter	FARXIGA + Metformin N=400†	Glipizide + Metformin N=401†
HbA1c (%)		
Baseline (mean)	7.7	7.7
Change from baseline (adjusted mean‡)	−0.5	−0.5
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	0.0§ (−0.1, 0.1)	
Body Weight (kg)		
Baseline (mean)	88.4	87.6
Change from baseline (adjusted mean‡)	−3.2	1.4
Difference from glipizide + metformin (adjusted mean‡) (95% CI)	−4.7¶ (−5.1, −4.2)	

* LOCF: last observation carried forward.

† Randomized and treated patients with baseline and at least 1 postbaseline efficacy measurement.

‡ Least squares mean adjusted for baseline value.

§ Noninferior to glipizide + metformin.

¶ p-value <0.0001.

Add-On Combination Therapy with Other Antidiabetic Agents

Add-On Combination Therapy with a Sulfonylurea

A total of 597 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10%) were randomized in this 24-week, placebo-controlled study to evaluate FARXIGA in combination with glimepiride (a sulfonylurea) (NCT00680745).

Patients on at least half the maximum recommended dose of glimepiride as monotherapy (4 mg) for at least 8 weeks lead-in were randomized to FARXIGA 5 mg, FARXIGA 10 mg, or placebo in addition to glimepiride 4 mg per day. Down-titration of glimepiride to 2 mg or 0 mg was allowed for hypoglycemia during the treatment period; no up-titration of glimepiride was allowed.

In combination with glimepiride, FARXIGA 10 mg provided statistically significant improvement in HbA1c, FPG, and 2-hour PPG, and statistically significant reduction in body weight compared with placebo plus glimepiride at Week 24 (see Table 11). Statistically significant ($p<0.05$ for both doses) mean changes from baseline in systolic blood pressure relative to placebo plus glimepiride were −2.8 mmHg and −3.8 mmHg with FARXIGA 5 mg and 10 mg plus glimepiride, respectively.

Add-on Combination Therapy with Metformin and a Sulfonylurea

A total of 218 patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled study to evaluate FARXIGA in combination with metformin and a sulfonylurea (NCT01392677). Patients on a stable dose of metformin (immediate- or extended-release formulations) ≥1500 mg/day plus maximum tolerated dose, which must be at least half the maximum dose, of a sulfonylurea for at least 8 weeks prior to enrollment were randomized after an 8-week placebo lead-in period to FARXIGA 10 mg or placebo. Dose-titration of FARXIGA or metformin

was not permitted during the 24–week treatment period. Down-titration of the sulfonylurea was permitted to prevent hypoglycemia, but no up-titration was permitted. As add-on treatment to combined metformin and a sulfonylurea, treatment with FARXIGA 10 mg provided statistically significant improvements in HbA1c and FPG and statistically significant reduction in body weight compared with placebo at Week 24 (Table 11). A statistically significant ($p < 0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with metformin and a sulfonyl urea was -3.8 mmHg with FARXIGA 10 mg in combination with metformin and a sulfonylurea at Week 8.

Add-On Combination Therapy with a Thiazolidinedione

A total of 420 patients with type 2 diabetes with inadequate glycemic control (HbA1c ≥7% and ≤10.5%) participated in a 24-week, placebo-controlled study to evaluate FARXIGA in combination with pioglitazone (a thiazolidinedione [TZD]) alone (NCT00683878). Patients on a stable dose of pioglitazone of 45 mg per day (or 30 mg per day, if 45 mg per day was not tolerated) for 12 weeks were randomized after a 2-week lead-in period to 5 or 10 mg of FARXIGA or placebo in addition to their current dose of pioglitazone. Dose titration of FARXIGA or pioglitazone was not permitted during the study.

In combination with pioglitazone, treatment with FARXIGA 10 mg provided statistically significant improvements in HbA1c, 2-hour PPG, FPG, the proportion of patients achieving HbA1c <7%, and a statistically significant reduction in body weight compared with the placebo plus pioglitazone treatment groups (see Table 11) at Week 24. A statistically significant ($p < 0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with pioglitazone was −4.5 mmHg with FARXIGA 10 mg in combination with pioglitazone.

Add-On Combination Therapy with a DPP4 Inhibitor

A total of 452 patients with type 2 diabetes who were drug naive, or who were treated at entry with metformin or a DPP4 inhibitor alone or in combination, and had inadequate glycemic control (HbA1c ≥7.0% and ≤10.0% at randomization), participated in a 24-week, placebo-controlled study to evaluate FARXIGA in combination with sitagliptin (a DPP4 inhibitor) with or without metformin (NCT00984867).

Eligible patients were stratified based on the presence or absence of background metformin (≥1500 mg per day), and within each stratum were randomized to either FARXIGA 10 mg plus sitagliptin 100 mg once daily, or placebo plus sitagliptin 100 mg once daily. Endpoints were tested for FARXIGA 10 mg versus placebo for the total study group (sitagliptin with and without metformin) and for each stratum (sitagliptin alone or sitagliptin with metformin). Thirty-seven percent (37%) of patients were drug naive, 32% were on metformin alone, 13% were on a DPP4 inhibitor alone, and 18% were on a DPP4 inhibitor plus metformin. Dose titration of FARXIGA, sitagliptin, or metformin was not permitted during the study.

In combination with sitagliptin (with or without metformin), FARXIGA 10 mg provided statistically significant improvements in HbA1c, FPG, and a statistically significant reduction in body weight compared with the placebo plus sitagliptin (with or without metformin) group at Week 24 (see Table 11). These improvements were also seen in the stratum of patients who received FARXIGA 10 mg plus sitagliptin alone (placebo-corrected mean change for HbA1c −0.56%; n=110) compared with placebo plus sitagliptin alone (n=111), and the stratum of patients who received FARXIGA 10 mg plus sitagliptin and

metformin (placebo-corrected mean change for HbA1c −0.40; n=113) compared with placebo plus sitagliptin with metformin (n=113).

Add-On Combination Therapy with Insulin

A total of 808 patients with type 2 diabetes who had inadequate glycemic control (HbA1c ≥7.5% and ≤10.5%) were randomized in a 24-week, placebo-controlled study to evaluate FARXIGA as add-on therapy to insulin (NCT00673231). Patients on a stable insulin regimen, with a mean dose of at least 30 IU of injectable insulin per day, for a period of at least 8 weeks prior to enrollment and on a maximum of 2 oral antidiabetic medications (OADs), including metformin, were randomized after completing a 2-week enrollment period to receive either FARXIGA 5 mg, FARXIGA 10 mg, or placebo in addition to their current dose of insulin and other OADs, if applicable. Patients were stratified according to the presence or absence of background OADs. Up- or down-titration of insulin was only permitted during the treatment phase in patients who failed to meet specific glycemic goals. Dose modifications of blinded study medication or OAD(s) were not allowed during the treatment phase, with the exception of decreasing OAD(s) where there were concerns over hypoglycemia after cessation of insulin therapy.

In this study, 50% of patients were on insulin monotherapy at baseline, while 50% were on 1 or 2 OADs in addition to insulin. At Week 24, FARXIGA 10 mg dose provided statistically significant improvement in HbA1c and reduction in mean insulin dose, and a statistically significant reduction in body weight compared with placebo in combination with insulin, with or without up to 2 OADs (see Table 11); the effect of FARXIGA on HbA1c was similar in patients treated with insulin alone and patients treated with insulin plus OAD. Statistically significant ($p<0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with insulin was −3.0 mmHg with FARXIGA 10 mg in combination with insulin.

At Week 24, FARXIGA 5 mg (−5.7 IU, difference from placebo) and 10 mg (−6.2 IU, difference from placebo) once daily resulted in a statistically significant reduction in mean daily insulin dose ($p<0.0001$ for both doses) compared to placebo in combination with insulin, and a statistically significantly higher proportion of patients on FARXIGA 10 mg (19.6%) reduced their insulin dose by at least 10% compared to placebo (11.0%).

Table 11: Results of 24-Week (LOCF[*]) Placebo-Controlled Studies of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	**FARXIGA 10 mg**	**FARXIGA 5 mg**	**Placebo**
In Combination with Sulfonylurea (Glimepiride)			
Intent-to-Treat Population	**N=151[†]**	**N=142[†]**	**N=145[†]**
HbA1c (%)			
Baseline (mean)	8.1	8.1	8.2
Change from baseline (adjusted mean[‡])	−0.8	−0.6	−0.1
Difference from placebo (adjusted mean[‡]) (95% CI)	−0.7[§] (−0.9, −0.5)	−0.5[§] (−0.7, −0.3)	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.7%[§]	30.3%[§]	13.0%
FPG (mg/dL)			
Baseline (mean)	172.4	174.5	172.7

Table 11: Results of 24-Week (LOCF*) Placebo-Controlled Studies of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	**FARXIGA 10 mg**	**FARXIGA 5 mg**	**Placebo**
Change from baseline (adjusted mean‡)	−28.5	−21.2	−2.0
Difference from placebo (adjusted mean‡) (95% CI)	−26.5§ (−33.5, −19.5)	−19.3§ (−26.3, −12.2)	
2-hour PPG¶ (mg/dL)			
Baseline (mean)	329.6	322.8	324.1
Change from baseline (adjusted mean‡)	−60.6	–54.5	−11.5
Difference from placebo (adjusted mean‡) (95% CI)	−49.1§ (−64.1, −34.1)	−43.0§ (–58.4, −27.5)	
Body Weight (kg)			
Baseline (mean)	80.6	81.0	80.9
Change from baseline (adjusted mean‡)	−2.3	−1.6	−0.7
Difference from placebo (adjusted mean‡) (95% CI)	−1.5§ (−2.2, −0.9)	−0.8§ (−1.5, −0.2)	
In Combination with Metformin and a Sulfonylurea			
Intent-to-Treat Population	**N=108†**	-	**N=108†**
HbA1c (%)			
Baseline (mean)	8.08	-	8.24
Change from baseline (adjusted mean‡#)	−0.86	-	−0.17
Difference from placebo (adjusted mean‡#) (95% CI)	−0.69§ (−0.89, −0.49)	-	
Percent of patients achieving HbA1c <7% adjusted for baseline	31.8%§	-	11.1%
FPG (mg/dL)			
Baseline (mean)	167.4	-	180.3
Change from baseline (adjusted mean‡)	−34.2	-	−0.8
Difference from placebo (adjusted mean‡) (95% CI)	−33.5§ (−43.1, −23.8)	-	
Body Weight (kg)			
Baseline (mean)	88.57	-	90.07
Change from baseline (adjusted mean‡)	−2.65	-	−0.58
Difference from placebo (adjusted mean‡) (95% CI)	−2.07§ (−2.79, −1.35)	-	
In Combination with Thiazolidinedione (Pioglitazone)			
Intent-to-Treat Population	**N=140Þ**	**N=141Þ**	**N=139Þ**
HbA1c (%)			
Baseline (mean)	8.4	8.4	8.3
Change from baseline (adjusted mean‡)	−1.0	−0.8	−0.4
Difference from placebo (adjusted mean‡) (95% CI)	−0.6§ (−0.8, −0.3)	−0.4§ (−0.6, −0.2)	
Percent of patients achieving HbA1c <7% adjusted for baseline	38.8%ß	32.5%ß	22.4%
FPG (mg/dL)			
Baseline (mean)	164.9	168.3	160.7
Change from baseline (adjusted mean‡)	−29.6	−24.9	−5.5

Table 11: Results of 24-Week (LOCF*) Placebo-Controlled Studies of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	FARXIGA 10 mg	FARXIGA 5 mg	Placebo
Difference from placebo (adjusted mean‡) (95% CI)	−24.1§ (−32.2, −16.1)	−19.5§ (−27.5, −11.4)	
2-hour PPG¶ (mg/dL)			
Baseline (mean)	308.0	284.8	293.6
Change from baseline (adjusted mean‡)	−67.5	−65.1	−14.1
Difference from placebo (adjusted mean‡) (95% CI)	−53.3§ (−71.1, −35.6)	−51.0§ (−68.7, −33.2)	
Body Weight (kg)			
Baseline (mean)	84.8	87.8	86.4
Change from baseline (adjusted mean‡)	−0.1	0.1	1.6
Difference from placebo (adjusted mean‡) (95% CI)	−1.8§ (−2.6, −1.0)	−1.6§ (−2.3, −0.8)	
In Combination with DPP4 Inhibitor (Sitagliptin) with or without Metformin			
Intent-to-Treat Population	**N=223†**	**–**	**N=224†**
HbA1c (%)			
Baseline (mean)	7.90	–	7.97
Change from baseline (adjusted mean‡)	−0.45	–	0.04
Difference from placebo (adjusted mean‡) (95% CI)	−0.48§ (−0.62, −0.34)	–	
Patients with HbA1c decrease ≥0.7% (adjusted percent)	35.4%	–	16.6%
FPG (mg/dL)			
Baseline (mean)	161.7	–	163.1
Change from baseline at Week 24 (adjusted mean‡)	−24.1	–	3.8
Difference from placebo (adjusted mean‡) (95% CI)	−27.9§ (−34.5, −21.4)	–	
Body Weight (kg)			
Baseline (mean)	91.02	–	89.23
Change from baseline (adjusted mean‡)	−2.14	–	−0.26
Difference from placebo (adjusted mean‡) (95% CI)	−1.89§ (−2.37, −1.40)	–	
In Combination with Insulin with or without up to 2 Oral Antidiabetic Therapies			
Intent-to-Treat Population	**N=194†**	**N=211†**	**N=193†**
HbA1c (%)			
Baseline (mean)	8.6	8.6	8.5
Change from baseline (adjusted mean‡)	−0.9	−0.8	−0.3
Difference from placebo (adjusted mean‡) (95% CI)	−0.6§ (−0.7, −0.5)	−0.5§ (−0.7, −0.4)	
FPG (mg/dL)			
Baseline (mean)	173.7	NTÀ	170.0
Change from baseline (adjusted mean‡)	−21.7	NTÀ	3.3
Difference from placebo (adjusted mean‡) (95% CI)	−25.0§ (−34.3, −15.8)	NTÀ	
Body Weight (kg)			

Table 11: Results of 24-Week (LOCF*) Placebo-Controlled Studies of FARXIGA in Combination with Antidiabetic Agents

Efficacy Parameter	FARXIGA 10 mg	FARXIGA 5 mg	Placebo
Baseline (mean)	94.6	93.2	94.2
Change from baseline (adjusted mean‡)	−1.7	−1.0	0.0
Difference from placebo (adjusted mean‡) (95% CI)	−1.7§ (−2.2, −1.2)	−1.0§ (−1.5, −0.5)	

* LOCF: last observation (prior to rescue for rescued patients) carried forward.

† Randomized and treated patients with baseline and at least 1 post baseline efficacy measurement.

‡ Least squares mean adjusted for baseline value based on an ANCOVA model.

§ p-value <0.0001 versus placebo.

¶ 2-hour PPG level as a response to a 75-gram oral glucose tolerance test (OGTT).

Least squares mean adjusted for baseline value based on a longitudinal repeated measures model.

Þ All randomized patients who took at least one dose of double-blind study medication during the short-term, double-blind period.

ß p-value <0.05 versus placebo.

À NT: Not formally tested because of failing to achieve a statistically significant difference in an endpoint that was earlier in the testing sequence.

Combination Therapy with Exenatide-Extended Release as Add-On to Metformin

A total of 694 adult patients with type 2 diabetes and inadequate glycemic control (HbA1c ≥8.0 and ≤12.0%) on metformin, were evaluated in a 28-week double-blind, active-controlled study to compare FARXIGA in combination with exenatide extended-release (a GLP-1 receptor agonist) to FARXIGA alone and exenatide extended-release alone, as add-on to metformin (NCT02229396). Patients on metformin at a dose of at least 1,500 mg per day were randomized following a 1-week placebo lead-in period to receive either FARXIGA 10 mg once daily (QD) in combination with exenatide extended-release 2 mg once weekly (QW), FARXIGA 10 mg QD, or exenatide extended–release 2 mg QW.

At Week 28, FARXIGA in combination with exenatide extended-release provided statistically significantly greater reductions in HbA1c (-1.77%) compared to FARXIGA alone (-1.32%, p=0.001) and exenatide extended-release alone (-1.42%, p=0.012). FARXIGA in combination with exenatide extended-release provided statistically significantly greater reductions in FPG (-57.35 mg/dL) compared to FARXIGA alone (-44.72 mg/dL, p=0.006) and exenatide extended-release alone (-40.53, p <0.001).

Use in Patients with Type 2 Diabetes and Moderate Renal Impairment

FARXIGA was assessed in two placebo-controlled studies of patients with type 2 diabetes and moderate renal impairment.

Patients with type 2 diabetes and an eGFR between 45 to less than 60 mL/min/1.73 m^2 inadequately controlled on current diabetes therapy participated in a 24-week, double-blind, placebo-controlled clinical study (NCT02413398). Patients were randomized to either FARXIGA 10 mg or placebo, administered orally once daily. At Week 24, FARXIGA provided statistically significant reductions in HbA1c compared with placebo (Table 12).

Table 12: Results at Week 24 of Placebo-Controlled Study for FARXIGA in Patients with Type 2 Diabetes and Renal Impairment (eGFR 45 to less than 60 mL/min/1.73 m^2)

	FARXIGA 10 mg	Placebo
Number of patients:	**N=160**	**N=161**
HbA1c (%)		
Baseline (mean)	8.3	8.0
Change from baseline (adjusted mean*)	-0.4	-0.1
Difference from placebo (adjusted mean*) (95% CI)	-0.3† (-0.5, - 0.1)	

* Least squares mean adjusted for baseline value; at Week 24, HbA1c was missing for 5.6% and 6.8% of individuals treated with FARXIGA and placebo, respectively. Retrieved dropouts, i.e. observed HbA1c at Week 24 from subjects who discontinued treatment, were used to impute missing values in HbA1c.

† p-value =0.008 versus placebo.

14.2 Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Dapagliflozin Effect on Cardiovascular Events (DECLARE, NCT01730534) was an international, multicenter, randomized, double-blind, placebo-controlled, clinical study conducted to determine the effect of FARXIGA relative to placebo on CV outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either established CVD or two or more additional CV risk factors (age ≥55 years in men or ≥60 years in women and one or more of dyslipidemia, hypertension, or current tobacco use). Concomitant antidiabetic and atherosclerotic therapies could be adjusted, at the discretion of investigators, to ensure participants were treated according to the standard care for these diseases.

Of 17160 randomized patients, 6974 (40.6%) had established CVD and 10186 (59.4%) did not have established CVD. A total of 8582 patients were randomized to FARXIGA 10 mg, 8578 to placebo, and patients were followed for a median of 4.2 years.

Approximately 80% of the trial population was White, 4% Black or African-American, and 13% Asian. The mean age was 64 years, and approximately 63% were male.

Mean duration of diabetes was 11.9 years and 22.4% of patients had diabetes for less than 5 years. Mean eGFR was 85.2 mL/min/1.73 m^2. At baseline, 23.5% of patients had microalbuminuria (UACR ≥30 to ≤300 mg/g) and 6.8% had macroalbuminuria (UACR >300 mg/g). Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m^2. At baseline, 10% of patients had a history of heart failure.

Most patients (98.1%) used one or more diabetic medications at baseline. 82.0% of the patients were being treated with metformin, 40.9% with insulin, 42.7% with a sulfonylurea, 16.8% with a DPP4 inhibitor, and 4.4% with a GLP-1 receptor agonist.

Approximately 81.3% of patients were treated with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 75.0% with statins, 61.1% with antiplatelet therapy, 55.5% with acetylsalicylic acid, 52.6% with beta-blockers, 34.9% with calcium channel blockers, 22.0% with thiazide diuretics, and 10.5% with loop diuretics.

A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio (HR) of the composite of CV death, myocardial infarction (MI), or

ischemic stroke [MACE] and to test for superiority on the dual primary endpoints: the composite of hospitalization for heart failure or CV death, and MACE, if non-inferiority was demonstrated.

The incidence rate of MACE was similar in both treatment arms: 2.3 MACE events per 100 patient-years on dapagliflozin vs. 2.46 MACE events per 100 patient-years on placebo. The estimated hazard ratio of MACE associated with dapagliflozin relative to placebo was 0.93 with a 95.38% confidence interval of (0.84,1.03). The upper bound of this confidence interval, 1.03, excluded a risk margin larger than 1.3.

FARXIGA was superior to placebo in reducing the incidence of the primary composite endpoint of hospitalization for heart failure or CV death (HR 0.83 [95% CI 0.73, 0.95]).

The treatment effect was due to a significant reduction in the risk of hospitalization for heart failure in subjects randomized to FARXIGA (HR 0.73 [95% CI 0.61, 0.88]), with no change in the risk of CV death (Table 13 and Figures 4 and 5).

Table 13: Treatment Effects for the Primary Endpoints* and Their Components* in the DECLARE Study

	Patients with events n(%)		
Efficacy Variable (time to first occurrence)	**FARXIGA 10 mg N=8582**	**Placebo N=8578**	**Hazard ratio (95% CI)**
Primary Endpoints			
Composite of Hospitalization for Heart Failure, CV Death†	417 (4.9)	496 (5.8)	0.83 (0.73, 0.95)
Composite Endpoint of CV Death, MI, Ischemic Stroke	756 (8.8)	803 (9.4)	0.93 (0.84, 1.03)
Components of the composite endpoints‡			
Hospitalization for Heart Failure	212 (2.5)	286 (3.3)	0.73 (0.61, 0.88)
CV Death	245 (2.9)	249 (2.9)	0.98 (0.82, 1.17)
Myocardial Infarction	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)
Ischemic Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)

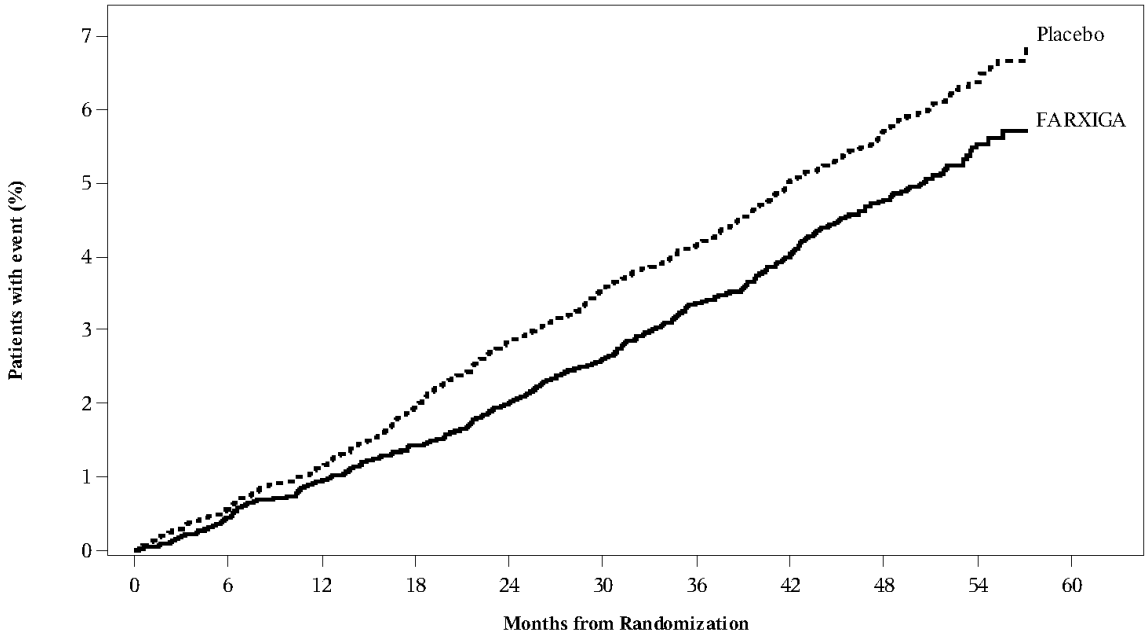
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction,

* Full analysis set.

† p-value =0.005 versus placebo.

‡ total number of events presented for each component of the composite endpoints

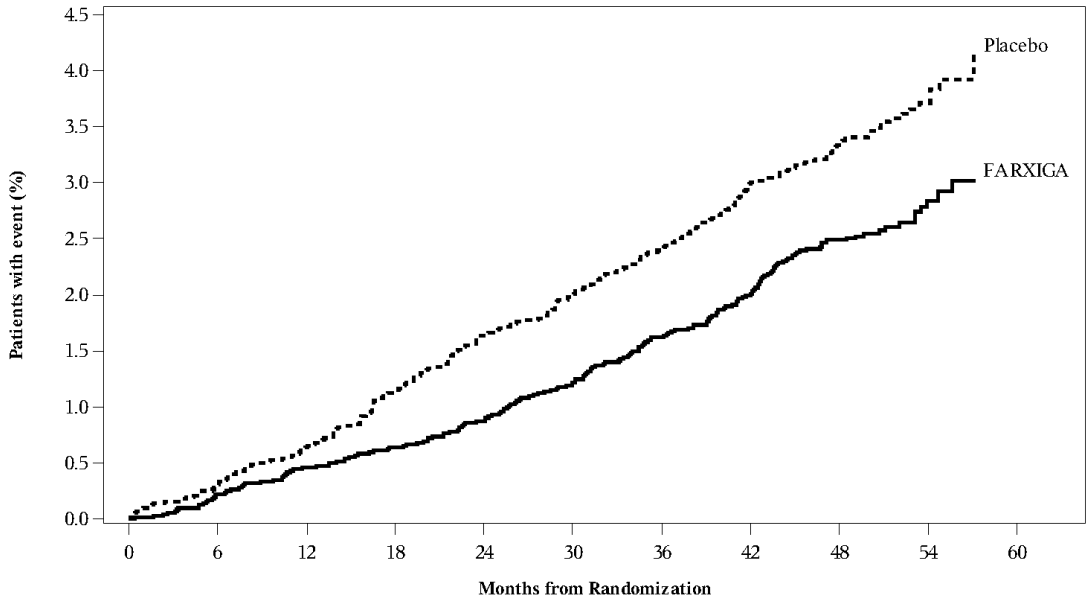
Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study



Patients at risk

FARXIGA:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

Figure 5: Time to First Occurrence of Hospitalization for Heart Failure in the DECLARE Study



Patients at risk

FARXIGA:	8582	8509	8403	8315	8218	8101	7965	7489	5439	1626
Placebo:	8578	8482	8380	8256	8121	7998	7874	7360	5358	1572

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

FARXIGA (dapagliflozin) tablets have markings on both sides and are available in the strengths and packages listed in Table 14.

Table 14: FARXIGA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	yellow, biconvex, round	"5" engraved on one side and "1427" engraved on the other side	Bottles of 30	0310-6205-30
10 mg	yellow, biconvex, diamond-shaped	"10" engraved on one side and "1428" engraved on the other side	Bottles of 30	0310-6210-30

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Hypotension

Inform patients that symptomatic hypotension may occur with FARXIGA and advise them to contact their healthcare provider if they experience such symptoms *[see Warnings and Precautions (5.1)]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis

Inform patients that ketoacidosis is a serious life-threatening condition. Cases of ketoacidosis have been reported during use of FARXIGA. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness and labored breathing) occur, instruct patients to discontinue FARXIGA and seek medical advice immediately *[see Warnings and Precautions (5.2)]*.

Acute Kidney Injury

Inform patients that acute kidney injury has been reported during use of FARXIGA. Advise patients to seek medical advice immediately if they have reduced oral intake (due to acute illness or fasting) or increased fluid losses (due to vomiting, diarrhea, or excessive heat exposure), as it may be appropriate to temporarily discontinue FARXIGA use in those settings *[see Warnings and Precautions (5.3)]*.

Serious Urinary Tract Infections

Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.4)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's Gangrene) have occurred with FARXIGA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions (5.6)]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis)

Inform female patients that vaginal yeast infections may occur and provide them with information on the signs and symptoms of vaginal yeast infections. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Genital Mycotic Infections in Males (e.g., Balanitis)

Inform male patients that yeast infections of the penis (e.g., balanitis or balanoposthitis) may occur, especially in patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions (5.7)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions (e.g., urticaria, anaphylactic reactions, and angioedema) have been reported with FARXIGA. Advise patients to immediately report any signs or symptoms suggesting allergic reaction or angioedema, and to take no more of the drug until they have consulted prescribing physicians.

Pregnancy

Advise pregnant patients of the potential risk to a fetus with treatment with FARXIGA. Instruct patients to immediately inform their healthcare provider if pregnant or planning to become pregnant *[see Use in Specific Populations (8.1)]*.

Lactation

Advise patients that use of FARXIGA is not recommended while breastfeeding *[see Use in Specific Populations (8.2)]*.

Laboratory Tests

Due to its mechanism of action, patients taking FARXIGA will test positive for glucose in their urine.

Missed Dose

If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of FARXIGA at the same time.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

FARXIGA® is a registered trademark of the AstraZeneca group of companies.

MEDICATION GUIDE
FARXIGA® (FAR-SEE-GUH)
(dapagliflozin)
tablets, for oral use

What is the most important information I should know about FARXIGA?

FARXIGA can cause serious side effects, including:

- **Dehydration.** FARXIGA can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). You may be at a higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including water pills (diuretics)
  - are 65 years of age or older
  - are on a low salt diet
  - have kidney problems
- **Vaginal yeast infection.** Women who take FARXIGA may get vaginal yeast infections. Symptoms of a vaginal yeast infection include:
  - vaginal odor
  - white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
  - vaginal itching
- **Yeast infection of the penis (balanitis).** Men who take FARXIGA may get a yeast infection of the skin around the penis. Certain men who are not circumcised may have swelling of the penis that makes it difficult to pull back the skin around the tip of the penis. Other symptoms of yeast infection of the penis include:
  - redness, itching, or swelling of the penis
  - rash of the penis
  - foul smelling discharge from the penis
  - pain in the skin around the penis

Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

What is FARXIGA?

FARXIGA is a prescription medicine used in adults with type 2 diabetes to:

- improve blood sugar (glucose) control along with diet and exercise
- reduce the risk of hospitalization for heart failure

FARXIGA is not for people with type 1 diabetes.

FARXIGA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if FARXIGA is safe and effective in children younger than 18 years of age.

Who should not take FARXIGA?

Do not take FARXIGA if you:

- are allergic to dapagliflozin or any of the ingredients in FARXIGA. See the end of this Medication Guide for a list of ingredients in FARXIGA. Symptoms of a **serious** allergic reaction to FARXIGA may include:
  - skin rash
  - raised red patches on your skin (hives)
  - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing

  If you have any of these symptoms, stop taking FARXIGA and contact your healthcare provider or go to the nearest hospital emergency room right away.
- have severe kidney problems or are on dialysis.

What should I tell my healthcare provider before taking FARXIGA?
Before you take FARXIGA, tell your healthcare provider if you:

- have type 1 diabetes or have had diabetic ketoacidosis.
- have kidney problems.
- have liver problems.
- have a history of urinary tract infections or problems urinating.
- are going to have surgery.
- are eating less due to illness, surgery or a change in your diet.
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking).
- are pregnant or plan to become pregnant. FARXIGA may harm your unborn baby. If you become pregnant while taking FARXIGA, your healthcare provider may switch you to a different medicine to control your blood sugar. Talk to your healthcare provider about the best way to control your blood sugar if you plan to become pregnant or while you are pregnant.
- are breastfeeding or plan to breastfeed. It is not known if FARXIGA passes into your breast milk. You should not breastfeed if you take FARXIGA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take FARXIGA?

- Take FARXIGA exactly as your healthcare provider tells you to take it.
- Do not change your dose of FARXIGA without talking to your healthcare provider.
- Take FARXIGA by mouth 1 time each day, with or without food.
- When your body is under some types of stress, such as fever, trauma (such as a car accident), infection, or surgery, the amount of diabetes medicine you need may change. Tell your healthcare provider right away if you have any of these conditions and follow your healthcare provider's instructions.
- Stay on your prescribed diet and exercise program while taking FARXIGA.
- FARXIGA will cause your urine to test positive for glucose.
- Your healthcare provider may do certain blood tests before you start FARXIGA and during your treatment.
- Your healthcare provider will check your diabetes with regular blood tests, including your blood sugar levels and your HbA1c.
- Follow your healthcare provider's instructions for treating low blood sugar (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose and take the medicine at the next regularly scheduled time. Do not take 2 doses of FARXIGA at the same time.
- If you take too much FARXIGA, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of FARXIGA? FARXIGA may cause serious side effects, including:
See **"What is the most important information I should know about FARXIGA?"**

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have **type 1 diabetes or type 2 diabetes,** during treatment with FARXIGA. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. **Ketoacidosis can happen with FARXIGA even if your blood sugar is less than 250 mg/dL. Stop taking FARXIGA and call your healthcare provider right away if you get any of the following symptoms:**
  - nausea
  - vomiting
  - stomach area (abdominal) pain
  - tiredness
  - trouble breathing

  If you get any of these symptoms during treatment with FARXIGA, if possible check for ketones in your urine, even if your blood sugar is less than 250 mg/dL**.**
- **Kidney problems.** Sudden kidney injury has happened to people taking FARXIGA. Call your healthcare provider right away if you:
  - reduce the amount of food or liquid you drink, for example, if you are sick and cannot eat or
  - you start to lose liquids from your body, for example, from vomiting, diarrhea or being in the sun too long.
- **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking FARXIGA. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.

- **Low blood sugar (hypoglycemia).** If you take FARXIGA with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take FARXIGA. Signs and symptoms of low blood sugar may include:
  - headache
  - weakness
  - confusion
  - shaking or feeling jittery
  - drowsiness
  - dizziness
  - irritability
  - sweating
  - hunger
  - fast heartbeat
- **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take FARXIGA. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries, and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired, or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around the anus and genitals:**
  - pain or tenderness
  - swelling
  - redness of skin (erythema)

The most common side effects of FARXIGA include:

- vaginal yeast infections and yeast infections of the penis
- stuffy or runny nose and sore throat
- changes in urination, including urgent need to urinate more often, in larger amounts, or at night

These are not all the possible side effects of FARXIGA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store FARXIGA?

Store FARXIGA at room temperature between 68°F to 77°F (20°C to 25°C).

General information about the safe and effective use of FARXIGA

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use FARXIGA for a condition for which it is not prescribed. Do not give FARXIGA to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about FARXIGA. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about FARXIGA that is written for healthcare professionals.

For more information about FARXIGA, go to www.farxiga.com or call 1-800-236-9933.

What are the ingredients in FARXIGA?

Active ingredient: dapagliflozin.

Inactive ingredients: microcrystalline cellulose, anhydrous lactose, crospovidone, silicon dioxide, and magnesium stearate. The film coating contains: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and yellow iron oxide.

Distributed by: AstraZeneca Pharmaceuticals LP Wilmington, DE 19850

FARXIGA is a registered trademark of the AstraZeneca group of companies.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised 10/2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

CROSS DISCIPLINE TEAM LEADER REVIEW

Division Summary Memo for Regulatory Action and CDTL review

Date	
From	Patrick Archdeacon, MD Acting Associate Director for Therapeutics Division of Metabolism and Endocrinology Products
NDA # / Sequence #:	NDA 202293 S-018 NDA 205649 S-011
Applicant	Astra Zeneca
Date of Submission Receipt	December 18, 2018
PDUFA Goal Date	October 18, 2019
Proprietary Name / Established (USAN) names	Dapagliflozin Dapagliflozin and metformin HCL extended-release
Trade names	Farxiga, Xigduo XR
Dosage forms / Strength	Tablets
	Farxiga: 5 mg and 10 mg; Xigduo XR 2.5/1000 mg, 5/500 mg, 5/1000 mg, 10/500 mg, 10/1000 mg
Recommended Action	Approval and Fulfillment of PMR 2121-5 and PMR 2121-6
New Recommended Indication(s)/Populations(s)	To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors

1. Introduction

This document serves as the 'Summary Basis for Regulatory Action' memo for sNDAs seeking to add information to the Prescribing Information (PI) for Farxiga (dapaglifozin; NDA 202293) and Xigduo XR (dapaglifozin and metformin HCl extended-release; NDA 205649) based on the results of the DECLARE trial. On the basis of the results of Study D1694C0001, Dapagliflozin Effect on Cardiovascular Events (DECLARE), the Applicant proposed to add (b) (4) new indications [one related to heart failure hospitalization, (b) (4) and to discharge two post-marketing requirements [PMR 2121-5 (to assess cardiovascular risk) and PMR 2121-6 (to assess risk of bladder cancer)].

DECLARE was conducted primarily to fulfill PMR 2121-5: it is a randomized, double-blind, placebo-controlled trial evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2D). Its primary objective was to exclude a 30% increase in the risk of non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death observed with dapaglifloxin compared with that observed with placebo. The study also evaluated the effects on liver toxicity, bone fractures, nephrotoxicity, breast and bladder cancer, and other adverse events of special interest (AESI).

During the conduct of DECLARE, data from an outcome trial of another product suggested that SGLT-2 inhibitors (the drug class to which dapagliflozin is a member) may have clinical effects related to heart failure and nephropathy. For that reason, the DECLARE protocol and statistical analysis plan (SAP) were amended to include hospitalization for heart failure and a composite renal endpoint in the formal hierarchical analysis.

As detailed below, the FDA review team concluded that the clinical data submitted suffice to fulfill PMR 2121-5 and PMR 2121-6 and to add a new indication to Farxiga and Xigduo XR for reducing the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors. (b) (4)

This memo references the following documents/sources:

Subject	Author	Date
Clinical	Michelle Carey	10/15/2019
Division of Cardiovascular and Renal Products Clinical Consult	Kim Smith	10/15/2019
Statistics (DB II)	Yun Wang	10/1/2019
Safety Statistics (DB VII)	Changming Xia	9/6/2019

Patient Labeling Team	Nyedra Booker, Samantha Bryant	10/4/2019
Office of Prescription Drug Promotion (OPDP)	Samantha Bryant	10/3/2019
Division of Medication Error Prevention and Analysis (DMEPA)	Ariane Conrad	6/12/2019
Office of Study Integrity and Surveillance (OSIS)	Cynthia Kleppinger	8/30/2019

2. Background

Dapagliflozin was approved under the trade name Farxiga on January 8, 2014 as an adjunct to diet and exercise to improve glycemic control in adults with T2D. It is administered as an oral tablet at a dose of 5 mg or 10 mg once daily. The mechanism of dapagliflozin is inhibition of sodium-glucose transport protein 2 (SGLT-2), thereby preventing reabsorption of glucose by the kidney and lowering blood glucose. Dapagliflozin has also been approved as a component of Xigduo XR, Qtern, and Qternmet. Xigduo XR (dapagliflozin and metformin extended release) is a fixed dose combination product (FDCP) approved on October 29, 2014 under NDA 205649. Two other FDCPs contain dapagliflozin have been approved: Qtern (dapagliflozin and saxgliptin, approved February 27, 2017 under NDA 209091) and Qternmet XR (dapagliflozin, saxagliptin, and metformin, approve May 2, 2019 under NDA 210874). The supplemental NDA submitted to NDA 202293 (Farxiga) was also submitted to NDA 205649 (Xigduo XR), but not to NDA 209091 (Qtern) or NDA 210874 (Qternmet).

In December 2008, FDA issued a Guidance for Industry[1] on "Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes." In this guidance, FDA indicated that the development programs of new type 2 antidiabetic therapies should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. Specifically, the guidance stated that, prior to approval, sponsors should demonstrate that the estimated risk ratio of important cardiovascular events occurring with the investigation agent compared to placebo is less than 1.8 and that, post-market, sponsors should demonstrate that the estimated risk ratio is less than 1.3.

In keeping with this 2008 Guidance, FDA issued PMR 2121-5 at the time of approval of NDA 202293: PMR 2121-5 required a "randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapaglifozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonephritis/urosepsis,

[1] https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf

serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function."

Due to an imbalance in bladder cancer events not favoring dapagliflozin (nine cases observed in dapagliflozin-treated subjects versus one case observed in comparator-treated subjects) in the dapagliflozin development program, FDA also issued PMR 2121-6 at the time of approval of NDA 202293: PMR 2121-6 required that "to assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%."

On December 23, 2015, the Applicant submitted a protocol amendment to change the statistical testing hierarchy of DECLARE (b) (4) The new SAP specified that if DECLARE established that dapagliflozin were non-inferior to placebo with regard to MACE, the next step in the testing hierarchy would be to determine whether dapagliflozin is superior to placebo in reducing the incidence of two co-primary endpoints: MACE and a composite of hospitalization for heart failure or CV death. If both of these co-primary endpoints were met, the next step in the testing hierarchy would be to determine whether dapagliflozin is superior to placebo in reducing the incidence of a composite renal endpoint.

DECLARE began its enrollment of patients on April 25, 2013 and completed its last subject study visit on September 11, 2018. Study data were unblinded on September 17, 2018. In general, based on inspection of six clinical sites, the inspectional findings of FDA's Offiec of Scientific Investigations support the validity of the data reported by the Applicant (see the Clinical Inspection Summary of Dr. Cynthia Kleppinger for additional details).

3. CMC

The submission does not contain new CMC data.

4. Nonclinical Pharmacology/Toxicology

The submission does not contain new nonclinical pharmacology/toxicology data.

5. Clinical Pharmacology/Biopharmaceutics

The submission does not contain new clinical pharmacology data.

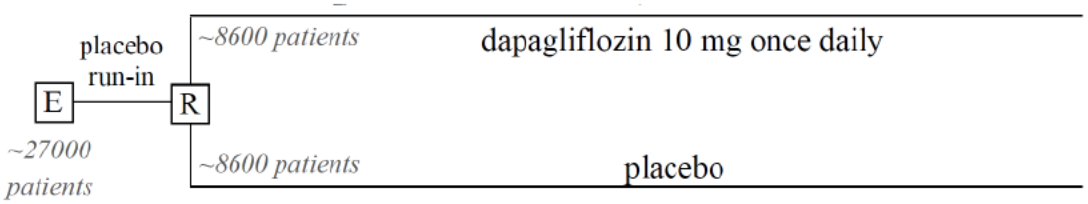
6. Clinical/Statistical- Efficacy

Dr. Changming (Sherman) Xia, the statistical reviewer from the Office of Biostatistics, Division of Biometrics VII (DBVII), evaluated the MACE and bladder cancer results from DECLARE from the point of view of safety. Dr. Xia also considered whether the data from DECLARE support a signal of an association between amputations and SLGT-2 exposure. Dr. Yun Wang, the statistical reviewer from the Office of Biostatistics, Division of Biometrics (DBII), evaluated the composite heart failure endpoint and the composite renal endpoint results from DECLARE from the point of view of efficacy. Dr. Michelle Carey, the clinical reviewer from the Office of New Drugs, Division of Metabolism and Endocrinology Products (DMEP) evaluated the data from DECLARE with regard to both safety and efficacy. Dr. Kim Smith, the clinical consultant from the Office of New Drugs, Division of Cardiovascular and Renal Products, evaluated the data from DECLARE with regard to the renal composite endpoint (b) (4)

Please see the reviews of Drs. Xia, Wang, Carey, and Smith for additional details. Please also see Section 7: Safety for a discussion of the overall safety results of DECLARE (including the elements of PMR 2121-5 beyond MACE and bladder cancer).

DECLARE was a multi-center, randomized, double-blind, parallel group placebo-controlled trial that compared the effect of dapagliflozin with placebo as an add-on therapy to standard of care treatment in patients with type 2 diabetes. The primary outcome studied was cardiovascular outcomes: DECLARE was designed as an event-driven trial that was to continue until at least 1390 positively adjudicated MACE events accrued; the number of MACE events was selected to give 85% power to demonstrate the superiority of dapagliflozin to placebo, assuming a true HR of 0.85 (see Figure 1).

Figure 1: Trial Schematic, DECLARE



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Source: Applicant Clinical Study Report for DECLARE

A version of the SAP (SAP Edition 6.0) submitted to the FDA on December 17, 2015 elevated the composite of heart failure hospitalization or CV death as a dual primary efficacy endpoint along with MACE and added a renal composite endpoint as first secondary endpoint in the testing hierarchy (see Table 1). DECLARE was analyzed according to the analysis sets described in Table 2.

Table 1: Confirmatory Testing Procedures Using One-sided Alpha

H1: Non-inferiority for MACE (α=0.0231)[a]	
The α splits into independent testing of the primary composites in parallel:	
H02: Superiority for MACE (α=50% of primary α)[c]	H03: Superiority for hospitalisation for heart failure or CV death (α=50% of primary α)[c]
H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death[b]	
H05: Superiority for all-cause mortality[d]	

[a] At the interim analyses, the α for superiority was replaced by 0.000095 (first interim) and 0.00614 (second interim), and no testing for non-inferiority was performed.

[b] With the exception of all-cause mortality, secondary endpoints were only tested once. The α was controlled for the overall Type I error across the primary and secondary variables and across the interims and final analysis.

[c] The α was 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalisation for heart failure or CV death.

[d] All-cause mortality was assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it was tested second following MACE. If the study had been stopped following an interim analysis, all-cause mortality would have remained as the 2nd endpoint following the test for superiority of MACE. Because the study ran to completion, all-cause mortality was tested as presented in this table.

CV Cardiovascular; eGFR Estimated glomerular filtration rate; ESRD End-stage renal disease; MACE Major adverse cardiovascular events

Source: Applicant Clinical Study Report for DECLARE

Table 2: Analysis Sets Used for Primary and Sensitivity Analysese for Efficacy and Safety

Variable	Primarily analysis	Sensitivity analysis
Primary variables	FAS	On-Treatment set
Secondary variables	FAS	On-Treatment set
Exploratory Efficacy variables	FAS	On-Treatment set for selected variables
Cancer, Amputations and Fractures	Safety analysis set	On-Treatment set
Other Safety variables	On-Treatment set	Safety analysis set

Source: SAP for DECLARE

The study was conducted at 882 clinical sites across 33 countries. The design called for the enrollment patients with T2D and with either a documented history of CV disease or two or more CV risk factors, randomized to the dapagliflozin treatment group or the placebo treatment group in a 1:1 ratio (see Dr. Carey's review for details regarding the definitions of

CV disease and CV risk factors, as well as key inclusion and exclusion criteria). A total of 25,698 subjects were enrolled, of which 17,160 were randomized. Of the patients randomized, 98.5% completed the trial (see Table 3). The baseline demographics and baseline history of CV disease in DECLARE are shown in Table 4.

Table 3: Patient Disposition

Disposition Event	Dapagliflozin 10mg n (%)	Placebo n (%)
Randomized	8582 (100.0)	8578 (100.0)
Completed trial	8473 (98.7)	8433 (98.3)
Discontinued from trial	109 (1.3)	145 (1.7)
Adverse event	0	0
Withdrawal of consent	97 (1.1)	127 (1.5)
Lost to follow-up	12 (0.1)	18 (0.2)
Discontinued treatment	1807 (21.1)	2144 (25.0)
Adverse event	671 (7.8)	548 (6.4)
Subject decision	825 (9.6)	1086 (12.7)
Study-specific discontinuation criteria	38 (0.4)	60 (0.7)
Liver enzyme elevation	6 (0.06)	8 (0.09)
Creatine clearance <30 mL/min	10 (0.1)	17 (0.2)
Bladder cancer	22 (0.3)	35 (0.4)
Pregnancy	0	0
Other Reason	273 (3.2)	450 (5.2)
Final Vital Status Available	8534 (99.4)	8514 (99.3)
Alive	8005 (93.3)	7944 (92.6)
Dead	529 (6.2)	570 (6.6)

Source: FDA Clinical Review

Table 4: Baseline Demographic Characteristics (FAS population)

Demographic Parameter	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Sex		
Male	5411 (63.1)	5327 (62.1)
Female	3171 (36.9)	3251 (37.9)
Age, mean (years ± SD)	63.9 ± 6.8	64.0 ± 6.8
Median (years)	64	64
Min, max (years)	40, 92	40, 88
Age Group		
< 50 years	202 (2.4)	220 (2.7)
< 65 years	4631 (54.0)	4622 (53.9)
≥ 65 years	3951 (46.0)	3956 (46.1)
≥ 75 years	538 (6.3)	558 (6.5)
Race		
White	6843 (79.7)	6810 (79.4)
Black or African American	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
American Indian or Alaska Native	52 (0.6)	52 (0.6)
Native Hawaiian or Other Pacific Islander	9 (0.1)	13 (0.2)
Other	235 (2.7)	240 (2.8)
Ethnicity		
Hispanic or Latino	1298 (15.1)	1270 (14.8)
Not Hispanic or Latino	7284 (84.9)	7308 (85.2)
Region		
North America	2737 (31.9)	2731 (31.8)
United States	1938 (22.6)	1947 (22.7)
Canada	799 (9.3)	784 (9.1)
Latin America	946 (11.0)	931 (10.9)
Europe	3390 (39.5)	3390 (39.5)
Eastern Europe	2370 (27.6)	2324 (27.1)
Western Europe	1020 (11.9)	1066 (12.4)
Asia/Pacific	882 (10.3)	890 (10.4)
Middle East/Central Asia	185 (2.2)	208 (2.4)
Africa	231 (2.7)	225 (2.6)
Australia	211 (2.5)	203 (2.4)

Source: FDA Clinical Review

Table 5: Baseline History of Cardiovascular Disease (FAS population)

Baseline Cardiovascular Disease	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Established CV disease	3474 (40.5)	3500 (40.8)
Ischemic heart disease	2824 (32.9)	2834 (33.0)
Cerebrovascular disease	653 (7.6)	648 (7.6)
Peripheral arterial disease	522 (6.1)	503 (5.9)
1 CV disease	2992 (34.9)	3064 (35.7)
2 CV diseases	439 (5.1)	387 (4.5)
3 CV diseases	43 (0.5)	49 (0.6)
Multiple risk factors, but without established CV disease*	5096 (59.3)	5063 (59.0)
Dyslipidemia	3738 (43.6)	3778 (44.0)
Hypertension	4686 (54.6)	4588 (53.5)
Current tobacco use	1277 (14.9)	1221 (14.2)
Left ventricular ejection fraction at baseline reported	2579 (30.1)	2623 (30.6)
<30% or severe dysfunction	61 (0.7)	65 (0.8)
30 to <45% or moderate dysfunction	257 (3.0)	288 (3.4)
45 to <55% or mild dysfunction	503 (5.9)	517 (6.0)
≥55% or normal	1758 (20.5)	1753 (20.4)

Source: FDA Clinical Review

Dr. Xia, Dr. Yang, and Dr. Carey all concluded (and I concur) that the data demonstrate the non-inferiority of dapagliflozin to placebo with regard to the primary MACE endpoint. As shown in Table 6, the estimated hazard ratio (HR) for MACE is 0.933 with a 95.38% CI of [0.843, 1.043]. Because the upper bound of the CI is less than 1.3, Dr. Xia and Dr. Carey concluded (and I concur) that DECLARE excludes a 30% increased risk of MACE, consistent with current FDA guidance and fulfilling PMR 2121-5. Because the upper bound of the CI is greater than 1, Dr. Xia, Dr. Yang, and Dr. Carey all concluded (and I concur) that DECLARE did not demonstrate a benefit of dapagliflozin with regard to MACE. The results for each of the individual components of the MACE composite endpoint were supportive of the overall conclusion (see again Table 6).

Table 6: Analysis of MACE in DECLARE (Full Analysis Set *)

	Dapagliflozin N = 8582 Events (%)	Placebo N = 8578 Events (%)	Dapagliflozin vs Placebo Hazard Ratio (95% CI)	P value°
MACE	756(8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.1723
CV-death	166 (1.9)	167 (1.9)		
Non-fatal MI	377 (4.4)	428 (5.0)		
Non-fatal Stroke	213 (2.5)	208 (2.4)		
MACE*	824 (9.6)	878 (10.2)	0.93 (0.85,1.02)	0.1353
All MI	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.0801
All Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.9156
Non-CV death	211 (2.5)	238 (2.8)	0.88 (0.74, 1.06)	0.1926
MACE-free survival§	1015 (11.8)	1090 (12.7)	0.92 (0.85,1.01)	0.0676

MACE: major adverse cardiovascular event; CV: cardiovascular; MI: Myocardial infarctions
* Undetermined deaths were included as CV deaths
§ MACE-free survival: Time to first event among adjudicated all-cause mortality, non-fatal MI, or non-fatal stroke.
°P value (two-sided) is based on the Wald statistic for superiority of Hazard Ratio. P-value for testing non-inferiority of dapagliflozin vs. placebo on MACE is 0.0003, where the non-inferiority margin is 1.3.

Source: FDA Statistical Review

Dr. Xia and Dr. Carey also both concluded (and I concur) that DECLARE collected a sufficient number of bladder cancer events to exclude a two-fold increase in the risk of bladder cancer at the nominal (unadjusted) 2-sided alpha level of 5% (see Table 7). The observed HR and nominal 95% CI was 0.572 [0.353, 0.927] for bladder cancer. Because the upper bound of CI was reassuring and because of the number of events of bladder cancer observed, Dr. Xia and Dr. Carey concluded (and I concur) that DECLARE also fulfilled PMR 2121-6. Due to an increased incidence of amputation observed in association with a different SGLT-2 inhibitor in another outcome trial, Dr. Xia also evaluated the DECLARE data with regard to amputation. The observed HR and nominal 95% CI was 1.062 [0.821, 1.373]. Based on these data, Dr. Xia concluded that DECLARE did not suggest an increased risk associated with dapagliflozin for amputation (see again Table 7).

Table 7: Analysis of Bladder Cancer and Amputation in DECLARE (Safety Analysis Set *)

	Dapagliflozin N = 8574	Placebo N = 8569	HR (Dapa to Pbo)^ [95% CI‡]
Bladder cancer (IR / 100 PY) †	26 (0.08)	45 (0.13)	0.572 [0.353, 0.927]
Amputation (IR / 100 PY) †	120 (0.36)	113 (0.34)	1.062 [0.821, 1.373]

* Safety Analysis Set included subjects who were randomized and treated. Subjects were analyzed according to the actual treatment they received.
^ HR: Hazard Ratio of dapagliflozin to placebo.
† IR: Incidence Rate; PY: Person Year.
‡ CI: Confidence Interval (nominal).

Source: FDA Safety Statistical Review

Dr. Wang and Dr. Carey both concluded (and I concur) that the data from DECLARE demonstrate the superiority of dapagliflozin to placebo with regard to the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors: the observed HR was 0.83 (95% CI: 0.73 to 0.95) (see Table 8). Both Dr. Wang and Dr. Carey noted that the difference between groups for the composite endpoint was driven almost entirely by hospitalization for heart failure [HR 0.73 (95% CI: 0.61 to 0.88)], whereas the results for CV death showed no difference [HR 0.98 (95% CI: 0.82 to 1.17)]. For that reason, both Dr. Wang and Dr. Carey recommended approval of an indication to reduce the risk of heart failure hospitalization, (b) (4)

Table 8: First Occurrence of Hospitalization for Heart Failure Or CV Death (FAS population)

Efficacy Endpoints	Dapagliflozin 10mg N=8582 Events (%)	Placebo N=8578 Events (%)	Hazard Ratio	p-value*
Composite endpoint				
Hospitalization for Heart Failure or CV death	417 (4.7%)	496 (5.8%)	0.83 (0.73, 0.95)	0.0052
Components				
Hospitalization for Heart Failure	212 (2.5%)	286 (3.3%)	0.73 (0.61, 0.88)	0.0006
CV Death	245 (2.9%)	249 (2.9%)	0.98 (0.82, 1.17)	0.8306
Other endpoints				
All-cause mortality	529 (6.2%)	570 (6.6%)	0.93 (0.82, 1.04)	0.198
Hospitalization for Heart Failure or death from congestive heart failure (1)	229 (2.7%)	304 (3.5%)	0.75 (0.63, 0.88)	0.007

Hazard ratios and CIs are calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk group and haematuria with treatment as a model term.
*Nominal P-value is calculated based on a stratified log-rank test.
(1) derived by the reviewer

Source: FDA Statistical Review

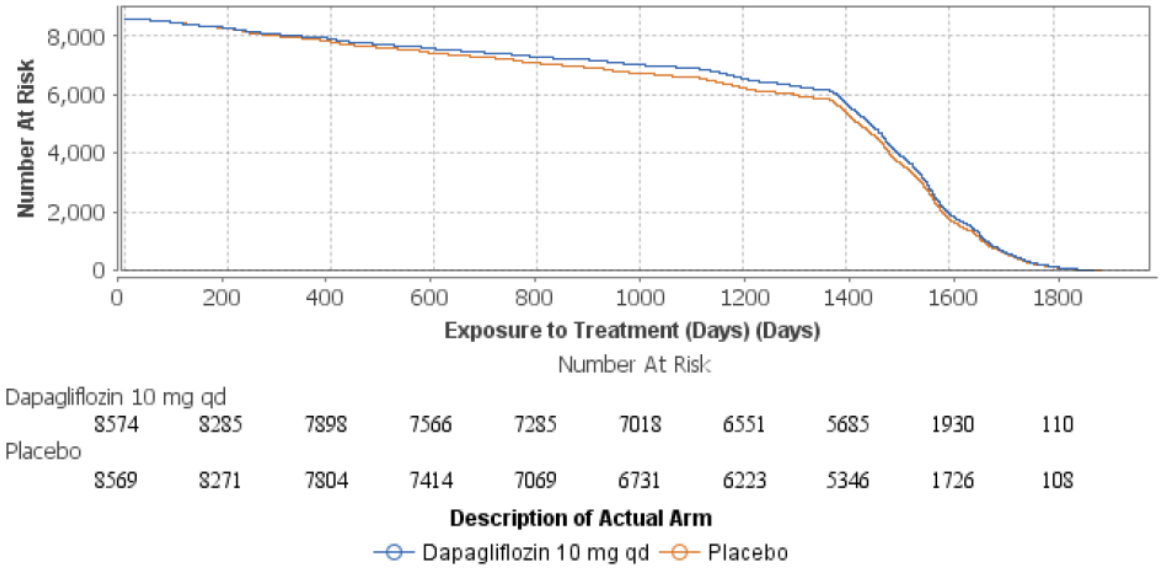
(b) (4)

(b) (4)

7. Safety

In addition to analyzing the efficacy endpoints of MACE, heart failure or CV death, and the renal composite endpoint, Dr. Carey completed a review of all the safety data collected in DECLARE. A total of 17,143 patients received study drug. Duration of exposure ranged from 0 to 62 months, with a total of 30,623 patient-years of treatment exposure in the dapagliflozin arm and 29,749 patient-years of exposure in the placebo arm (see also Figure 2). Dr. Carey concluded that the safety database and safety results of DECLARE are adequate to fulfill the requirements of PMR 2121-5 and PMR 2121-6. For details on the results of the safety review, please see Dr. Carey's full review. A brief summary of the topline results is included below.

Figure 2: Exposure Duration by Treatment Arm (Safety Population)



Source: FDA Clinical Review

Deaths

A total of 1,098 patients in the safety population died. The deaths were numerically balanced across treatment groups (529 deaths in the dapagliflozin arm versus 569 deaths in the placebo arm).

Serious Adverse Events (SAE)

A total of 3,205 (37.4%) of patients in the dapagliflozin arm and 3,418 (39.9%) of patients in the placebo arm experienced at least one SAE during the trial (see Table 10).

Table 10: Frequency of Patients with SAEs by SOC and Treatment Arm

System Organ Class	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Cardiac disorders	1045 (12.2)	1108 (12.9)
Infections and infestations	610 (7.1)	692 (8.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	484 (5.6)	473 (5.5)
Nervous system disorders	430 (5.0)	412 (4.8)
Injury, poisoning and procedural complications	295 (3.4)	275 (3.2)
Vascular disorders	268 (3.1)	254 (3.0)
Musculoskeletal and connective tissue disorders	234 (2.7)	236 (2.8)
General disorders and administration site conditions	222 (2.6)	225 (2.6)
Gastrointestinal disorders	214 (2.5)	224 (2.6)
Metabolism and nutrition disorders	189 (2.2)	258 (3.0)
Respiratory, thoracic and mediastinal disorders	180 (2.1)	232 (2.7)
Renal and urinary disorders	144 (1.7)	225 (2.6)
Hepatobiliary disorders	87 (1.0)	110 (1.3)
Skin and subcutaneous tissue disorders	70 (0.8)	62 (0.7)
Reproductive system and breast disorders	66 (0.8)	65 (0.8)
Eye disorders	50 (0.6)	56 (0.7)
Blood and lymphatic system disorders	47 (0.5)	49 (0.6)
Psychiatric disorders	28 (0.3)	46 (0.5)
Investigations	26 (0.3)	25 (0.3)
Ear and labyrinth disorders	20 (0.2)	29 (0.3)
Endocrine disorders	10 (0.1)	12 (0.1)
Product issues	10 (0.1)	4 (0.0)
Immune system disorders	8 (0.1)	12 (0.2)
Congenital, familial and genetic disorders	5 (0.1)	1 (0.0)
Surgical and medical procedures	0	0

*Because some patients experienced more than one SAE during the trial, the total number of subjects in each column is greater than the number experiencing at least one SAE stated above

Source: FDA Clinical Review

Dropouts and Discontinuations

Overall, numerically more patients discontinued the study drug due to adverse events in the dapagliflozin arm than the placebo arm (693 vs 592), but numerically fewer patients discontinued the study drug due to an SAE in the dapagliflozin arm than the placebo arm (255 vs 303).

Adverse Event of Special Interest (AESI)

Consistent with the known safety profile of dapagliflozin, more events of diabetic ketoacidosis were observed in the dapagliflozin treatment group than the placebo group. No increased risk of fracture or AKI or hypoglycemia was observed. As previously discussed, fewer events of bladder cancer were observed in the dapagliflozin treatment arm than the placebo arm and no increased risk of amputation was observed.

Table 11: Summary of AESIs in DECLARE

AESI	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Bladder Cancer*	26 (0.3)	45 (0.5)
Breast Cancer*	36 (0.4)	35 (0.4)
Prostate Cancer*†	73 (1.4)	63 (1.2)
Any malignancy*‡	481 (5.6)	486 (5.7)
Hepatic Events*	21 (0.2)	31 (0.4)
Major Hypoglycemic Events	58 (0.7)	83 (1.0)
Fractures‡	457 (5.3)	440 (5.1)
Renal Events	422 (4.9)	526 (6.1)
Symptoms Suggestive of Volume Depletion	213 (2.5)	207 (2.4)
Hypersensitivity Reactions	32 (0.4)	36 (0.4)
Diabetic Ketoacidosis*§	27 (0.3)	12 (0.1)
Amputations‡	123 (1.4)	113 (1.3)
Urinary Tract Infections	127 (1.5)	133 (1.6)
Genital Infections	76 (0.9)	9 (0.1)
Fournier's gangrene‡	1 (0.02)	5 (0.06)

*Adjudicated events
†Percentage of patients calculated based on denominator of male patients only
‡Number of patients based on the SAS population instead of the OT-SAS population, as was prespecified in the protocol. See Table 4 for analysis set definitions.
§Events presented in this table were adjudicated as "definite" or "probable" DKA

Source: FDA Clinical Review

8. Advisory Committee Meeting

No new efficacy or safety issue rose to the level of requiring the input from an advisory panel. Therefore, an advisory committee meeting was *not* convened for this NDA.

9. Pediatrics

The approval of a new indication ("To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors") triggers the Pediatric Research Equity Act (PREA). However, the pediatric study requirement for this application is waived because the necessary studies are impossible or highly impracticable because the disease is rare in children. For a meaningful study to be conducted the population would require a diagnosis of T2D and established cardiovascular disease or multiple cardiovascular risk factors. The number of pediatric patients fitting these criteria is small. A clinical trial for the new indication is therefore not feasible.

10. Labeling

The Applicant proposed (b) (4) new indication statements for Farxiga/dapagliflozin and Xigduo/dapagliflozin+metformin HCl XR:

(b) (4)

As discussed in Section 6, the FDA reviewers determined (and I concur) that the data from DECLARE supports a new indication related to heart failure hospitalization. While the primary endpoint supporting the new indication was a composite combining the first occurrence of heart failure hospitalization (b) (4) the patient population of DECLARE is most reliably described as adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors. For that reason, the FDA reviewers recommend (and I concur) granting an indication "to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors."

(b) (4) I concur with these recommendations.

Based on the bladder cancer events observed in DECLARE (strongly favoring the dapagliflozin treatment group compared to the placebo group), the Warning and Precaution related to bladder cancer was removed from the Farxiga and Xigduo XR labeling. (b) (4) those data supported removal of the Warning and Precaution related to macrovascular outcomes and also the Warning and Precaution related to Increased LDL-C.

The Farxiga and Xigduo Adverse Reactions sections were updated to include DECLARE data related to diabetic ketoacidosis.

The Farxiga and Xigduo Clinical Studies sections were updated to include a description of DECLARE, including the results for the endpoints of MACE, heart failure hospitalization, and heart failure hospitalization or CV death. (b) (4)

(b) (4)

[redacted]

11. Recommendations

- Recommended Regulatory Action

Approval: sNDA 202293/S-018 (Farxiga/dapagliflozin) and sNDA 205649/S-011 (Xigduo XR/dapagliflozin and metformin HCl extended-release) should be approved to support a new indication "to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors."

Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

Recommendation for other Postmarketing Requirements and Commitments

None

The data contained in the sNDA 202293/S-018 fulfills post-marketing requirements 2121-5 and 2121-6

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/s/

PATRICK ARCHDEACON
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

MEDICAL REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Date: October 15, 2019
Drug: Dapagliflozin
NDAs: 202293 (IND 68652)
Applicant: AstraZeneca
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Deputy Director
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Rich Whitehead, Regulatory Project Manager, Division of Metabolism and Endocrinology Products
Subject: Renal findings in the DECLARE trial

Background

Dapagliflozin is a sodium glucose co-transporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). As a post-marketing safety requirement, the applicant conducted a cardiovascular outcomes trial titled "Dapagliflozin Effect on CardiovascuLAR Events (DECLARE)," a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes (Protocol D1693C00001).

On December 18, 2018, AstraZeneca submitted an efficacy supplement to the Division of Metabolism and Endocrinology Products (DMEP) containing (b) (4) new indications for dapagliflozin in adults with T2DM based on the results of the DECLARE trial:

(b) (4)

In addition, AstraZeneca has proposed changes to Sections 5 and 6 related to the risk of acute kidney injury (AKI). DMEP has requested input from the Division of Cardiovascular Products (DCRP) on the renal-related labeling changes.

Materials Reviewed

1. Clinical Study Report for DECLARE
2. Protocol Amendment 5 dated September 25, 2016
3. Statistical Analysis Plan and amendments
4. Clinical Events Committee Charter and amendments
5. DCRP consult dated October 15, 2015 and Advice/Information Request letter dated March 22, 2016
6. Select narratives and laboratory data for patients who experienced renal events
7. Meeting minutes dated June 30, 2016 under IND 130647 for dapagliflozin for the treatment of chronic kidney disease

Overview of Study Design

DECLARE was a randomized, double-blind, event-driven CV safety trial conducted between April 25, 2013 and September 11, 2018. In total, 17,160 patients with T2DM and CV disease or at least two risk factors for CV disease were randomized 1:1 to dapagliflozin 10 mg daily (n=8582) or placebo (n=8578) at 882 sites in 33 countries.

The primary objective was to determine the effect of dapagliflozin relative to placebo on CV outcomes when added to current background therapy in patients with T2DM with either established CV disease or at least two CV risk factors.

The secondary renal objective was to determine whether treatment with dapagliflozin compared with placebo, when added to current background therapy in patients with T2DM with either established CV disease or at least two CV risk factors in addition to T2DM, would result in a reduction of a renal composite endpoint: confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death.

Reviewer's comments:

1. *The secondary renal objective and associated secondary endpoint were added with Protocol Amendment 5 dated September 25, 2016. The amendment and an associated amendment to the Statistical Analysis Plan (Edition 6) were submitted to the IND on October 7, 2016. DCRP provided input on the definition of the renal endpoint before the amendment was issued (see consult dated October 15, 2015 and Advice/Information Request dated March 22, 2016).*
2. (b) (4)

Renal-Related Eligibility Criteria

The eligibility criteria pertinent to the renal findings were:

Key Inclusion Criteria

1. Female or male aged ≥ 40 years
2. Diagnosed with T2DM
3. High Risk for CV event defined as having either established CV disease (defined in protocol) or no known CV disease but at least two risk factors in addition to T2DM, defined as age > 55 years in men and > 60 in women AND one or more of the following:
    a. Dyslipidemia
    b. Hypertension
    c. Current tobacco use

Key Exclusion Criteria

1. CrCl < 60 ml/min (Cockcroft-Gault)
2. Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the investigator.

Reviewer's comment: The eligibility criteria were not designed to identify subjects with pre-existing diabetic nephropathy or chronic kidney disease (i.e., subjects were not required to have reduced eGFR or albuminuria at baseline). Moreover, subjects with a CrCl <60 mL/min, which would be considered moderate to severe disease, were excluded. As noted above, the applicant initiated a separate study under IND 130647 to evaluate the efficacy of dapagliflozin in patients with lower eGFRs (≥25 and ≤75 mL/min/1.73m^2) and albuminuria.

Overview of Renal-Related Study Procedures

Study Assessments

Subjects returned to the study site every six months and were contacted by phone at the mid-point between visits. Subjects who prematurely discontinued treatment were to have an End of Treatment visit but continue in the study for follow-up.

Subjects had central laboratory measurements of serum creatinine, urinalysis including microscopy, and urine albumin-to-creatinine ratio (UACR) at randomization, months 6 and 12, annually thereafter, at the end of treatment, and at the end of study. Per Protocol Amendment 5, a central laboratory serum creatinine measurement was to be obtained at the earliest possible time after detection of a doubling of serum creatinine, a serum creatinine >6 mg/dL, a decrease in eGFR of ≥ 30% to an eGFR <60 mL/min/1.73 m^2, or an eGFR <15 mL/min/1.73 m^2 by central or local laboratory testing. If confirmed, a repeat measure was to be obtained after at least four weeks.

Discontinuation of Study Drug
Patient's with a confirmed Cockcroft-Gault creatinine clearance below 30 ml/min were to discontinue study drug.

Concomitant Therapy
Study drug was to be given on top of current therapy, and patients were to be treated for their T2DM to meet glycemic goals as recommended by treatment guidelines and best practices. Patients were also to be treated according to regional standards of care "for CV risk factors (e.g., hypertension and dyslipidemia)."

Reviewer's comment: The protocol did not specify that ACE inhibitors or ARBs were to be used for subjects with diabetic nephropathy or those who developed diabetic nephropathy during the trial.

Endpoints
There were two primary endpoints:
- a composite of CV death, myocardial infarction (MI), and ischemic stroke (MACE)
- a composite of hospitalization for heart failure (HHF) and CV death.

The first secondary endpoint was a composite of a confirmed, sustained ≥ 40% decrease in eGFR to an eGFR <60 mL/min/1.73 m^2 (CKD-EPI), ESRD (dialysis ≥ 90 days or kidney transplantation, a confirmed sustained eGFR <15 mL/min/1.73 m^2), and/or renal or CV death. Baseline was defined as the last assessment on or before the date of randomization.

Deaths were adjudicated, and one category on the list of suggested non-CV causes of death was "renal." Renal death was first defined in Version 2.0 of the Clinical Events Committee charter dated June 2, 2017 as "death occurring after a patient refuses or a physician withholds renal replacement therapy (i.e., initiation of chronic dialysis or renal transplantation) or in cases where dialysis is unavailable. Deaths due to another primary process and/or when another cause is adjudicated (e.g., sepsis, end-stage heart failure, malignancy) will be adjudicated as death resulting from the primary process and will not be considered renal death."

Decline in eGFR and ESRD events were not adjudicated.

Reviewer's comment: It is not clear from the protocol how potential events based on declines in eGFR or ESRD were identified (e.g., investigator reporting, evaluation of local/central laboratory data, etc.).

(b) (4)

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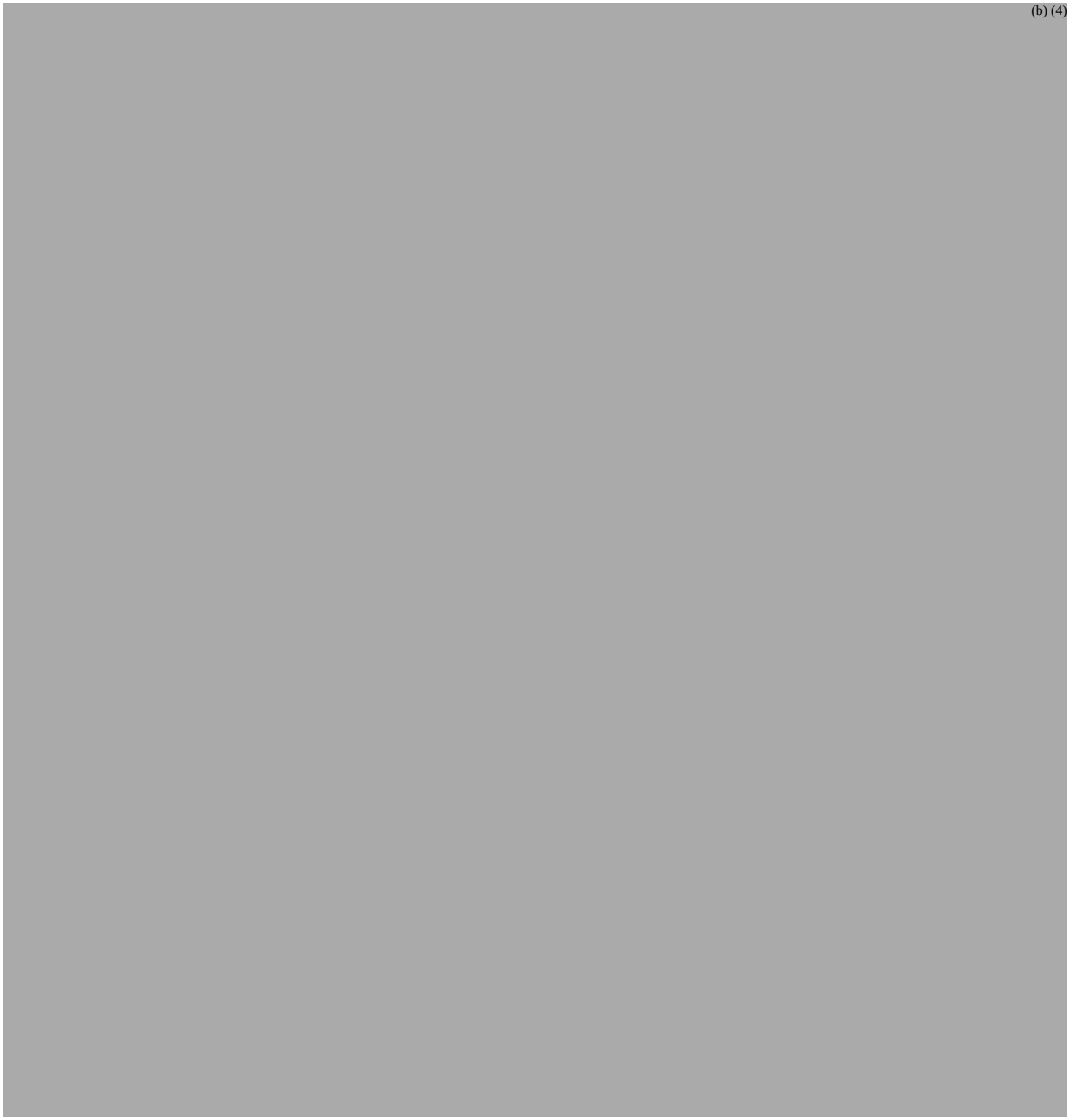
(b) (4)



4. The Applicant has proposed changes to Sections 5.3 and 6 of the label removing or changing class labeling language describing the risks of acute kidney injury and impairment of renal function. Do you conclude that the submitted data from DECLARE support removal or changing of this language from the label?

DCRP Response to Question 4: We refer DMEP to the revised label for canagliflozin (approved on September 27, 2019) for text related to these issues, some of which we believe is also applicable to dapagliflozin.

Appendix A: Review of Select ESRD Events

(b) (6) – 65-year-old man randomized to dapagliflozin with a history of T2DM since 1990, "nephropathy" with an eGFR 48 mL/min/1.73 m^2, peripheral arterial disease, HTN, atrial fibrillation/flutter, and dyslipidemia. By Day 1452, his eGFR had declined to 17 mL/min/1.73 m^2. The patient was diagnosed with ESRD on Day 1480 after presenting to the hospital with hypoxia and shortness of breath. A chest x-ray showed pulmonary edema. He started hemodialysis on Day 148 and was discharged five days later with a "final diagnosis of acute pulmonary congestion secondary to ACS-NSTEMI coronary artery disease status post angioplasty end stage renal disease secondary to DM." The event was reported as not recovered/not resolved but no additional documents were provided.

(b) (6) – 52-year-old woman randomized to placebo with a history of T2DM since 2000, retinopathy, neuropathy, ischemic stroke, peripheral arterial disease, hypertension, and dyslipidemia. Her eGFR was 80 mL/min/1.73 m^2 on Day 1, which had declined to 17 mL/min/1.73 m^2 by Day 1278. On Day 1429, the patient was admitted to the hospital for progression of CKD, anasarca, and uremia with >4 grams/day of proteinuria. Hemodialysis was initiated during the hospitalization and "the patient continues with hemodialysis 3 times per week (chronic HD program)."

Reviewer's comment: It is not clear how dialysis was confirmed as ongoing for >90 days for the two cases above.

(b) (6) – 60-year-old man randomized to placebo with a history of T2DM since 1997, coronary artery disease, hypertension, hyperlipidemia, "chronic kidney disease (since 2008)" with an eGFR of 75 mL/min/1.73 m^2 on Day 1 that had declined to 40 mL/min/1.73 m^2 by Day 1085. The patient was admitted on Day 1470 with confusion, severe anemia, diarrhea, and a chronic foot ulcer. He was diagnosed with "progressing acute kidney injury, likely acute tubular necrosis, progressing into end-stage renal disease" and was started on dialysis on 8/17/17. Patient was reported to still be on dialysis on 12/3/2017.

(b) (6) – 67-year-old man randomized to placebo with a history of T2DM since 1980, ischemic stroke, and hypertension with an eGFR of 65 mL/min/1.73 m^2 on Day 1 declining to 11 mL/min/1.73 m^2 by Day 1442. The value was again 11 mL/min/1.73 m^2 on Days 1454 and 1713.

(b) (6) – 60-year-old man randomized to placebo with a history of T2DM since 2000, retinopathy, nephropathy, neuropathy, hypertension, and hyperlipidemia. Kidney function was not reported in the programmed narrative. According to the full analysis dataset, the ESRD event date was Day 442. According to the programmed narrative, the subject was hospitalized from Day 441 to 444 after the "Subject had routine laboratory samples done by nephrologist which showed potassium level of 6.7mmol/l. The nephrologist had the subject go to the Emergency Department for admission to the hospital for treatment. He received calcium gluconate and Kayexalate. Potassium level returned to normal level." There is no mention of dialysis or eGFR values during this hospitalization. As of the next hospitalization on Day 535, the patient was noted to have "kidney disease on hemodialysis."

Reviewer's comment: It is not clear how the date of onset of ESRD was determined for the above case or how the applicant confirmed dialysis was ongoing for >90 days.

<u>Appendix B:</u> Review of Select ≥ 40% Decline in eGFR Events

(b) (6) – 66-year-old man randomized to placebo with the following eGFR values during the trial:

- (b) (6) (Day -63): 74
- (b) (6) (Day 1): 89 **[40% decline: 53.4]**
- (b) (6) (Day 183): 66
- (b) (6) (Day 351): 71
- (b) (6) (Day 638): 75
- (b) (6) (Day 1079): 61
- (b) (6) **(Day 1422): 30**
- (b) (6) **(Day 1436): 29 -- 14 days (from initial detection)**
- (b) (6) **(Day 1462): 35 -- 40 days**

(b) (6) - 63-year-old man randomized to dapagliflozin with the following eGFR values during the trial:

- (b) (6) (Day -63): 55
- (b) (6) (Day 1): 58 **[40% decline: 34.8]**
- (b) (6) (Day 183): 56
- (b) (6) (Day 365): 41
- (b) (6) **(Day 736): 29**
- (b) (6) **(Day 904): 19 – 168 days**
- (b) (6) (Day 909): 62
- (b) (6) (Day 918): 25
- (b) (6) (Day 932): 40
- (b) (6) (Day 1072): 46
- (b) (6) (Day 1266): 55
- (b) (6) (Day 1366): 39

Reviewer's comment: Although the above decline in kidney function was "confirmed" with a consecutive value after 168 days, kidney function appears to have later recovered.

(b) (6) - 70-year-old man randomized to placebo with the following eGFR values during the trial:

- (b) (6) (Day -39): 68
- (b) (6) (Day 1): 64 **[40% decline: 38.4]**
- (b) (6) (Day 189): 57
- (b) (6) (Day 365): 62
- (b) (6) (Day 721): 55
- (b) (6) (Day 1149): 45
- (b) (6) **(Day 1498): 31**
- (b) (6) **(Day 1636): 33 – 138 days**

(b) (6) - 56-year-old man randomized to dapagliflozin with the following eGFR values during the trial:

- (b) (6) (Day -58): 56
- (b) (6) (Day 1): 101 **[40% decline: 60.6]**
- (b) (6) **(Day 198): 55**
- (b) (6) **(Day 364): 57 – 166 days**
- (b) (6) **(Day 724): 57**

(b) (6) **(Day 1088): 52**
(b) (6) **(Day 1486): 50**

Reviewer's comment: The baseline value in this case appears to be spuriously elevated compared with the screening value and values obtained during the trial. It is not clear that the patient had a meaningful decline in kidney function.

(b) (6) - 62-year-old man randomized to placebo with the following eGFR values during the trial:
(b) (6) (Day -57): 93
(b) (6) (Day 1): 89 **[40% decline: 53.4]**
(b) (6) (Day 176): 87
(b) (6) (Day 370): 85
(b) (6) (Day 727): 58
(b) (6) (Day 1070): 55
(b) (6) **(Day 1434): 53**
(b) (6) **(Day 1658): 51 – 224 days**

(b) (6) - 61-year-old man randomized to placebo with the following eGFR values during the trial:
(b) (6) (Day -31): 33
(b) (6) (Day 1): 31 **[40% decline: 18.6]**
(b) (6) **(Day 166): 18**
(b) (6) **(Day 264): 19 – 98 days**
(b) (6) (Day 357): 26
(b) (6) (Day 720): 17
(b) (6) (Day 1082): 24
(b) (6) (Day 1098): 20
(b) (6) (Day 1113): 23

Reviewer's comment: Although the above decline in kidney function was "confirmed" with a consecutive value after 98 days (presumably by rounding the eGFR cutoff for a 40% decline of 18.6 up to 19), kidney function appears to have later recovered.

(b) (6) - 66-year-old woman randomized to dapagliflozin with the following eGFR values during the trial:
(b) (6) (Day -36): 100
(b) (6) (Day 1): 90 **[40% decline: 54.0]**
(b) (6) (Day 189): 102
(b) (6) **(Day 362): 6**
(b) (6) **(Day 380): 32 – 18 days**
(b) (6) **(Day 414): 35 – 34 days**
(b) (6) **(Day 490): 45**
(b) (6) **(Day 554): 49**
(b) (6) **(Day 727): 46**
(b) (6) (Day 1101): 58
(b) (6) (Day 1436): 45

(b) (6) - 64-year-old woman randomized to dapagliflozin with the following eGFR values during the trial:

(b) (6) (Day -29): 90
(b) (6) (Day 1): 83 **[40% decline: 49.8]**
(b) (6) (Day 181): 55
(b) (6) (Day 364): 106
(b) (6) (Day 707): 66
(b) (6) **(Day 1066): 51**
(b) (6) **(Day 1380): 46 – 314 days**

Reviewer's comment: Based on the eGFR values provided in the narrative for this event, it is not clear how this event qualified as a 40% decline in eGFR.

(b) (6) - 64-year-old man randomized to dapagliflozin with the following eGFR values during the trial:

(b) (6) (Day -28): 105
(b) (6) (Day 1): 103 **[40% decline: 61.8]**
(b) (6) (Day 184): 119
(b) (6) (Day 350): 123
(b) (6) (Day 715): 115
(b) (6) (Day 1085): 116
(b) (6) **(Day 1428): 26**
(b) (6) **(Day 1445): 31 – 27 days**
(b) (6) **(Day 1466): 28 – 38 days**
(b) (6) **(Day 1480): 34**

(b) (6) - 74-year-old woman randomized to dapagliflozin with the following eGFR values during the trial:

(b) (6) (Day -35): 70
(b) (6) (Day 1): 62 **[40% decline: 37.2]**
(b) (6) (Day 176): 59
(b) (6) (Day 352): 60
(b) (6) **(Day 772): 33**
(b) (6) **(Day 868): 33 – 96 days**

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CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 202293 Supplement 018 NDA 205649 Supplement 011
Priority or Standard	Standard
Submit Date(s)	December 18, 2018
Received Date(s)	December 18, 2018
PDUFA Goal Date	October 18, 2019
Division/Office	Division of Metabolism and Endocrinology Products (DMEP) Office of Drug Evaluation II (ODE II)
Reviewer Name(s)	Michelle Carey, M.D., M.P.H.
Review Completion Date	September 16, 2019
Established/Proper Name	Dapagliflozin Dapagliflozin and metformin HCl extended-release
Trade Name	Farxiga (dapagliflozin) Xigduo XR (dapagliflozin and metformin HCl extended-release)
Applicant	AstraZeneca Pharmaceuticals, LP
Dosage Form(s)	Tablets
Applicant Proposed Dosing Regimen(s)	Farxiga: 5mg or 10mg once daily Xigduo XR: 2.5/1000 mg, 5/500 mg, 5/1000 mg, 10/500 mg, 10/1000 mg once daily
Applicant Proposed Indication(s)/Population(s)	(b) (6) (b) (6)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	To reduce the risk of hospitalization for heart failure in adults with T2DM and established CV disease or multiple CV risk factors

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement

PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Dapagliflozin (trade name Farxiga) is an antihyperglycemic agent approved for marketing in the United States on January 8, 2014, for the indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus". Dapagliflozin is an orally active, competitive, reversible inhibitor of the sodium-glucose co-transporter 2 (SGLT2). SGLT2 inhibition reduces renal reabsorption of filtered glucose and increases urinary glucose excretion, thereby lowering plasma glucose levels in patients with T2DM via an insulin-independent mechanism. Dapagliflozin is marketed as film-coated tablets containing 5 or 10 mg of dapagliflozin for once daily oral administration.

Dapagliflozin and metformin extended-release (trade name Xigduo XR) is a fixed combination drug product approved on October 29, 2014, for the indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate." The metformin component of the combination product contributes to glycemic control through several mechanisms, including improved glucose tolerance, decreased hepatic glucose production, and enhanced peripheral insulin sensitivity. Xigduo XR is marketed as film-coated tablets for once daily oral administration, containing the following dapagliflozin/metformin XR formulations: 2.5 mg/1000 mg, 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, and 10 mg/1000 mg. The dapagliflozin component is labeled to be started at 5 mg once daily with a maximum daily dose of 10 mg.

Because the efficacy of dapagliflozin depends upon the filtered load of glucose, a function of the estimated glomerular filtration rate (eGFR), at the time of initial approval the Applicant proposed that dapagliflozin should not be taken by patients by patients with moderate renal impairment (defined as eGFR <60 mL/min/1.73m^2 or creatinine clearance [CrCl] <60 mL/min]). The rationale was that the original clinical development program offered insufficient evidence of efficacy at lower eGFR rates. As such, the initial approved labeling stated that dapagliflozin should not be started when eGFR is <60 mL/min/1.73m^2 and should be discontinued if eGFR falls below this rate. On February 22, 2019 efficacy supplements NDA 202293/S-015 and 205649/S-009 were approved based on results of Study D1690C00024 (the DERIVE trial), which demonstrated safety and efficacy of dapagliflozin in patients with moderate renal impairment. The labeling was updated to reflect that dapagliflozin is not recommended when the eGFR is less than 45 mL/min/1.73m^2, and no dose adjustment is needed in patients with an eGFR ≥45 mL/min/1.73m^2. Dapagliflozin use is contraindicated in patients with an eGFR <30 mL/min/1.73m^2, end-stage renal disease (ESRD), or patients on dialysis; the benefit derived from improved glycemic control in these populations is unclear given the drug's mechanism of action.

1.2. Conclusions on the Substantial Evidence of Effectiveness

In these efficacy supplements, the Applicant has proposed (b) (4) new indications for dapagliflozin (b) (4) The Applicant's evidence of clinical effectiveness derives from one large cardiovascular outcome trial, comparing addition of dapagliflozin 10 mg daily or placebo to standard of care diabetes therapy in 17,160 randomized patients with either established CV disease or multiple CV risk factors. Evaluating time-to-first event of hospitalization for heart failure or CV death was a primary efficacy variable prespecified in the statistical analysis plan and controlled for Type 1 error via alpha spending rules. In the studied population, there were significantly fewer patients with adjudicated first events of hospitalization for heart failure or CV death in the dapagliflozin arm compared to placebo (HR 0.83; 95% CI 0.73, 0.95; p=0.005). Adjudicated CV deaths were balanced between treatment arms; therefore, the treatment effect was driven entirely by the hospitalization for heart failure component of the composite endpoint. I conclude that the submitted data demonstrates substantial evidence of effectiveness of dapagliflozin in reducing the risk of hospitalization for heart failure in the studied population compared to placebo when added to standard of care T2DM treatment.

(b) (4)

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

T2DM is a chronic disease characterized by insulin resistance and inadequate insulin secretion, resulting in hyperglycemia and increased risk of serious microvascular (i.e., retinopathy, nephropathy, neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications. T2DM affects approximately 30 million people in the United States, and approximately 84 million people have prediabetes with high risk of progressing to T2DM. Improved glycemic control, as measured by HbA1c reduction, has clearly demonstrable benefits in improving microvascular outcomes and may also improve macrovascular outcomes. However, despite these clear benefits and the availability of a substantial therapeutic armamentarium comprising 12 classes of antihyperglycemic agents, up to half of patients with T2DM fail to achieve recommended glycemic targets.

Heart failure is a common comorbid condition among patients with T2DM and is associated with significant morbidity and mortality, even when ejection fraction is preserved. In addition, the risk of hospitalization for heart failure among patients with T2DM is significantly higher than among healthy controls, even when CV risk factors are well-controlled. Thus, heart failure and T2DM are related conditions that are important public health concerns. While a few antihyperglycemic agents have been shown to reduce the incidence of major adverse cardiovascular outcomes, until recently no antihyperglycemic agents have been approved to reduce the risk of hospitalization for heart failure in patients with T2DM. Canagliflozin, an agent in the SLGT2 inhibitor class, recently received an indication to reduce the risk of hospitalization for heart failure in the more narrow population of adults with T2DM and diabetic nephropathy.

The Dapagliflozin Effect on Cardiovascular Events (DECLARE) trial was designed to fulfill post-marketing requirements to exclude a 30% increase in the risk of major adverse cardiovascular events (MACE) with addition of dapagliflozin compared with placebo to standard of care therapy in adults with T2DM and established CV disease or multiple CV risk factors (PMR 2121-5), and to observe 66 events of bladder cancer to have 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo (PMR 2121-6). The trial also evaluated the time-to-first event of the composite of hospitalization for heart failure or CV death as a primary efficacy variable, and time-to-first event of the composite of sustained eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2, end-stage renal disease (ESRD), renal or CV death as a secondary efficacy variable. Both endpoints were included in the trial Statistical Analysis Plan and controlled for Type 1 error via alpha spending rules. The DECLARE trial demonstrated that dapagliflozin is non-inferior, but not superior, to placebo for the composite MACE endpoint of CV death, MI or stroke, or any of the individual components of MACE (HR 0.93; 95% CI 0.84, 1.03). Dapagliflozin use was also not associated with an increased incidence of bladder cancer compared to placebo (Incidence Rate Ratio 0.58; 95% CI 0.34, 0.95). Therefore, the data from the DECLARE trial are sufficient to discharge PMRs 2121-5 and 2121-6.

Dapagliflozin reduced the incidence of hospitalization for heart failure or CV death in the studied population compared to placebo (HR 0.83; 95% CI 0.73, 0.95; p=0.005); this finding was driven by the hospitalization for heart failure component of the composite, with no difference in the incidence of CV death between treatment arms. (b) (4)

Safety findings from the DECLARE trial were overall reassuring. Key safety findings included imbalances in genital infections and diabetic ketoacidosis. Other adverse events of special interest were either balanced between treatment arms (e.g., amputations, hepatic events, symptoms suggestive of volume depletion, and fractures), or any imbalances observed were favorable to dapagliflozin (e.g., major hypoglycemia, renal events including acute kidney injury, and Fournier's gangrene). As such, the benefit-risk profile of this product from the submitted data supports addition of an indication statement capturing the substantial benefit in reducing the risk of hospitalization for heart failure in the studied population.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• T2DM is a chronic disease 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, neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications • T2DM affects approximately 30 million people in the United States • Improved glycemic control, measured by HbA1c reduction, improves microvascular outcomes and may improve macrovascular outcomes • Despite known benefits of glycemic control, approximately half of	T2DM is a common, serious chronic disease in the United States. Achievement of recommended glycemic targets is an important therapeutic goal in treatment of T2DM, as it reduces the risk of end-organ complications. Heart failure is an important clinical problem in T2DM and treatment modalities that confer clinical benefit for both conditions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with T2DM do not achieve recommended treatment goals • Heart failure is a common comorbid condition among patients with T2DM and is associated with significant morbidity and mortality, even when ejection fraction is preserved[1,2,3] • The risk of hospitalization for heart failure among patients with T2DM is significantly higher than among healthy controls, even when CV risk factors are well-controlled[4]	concomitantly are needed.
Current Treatment Options	• Twelve (12) pharmacologic classes of drugs are approved in the U.S. for the treatment of T2DM (most containing multiple members in the class) and many fixed dose combination products are also available • Professional societies recommend initiating treatment with lifestyle interventions and metformin, followed by other drugs if needed for glycemic control, with choice of additional therapies based on factors such as baseline CV risk, patient preference, and cost • In addition to indications for glycemic control, two SGLT2 inhibitors (canagliflozin and empagliflozin) and one GLP-1 agonist (liraglutide) have indications to reduce the risk of CV events • Canagliflozin also has an indication statement to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death and	A substantial therapeutic armamentarium is available for glycemic management of T2DM. Since some drugs have also received regulatory approval for cardiovascular and/or renal benefits, patient factors such as baseline CV risk and kidney function are important considerations in tailoring therapeutic regimens for individual patients.

[1] Bertoni AG, Hundley WG, Massing MW et al. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care* 2004;27:699-703
[2] Van den Berge JC, Constantinescu AA, Boiten HJ et al. Short- and long-term prognosis of patients with acute heart failure with and without diabetes: changes over the last three decades. *Diabetes Care* 2018;41:143-149
[3] Sandesara PB, O'Neal WT, Kelli HM et al. The prognostic significance of diabetes and microvascular complications in patients with heart failure with preserved ejection fraction. *Diabetes Care* 2018;41:150-155
[4] Rawshani A, Rawshani A, Franzen S, et al. Risk factors, mortality and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633-44

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hospitalization for heart failure in patients with T2DM and diabetic nephropathy with albuminuria	
Benefit	• The DECLARE trial demonstrated that dapagliflozin is non-inferior, but not superior, to placebo for reducing the incidence of the composite endpoint of CV death, MI or stroke (MACE) or any of the individual components of MACE • Dapagliflozin use was not associated with an increased incidence of bladder cancer compared to placebo • Dapagliflozin reduced the incidence of hospitalization for heart failure or CV death in the studied population compared to placebo • Dapagliflozin reduced the incidence of the renal composite endpoint compared with placebo, an effect driven by the sustained confirmed eGFR decrease ≥40% to eGFR <60 mL/min/1.73m^2 component. (b) (4) [redacted]	The DECLARE trial demonstrated non-inferiority, but not superiority, of dapagliflozin to placebo for the MACE endpoint. This trial also demonstrated substantial evidence of benefit of dapagliflozin compared to placebo for the prespecified primary efficacy endpoint of time-to-first event of hospitalization for heart failure or CV death, an effect driven entirely by reduction in the incidence of hospitalization for heart failure. (b) (4) [redacted]
Risk and Risk Management	• Key safety findings in the DECLARE trial included imbalances in genital infections and diabetic ketoacidosis; these adverse events are described in the labeling for the product • Other adverse events of special interest were either balanced between treatment arms (e.g., amputations, hepatic events, symptoms suggestive of volume depletion, and fractures), or any imbalances observed were favorable to dapagliflozin (e.g., major hypoglycemia, renal events including acute kidney injury, and Fournier's gangrene).	The DECLARE trial demonstrated non-inferiority, but not superiority, of dapagliflozin to placebo for the MACE endpoint; it also excluded a relative risk of 2.0 for bladder cancer for dapagliflozin versus placebo. The DECLARE trial therefore fulfills the post-marketing requirements to evaluate dapagliflozin's effect on the incidence of MACE (PMR 2121-5) and bladder cancer (PMR 2121-6). There were no new safety findings in the

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		DECLARE trial that would offset the substantial benefit observed for hospitalization for heart failure in the studied population.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Diabetes mellitus is a chronic disease characterized by insulin deficiency or insulin resistance, resulting in hyperglycemia. Traditionally two major forms of diabetes have been recognized: type 1 diabetes (T1DM), formerly known as insulin-dependent diabetes, results from reduced endogenous insulin secretion by the pancreas via autoimmune destruction of pancreatic β-cells; type 2 diabetes (T2DM), formerly known as non-insulin-dependent diabetes, is characterized by insulin resistance and progressive loss of β-cell function over time. Both T1DM and T2DM are heterogenous conditions that may have different clinical presentations and courses of disease progression.[5] Other important categories of diabetes include gestational diabetes mellitus (GDM), a disorder of glucose handling usually diagnosed in the second or third trimester of pregnancy that often resolves after delivery; and diabetes due to a variety of other conditions including the monogenic diabetes syndromes (e.g., maturity-onset diabetes of the young [MODY]), drug- or chemical-induced diabetes (e.g., following prolonged glucocorticoid use, organ transplantation, or certain therapies for HIV/AIDS), and diseases of the exocrine pancreas that lead to fibrosis (e.g., cystic fibrosis, pancreatitis).[6] Finally, impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are important conditions in which glycemic handling is abnormal but not yet as severe as that seen in diabetes; these conditions often progress to overt diabetes (usually T2DM).[7] In the United States, an estimated 30.3 million people (9.4% of the population) have diabetes mellitus, with T2DM comprising about 90-95% of cases. An additional estimated 84.1 million people (33.9% of the population) have prediabetes based on their fasting glucose or HbA12c levels. Racial, ethnic and geographic differences in diabetes prevalence are notable, with American Indians/Alaska Natives, Black and Hispanic Americans disproportionately affected, along with Americans living in the South, Midwest and Puerto Rico.[8]

Depending on diabetes type and chronicity, the initial clinical presentation may vary from acute symptoms of hyperglycemia (i.e., polyuria, polydipsia, diabetic ketoacidosis) to diagnosis based on clinical screening tests in an asymptomatic patient. Due to chronic hyperglycemia resulting from diabetes mellitus, all patients are at increased risk of microvascular (i.e., retinopathy, nephropathy, peripheral neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications. Large long-term randomized clinical trials such as the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) in

[5] Ahlqvist E, Storm P, Karajamaki A et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018;6:361-369
[6] American Diabetes Association Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. *Diabetes Care* 2018;41:S13-27
[7] World Heath Organization Global Report on Diabetes; 2016
[8] Centers for Disease Control National Diabetes Statistics Report, 2017

patients with T1DM and the United Kingdom Prospective Diabetes Study (UKPDS) in patients with T2DM have demonstrated that intensive glycemic control, measured by HbA1c, reduces the incidence of microvascular complications.

2.2. Analysis of Current Treatment Options

While patients with T1DM require exogenous insulin as part of their treatment regimen, patients with T2DM have a wide range of therapeutic options available if lifestyle interventions fail to control their dysglycemia. Twelve classes of drugs have been approved for treatment of T2DM (Table 1). The 2018 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on management of hyperglycemia in T2DM recommends initiation of metformin in most patients, and additional therapy based on the presence of absence of established cardiovascular disease (eCVD) or chronic kidney disease (CKD) if additional glycemic control is needed.[9] Prior recommendations from professional societies focused on individualized assessment of patient preferences and the benefits and risks of each drug class in optimizing treatment regimens beyond lifestyle interventions and metformin. However, data from large cardiovascular outcome trials has been incorporated into the latest ADA/EASD recommendations to reflect that patients with eCVD should receive one of the SGLT2 inhibitors or GLP-1 receptor agonists with labeled CV indications reflecting substantial evidence of benefit in reducing the incidence of major adverse cardiovascular events in adults with T2DM and eCVD.

[9] Davies MJ, D'Alessio DA, Fradkin J et al. Management of hyperglycemia in type 2 diabetes, 2018: a consensus report by the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2018;41:2669-2701

Table 1. Available Therapies Indicated to Improve Glycemic Control in Diabetes Mellitus

Pharmacologic Class	Antihyperglycemic Drug Products*
Alpha-Glucosidase Inhibitors	Acarbose; Meglitol
Amylin Mimetics	Pramlintide
Biguanides	Metformin
Bile Acid Sequestrants	Colesevelam
Dopamine-2 Agonists	Bromocriptine
DPP-4 Inhibitors	Alogliptin; Linagliptin; Saxagliptin; Sitagliptin
GLP-1 Receptor Agonists	Albiglutide; Dulaglutide; Exenatide; Exenatide extended-release; Liraglutide; Lixisenatide, Semaglutide
Insulins and Insulin Analogues	Inhaled insulin human; Insulin aspart: Insulin aspart protamine plus insulin aspart; Insulin degludec; Insulin degludec plus insulin aspart; Insulin detemir; Insulin glargine; Insulin glulisine; Insulin isophane (NPH); Insulin isophane plus regular; Insulin lispro; Insulin lispro protamine plus insulin lispro; Insulin regular (human); Pre-mixed insulins (various)
Meglitinides	Nateglinide; Repaglinide
SGLT2 Inhibitors	Canagliflozin; Dapafliflozin; Empagliflozin, Ertugliflozin
Sulfonylureas	Chlorpropamide; Glimepiride; Glipizide; Glipizide extended-release; Glyburide; Tolazamide; Tolbutamide
Thiazolidinediones	Pioglitazone; Rosiglitazone

*Products that also have a CV indication in patients with established CV disease: liraglutide, canagliflozin, and empagliflozin
Source: Clinical Review NDA 202293 S-15 (authored by Frank Pucino, PharmD, MPH)

To date, the large CVOTs that have led to FDA approval of a CV indication were conducted using liraglutide (LEADER trial), canagliflozin (CANVAS program, comprising the CANVAS and CAVNS-R trials) and empagliflozin (EMPA-REG OUTCOME trial). Liraglutide and canagliflozin have approved CV indication statements to reduce the risk of major adverse cardiovascular events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with T2DM and established CV disease. Empagliflozin was granted the indication to reduce the risk of cardiovascular death in adult patients with T2DM and established CV disease. The CVOTS evaluating DPP-4 inhibitors such as saxagliptin did not show macrovascular risk reduction but did demonstrate that there was no excess CV risk with use of these products (i.e., they were non-inferior to comparators with respect to CV risk). Recently, canagliflozin also received an indication statement to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death and hospitalization for heart failure in patients with T2DM and diabetic

nephropathy with albuminuria, based on the results of a large renal outcomes trial (CREDENCE).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dapagliflozin was approved in its second NDA review cycle for the indication as an adjunct to diet and exercise to improve glycemic control in adults with diabetes mellitus on January 8, 2014 via the 505(b)(1) pathway, under the trade name Farxiga.

During the first NDA review cycle, a Complete Response (CR) letter was issued on January 17, 2012 due to the Division's assessment that the benefit-risk profile of the product was unfavorable to support a glycemic control indication; this was based on the conclusion of modest efficacy of the product and significant safety concerns, including hepatotoxicity, cardiovascular safety, and a possible safety signal of increased bladder cancer risk. In the second NDA submission, the Applicant provided updated clinical and nonclinical data to address the deficiencies outlined in the CR letter. The Applicant also initiated a large CVOT and pharmacoepidemiology study to definitively quantify the CV risk profile of dapagliflozin as well as assess bladder cancer, hepatotoxicity risks, and several other adverse events of special interest (AESIs). See **Section 3.2** for a detailed discussion of the regulatory activity pertaining to this efficacy supplement.

On October 29, 2014 the combination product Xigduo XR (dapagliflozin and metformin extended-release) was approved for the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate. Other approved dapagliflozin-containing products are Qtern (dapagliflozin and saxagliptin, approved February 27, 2017 under NDA 209091) and Qternmet XR (dapagliflozin, saxagliptin, and metformin extended-release, approved under NDA 210874 on May 2, 2019).

The initial approved dapagliflozin labeling stated that its use was not recommended in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2, due to the relatively small effect size in patients with mild renal impairment and apparent lack of efficacy in achieving significant HbA1c reduction in patients with eGFR <45 mL/min/1.73m^2. On February 22, 2019, sNDA 202293 S-15 was approved to provide for changes to the labeling reflecting that no dose adjustment is needed for patients with eGFR ≥45 mL/min/1.73m^2, as supported by a clinical study evaluating efficacy and renal safety of dapagliflozin in patients with T2DM and moderate renal impairment. Dapagliflozin is not recommended in patients with eGFR <45 and is contraindicated in patients with eGFR <30 mL/min/1.73m^2.

3.2. Summary of Presubmission/Submission Regulatory Activity

During the first NDA review cycle, the benefit-risk profile of dapagliflozin was determined to be unfavorable due to modest efficacy and several safety concerns. First, the CV risk profile of the product was not adequately characterized: discordant findings were noted regarding the drug's CV safety profile based on pooled results from the two large Phase 3 clinical trials, versus an overall meta-analysis of 19 Phase 2b/3 clinical trials. The overall CV meta-analysis appeared to be reassuring with regard to the primary endpoint of major adverse cardiovascular events (MACE, a composite of time-to-first-event of CV death, myocardial infarction [MI], or ischemic stroke), yielding a hazard ratio (HR) for MACE of 0.79 (95% CI 0.54, 1.17) for dapagliflozin versus comparators, and excluding an upper bound of the 95% CI of 1.8. This HR and 95% CI supported the conclusion that dapagliflozin was not associated with an unacceptable increase in CV risk based on FDA Guidance.[10] However, two of the Phase 3 clinical trials included in the meta-analysis had been enriched with subjects at higher CV risk, and these two trials contributed approximately 40% of the total CV events to the larger meta-analysis. The pooled stratified HR for MACE from these two Phase 3 trials was 1.26 with an upper bound of the 95% confidence interval (CI) greater than 1.8 (95% CI 0.69, 2.31). The discordant results of the CV analyses of the two pooled Phase 3 trials versus the 19-trial meta-analysis was considered in the context of the overall benefit-risk assessment of the product and was cited in the January 12, 2012 CR letter. Also of concern to the Division were the liver and cancer safety signals observed in the clinical development program: there was a case of drug-induced liver injury (DILI) assessed as "probably" related to dapagliflozin, and a numeric imbalance in bladder cancer cases unfavorable to dapagliflozin (nine cases in dapagliflozin-treated subjects vs. one case in the comparator-treated subjects, all in male subjects). As a path forward, the CR letter recommended that the Applicant submit additional clinical trial data to increase the patient-years of exposure to dapagliflozin and comparators, including data from subjects who completed at least 52 weeks of treatment in the two large Phase 3 trials. Specifically, the Division requested updated data on bladder cancer, hepatic safety, and an updated CV meta-analysis. The CR letter also acknowledged the Applicant's plan to initiate a large CVOT and recommended that that Applicant proceed with this trial.

On July 17, 2012 the Applicant submitted a Formal Dispute Resolution Request specifically addressing the CV safety analysis and the Division's overall benefit-risk assessment. The Applicant requested that the CV data from the two large Phase 3 trials be viewed in the context of the overall CV risk assessment of dapagliflozin rather than as stand-alone studies, and argued that dapagliflozin's effects on glycemic control, weight loss, and blood pressure (BP) supported a favorable benefit-risk profile. The Applicant proposed that dapagliflozin should be approved

[10] Guidance for Industry. Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008.

based on data already submitted to the NDA, and committed to conducting a large CVOT and a large pharmacoepidemiology study to definitively quantify the CV risk profile of dapagliflozin as well as assess bladder cancer and hepatotoxicity risks. On September 14, 2012 the Agency issued an Appeal Denied letter, stating that the path forward outlined in the CR letter was reasonable and that a resubmitted NDA should be brought before an Advisory Committee. The letter also required the Applicant to conduct a preclinical toxicology study to address the issue of tumor promotion of bladder cancer.

On July 11, 2013 the Applicant resubmitted the NDA with an updated CV meta-analysis comprising 21 Phase 2b/3 clinical trials submitted in the 30-month safety update. The primary CV composite endpoint was MACE-plus (time-to-first-event of MACE or hospitalization for unstable angina), with MACE as a secondary endpoint. The results were reassuring for both endpoints: MACE-plus (HR 0.81 [95% CI 0.59, 1.09]) and MACE (HR 0.78 [95% CI 0.55, 1.11]). The results were consistent in patients with eCVD for both MACE-plus (HR 0.81 [95% CI 0.56, 1.16]) and MACE (HR 0.80 [95% CI 0.53, 1.22]). The Applicant also submitted updated pooled analyses of data from extensions of the two original Phase 3 trials enriched with patients at risk for CV events: for MACE the HR was now 1.11 (95% CI 0.67, 1.83). These data were presented at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting on December 13, 2013. Members concluded that the CV risk profile of dapagliflozin relative to comparators was acceptable, with 13 members voting to approve the drug for the glycemic control indication and one voting against approval. Several members, however, acknowledged that existing data were not sufficient to rule out a potential CV risk. The DECLARE CVOT was ongoing at the time of the EMDAC meeting.

Key regulatory interactions related to this efficacy supplement are presented in Table 2.

Table 2. Key Meetings and Regulatory Interactions for NDA 202293 S-018/205649 S-011

Date	Meeting/Submission	Comments
11/9/2010	Pre-NDA meeting under IND 68652	The Applicant inquired whether their CV meta-analysis of clinical trial data would fulfill the CV safety requirements for NDA filing, with no need to conduct further post-marketing CV trials. FDA stated they could not agree to this until after detailed review of the CV meta-analysis during the NDA review.
5/5/2011	Teleconference	The Division informed the Applicant a dedicated CVOT would be a post-marketing requirement if dapagliflozin were approved. The Applicant informed the Division they were in the process of planning such a trial and would submit a synopsis for feedback.
7/7/2011	Teleconference	The Division provided clarification of the rationale for requiring a large post-marketing CVOT, noting that

		the CV meta-analysis submitted to the NDA was not adequately designed (i.e., with a prespecified number of CV events) to conclude dapagliflozin had met the more stringent CV risk assessment of ruling out the 1.3 upper bound of the 95% CI. The Division noted the low event rate in the meta-analysis, reflecting the low-risk population studied. The Division also noted that a large CVOT could provide additional safety data for liver and cancer risks, and that demonstration of a potential CV benefit could offset the liver and cancer safety signals raised during the review.
7/19/2011	EMDAC Meeting	Nine committee members voted against approval (versus six who voted for approval) of dapagliflozin mainly due to hepatic and cancer safety signals. The CV safety profile was not a focus of discussion at the first EMDAC for dapagliflozin, but after the AC the Division requested the 19-trial CV meta-analysis as a major amendment to better inform the benefit-risk assessment of the drug.
10/4/2011	Type C Meeting	Design of the CVOT and the overall pharmacovigilance plan for dapagliflozin were discussed. FDA inquired as to the rationale for the Applicant's inclusion of hospitalization for heart failure as a component of the secondary efficacy variable, especially given dapagliflozin's diuretic effect. The Applicant stated the diuretic effect appears to be small, and HF causes significant morbidity and mortality in diabetes patients. Therefore, they included HF hospitalization as a secondary endpoint component, noting it would not affect the conclusion regarding the drug's CV risk based on MACE. FDA considered this explanation acceptable. The Applicant also agreed to enrich the trial population as was being done in the SAVOR trial for saxagliptin.
10/20/2011	Major Amendment Submitted	The submission included the 19-trial CV meta-analysis, and updated analyses of malignancy and hepatic safety, triggering a three-month PDUFA clock extension.
1/17/2012	CR Letter	FDA could not reach a conclusion of a favorable benefit-risk profile for dapagliflozin based on the CV

		risk analyses, and the possible safety signals for bladder cancer and hepatotoxicity.
8/15/2012	Formal Dispute Resolution Request Meeting	The Applicant disputed the Agency's CV risk assessment and conclusions on overall benefit-risk profile of dapagliflozin.
9/14/2012	Dispute Appeal Denied Letter	OND Deputy Director, Dr. Kweder, concluded the path forward outlined in the CR letter was reasonable and advised the Applicant to provide updated CV data and conduct the CVOT.
5/30/2012	Advice Letter	FDA provided feedback on the CVOT draft protocol submitted 4/2/2012, and the Clinical Events Committee charter.
11/19/2012	DECLARE updated protocol submission	Included initial draft statistical analysis plan (SAP), draft data monitoring committee (DMC) charter and events reporting manual.
2/7/2013	Advice Letter	FDA feedback on DECLARE draft protocol with comments focused on SAP.
4/25/2013	**Trial milestone**	**First patient enrolled** in DECLARE trial
7/10/2013	Email communication	FDA stated the revised protocol and DMC charter for DECLARE were acceptable and there were no further statistical comments.
7/11/2013	NDA resubmission	Six-month review clock; PDUFA goal date 1/11/2014.
1/8/2014	Approval Letter	• **PMR 2121-5:** DECLARE CVOT with primary objective to demonstrate the upper bound of the 95% CI for the estimated risk ratio comparing incidence of MACE observed with dapagliflozin to that observed in the placebo group is less than 1.3. The trial should also assess long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, and urogenital infections. The eGFR should be monitored over time. • **PMR 2121-6:** To assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of DECLARE to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo.
2/19/2014	Email communication	FDA informed the Applicant that the amended protocol for DECLARE submitted on 12/26/2013 was

		not acceptable to fulfill the PMR 2121-5 requirements outlined in the approval letter. Specifically, the protocol did not include adequate plans for assessing long-term effects of dapagliflozin on serious hypersensitivity reactions, bone fractures, serious genital infections, and monitoring of eGFR changes.
4/22/2014	Email communication	FDA advised the Applicant that based on the information submitted on 2/27/2014, including updated protocol and SAP information, the DECLARE protocol appears adequate to fulfill the needs of PMR 2121-5.
9/9/2014	Written Responses Only	To fulfill the requirements of PMR 2121-6, the Applicant proposed to evaluate the blinded bladder cancer event rate when approximately half of the planned 1390 primary CV events had been reached, and if necessary, to extend DECLARE by six months after the 1390 CV events were reached to achieve 66 bladder cancer events. FDA agreed with this approach and acknowledged the proposed revised milestone date of October 2017 for final protocol submission.
6/20/2015	**Trial Milestone**	**Final patient randomized** in DECLARE trial
11/20/2015	Email communication	FDA provided feedback on the proposed secondary renal endpoints based on consult responses from the Division of Cardiorenal Products.
12/23/2015	**DECLARE Protocol Amendment 5 submission**	This protocol amendment changed the statistical testing hierarchy for the trial analysis based on external scientific data, primarily publication of the EMPA-REG OUTCOME study. The new testing hierarchy specified that if dapagliflozin were non-inferior to placebo for the composite MACE endpoint with an NI margin of 1.3, the second step would determine if dapagliflozin were superior to placebo in reducing the incidence of the following co-primary endpoints: MACE and a composite of hospitalization for heart failure or CV death. If both co-primary endpoints were statistically significant, the testing hierarchy would proceed to the secondary renal composite endpoint.
2/8/2016	**Trial Milestone-First Interim Analysis of DECLARE results**	Triggered by reaching 1/3 the goal number of MACE events and 32 bladder cancer events. Unblinded data was reviewed by the DSMB and all members

		concluded the trial should continue. No analyses of heart failure data were performed and the committee did not provide input on the revised SAP.
3/22/2016	Advice Letter	FDA provided further comments on the Applicant's proposed secondary composite renal endpoint.
5/18/2016	Advice Letter	FDA informed Applicant of the May 18, 2016 Drug Safety Communication (DSC) regarding canagliflozin and the risk of foot and leg amputations, most affecting the toes, identified from an interim safety analysis of CANVAS. FDA advised the following: • DMC should review available DECLARE data for amputations and related events • Designate amputations as a prospectively monitored AESI • Revise the trial Case Report Form (CRF) to capture amputations and related events • The Applicant should submit a plan for analysis of this safety signal
6/30/2016	Type B Meeting with DCRP (PIND 130631)	The Applicant discussed the following issues with DCRP related to design of a Phase 3 study to support development of dapagliflozin for the indication (b) (4) [redacted] • Study population would include at least 30% of patients with T2DM • The Applicant proposed a composite primary endpoint of time-to-first event of CV death, heart failure hospitalization, or urgent heart failure visit • DCRP noted that other trials such as DECLARE may provide supportive evidence for the proposed indication, but unless baseline HF status and background therapy were well-characterized the findings may be difficult to interpret to support an efficacy claim in HF with reduced EF • The Applicant proposed a pre-planned meta-analysis combining interim data from the Phase 3 HF study and the final DECLARE results, stating that approximately 9% of enrolled DECLARE subjects had baseline HF (but LVEF data was not available in all these subjects). FDA did not recommend such a

		meta-analysis due to the concern that HF status in DECLARE was not adequately characterized • FDA encouraged the Applicant to include subjects with eGFR <30 mL/min/1.73m^2 in the study
		(b) (4)
3/15/2017	Advice Letter	FDA informed the Applicant that on December 2, 2016 FDA approved a new indication for empagliflozin (Jardiance) to "reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease." FDA noted that this approval had "ethical implications for the conduct of trials in patients with

		established CV disease, particularly trials evaluating other members of the SGLT-2 inhibitor class. Specifically, designs that prohibit use of empagliflozin…may be problematic." FDA requested that the Applicant "perform an analysis of this issue for your drug and submit a plan to ensure ongoing or future trials you conduct in this population conform to established ethical principles, in light of this new information."
6/6/2017	**Trial Milestone-Second DECLARE Interim Analysis**	Triggered by reaching 2/3 of the goal number of MACE events. All DSMB members voted that the trial should continue.
7/5/2017	Advice Letter	FDA responded to the Applicant's April 21, 2017 submission proposing reconsenting DECLARE patients to inform them of alternative treatment (i.e., empagliflozin). FDA recommended that the informed consent form (ICF) and Investigator's Brochure (IB) be updated to state there is now a drug approved to reduce the risk of CV death in adult patients with T2DM and established CV disease. Patients should be reconsented and given the option to switch to empagliflozin. Those who choose to switch should continue to be followed and have all study data collected.
8/16/2017	Teleconference	Discussion of the Applicant's August 4, 2017 submission stating they had sent a letter and White Paper to investigators regarding empagliflozin in December 2015, and that DECLARE patients had already been informed of the EMPA-REG results and reconsented in December 2016. The Applicant considered the most recent ICF version adequate and noted that DECLARE was almost complete. FDA informed the Applicant that it considered the letter to investigators, White Paper, and language in the revised ICF inadequate because they did not reflect FDA's regulatory decision regarding empagliflozin (i.e., approval for the indication to reduce CV mortality in T2DM patients with established CV disease). The Applicant agreed to reconsent patients with CV disease but argued that only U.S. patients should be reconsented because other regulatory

		agencies had not taken any action based on the EMPA-REG results, which were considered controversial in the academic community. FDA requested submission of a detailed ethical justification for this plan and the updated ICF (these were submitted 8/30/17).
10/25/2017	**Trial Milestone-DECLARE Bladder Cancer Case Collection completed**	Applicant informed FDA that based on the number of bladder cancer cases adjudicated to date in DECLARE, extension of the study would not be necessary to meet 66 cases and to fulfill the requirements of PMR 2121-6.
4/19/2018	Written Responses Only	FDA provided feedback regarding the presentation and key contents for the sNDA submission and agreed to waive the 4-Month Safety Update requirement because no clinical trials would be ongoing.
9/11/2018	**Trial Milestone**	**Final patient visit** completed for DECLARE trial
9/16/2018	**Trial Milestone**	**Trial database locked** for DECLARE
11/4/2018	Agreement on agreed iPSP	Agreement on DECLARE Agreed iPSP full waiver for cardiovascular events.
12/18/2018	sNDA submission	DECLARE trial results submitted to NDA 202293-S18 and NDA 205649-S11

3.3. Foreign Regulatory Actions and Marketing History

Dapagliflozin is currently marketed in over 40 countries, including the European Union (EU), Japan, and Australia. Dapagliflozin received marketing authorization in the EU under the trade name Forxiga on November 11, 2012. Forxiga was approved for indication "to improve glycemic control in adults aged 18 years and older with type 2 diabetes mellitus" as monotherapy or add-on combination therapy. The DECLARE study was a Category 3 post-authorization safety study (PASS) in the EU. The PASS requirement was that DECLARE be designed to evaluate bladder cancer risk and to assess other safety concerns including increased hematocrit, renal impairment/failure, bone fracture, liver injury, breast cancer, prostate cancer, DKA, amputations, and pancreatitis.

On January 31, 2019 the Committee for Medicinal Products for Human Use (CHMP) in the EU adopted a new indication for Forxiga in patients with "type 1 diabetes mellitus as an adjunct to insulin in patients with BMI ≥ 27 kg/m^2, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy."

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspected two domestic and four foreign clinical sites for this trial (see Dr. Cynthia Kleppinger's review dated August 30, 2019 for detailed findings). In total, 528 subjects out of 17,160 were enrolled at these six study sites. Site inspections focused on review of informed consent documents, institutional review board and ethics committee correspondences, 1572 forms/investigator agreements, financial disclosures, training records, *curriculum vitae* and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the Applicant's data line listing. The conclusion of OSI is that these inspections supported validity of the data as reported by the Applicant under this sNDA.

4.2. Product Quality

There is no new product quality information included in this supplement.

4.3. Clinical Microbiology

There is no new information related to clinical microbiology included in this supplement.

4.4. Nonclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology information included in this supplement.

4.5. Clinical Pharmacology

There is no new clinical pharmacology information included in this supplement.

4.6. Devices and Companion Diagnostic Issues

There is no device or companion diagnostic information included in this supplement.

4.7. Consumer Study Reviews

These supplements did not include information related to label comprehension, patient self-selection, or other human factors studies.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

In support of this efficacy supplement, the Applicant submitted a complete clinical study report (CSR) for one clinical trial. Study D1693C00001, **D**apagliflozin **E**ffect on **C**ardiovascu**lar** **E**vents (**DECLARE**), initiated enrollment on April 25, 2013 and completed enrollment on September 11, 2018. DECLARE enrolled a total of 25,698 patients in the trial; 17,160 patients were randomized and 16,906 completed the study. Because only one trial was submitted in this efficacy supplement, it will not be presented in tabular format.

5.2. Review Strategy

This review is based on the Study D1693C00001 (DECLARE) efficacy supplement submission for NDAs 202293 and 205649, and the Applicant's responses to multiple information requests (IRs).

Review of efficacy (benefit) for the (b) (4) new proposed indications was based on review of data presented in the DECLARE trial and associated IRs. Review of CV safety was based on ruling out an upper bound of the 95% CI of 1.3 for the MACE HR point estimate. Separate statistical reviews were conducted by Sherman Xia, PhD and Susie Sinks, PhD evaluating CV safety and efficacy findings in support of the (b) (4) new proposed indications, respectively.

For the review of efficacy and safety, I reviewed the Study D1693C00001 clinical study report (DECLARE CSR), Summaries of Clinical Efficacy and Safety, study datasets, all versions of the study protocol, CEC charter, and statistical analysis plan, and the DMC/DSMB meeting minutes. I also reviewed selected CEC adjudication packages and narratives for deaths, AEs, and AESIs as discussed in the relevant safety subsections.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study D1693C00001: Dapagliflozin Effect on Cardiovascular Events (DECLARE): A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction, or ischemic stroke in patients with type 2 diabetes

6.1.1. Study Design

Overview and Objective

The glycemic lowering efficacy of dapagliflozin was established during the initial NDA submission. The DECLARE trial was a post-marketing trial to assess the cardiovascular safety (and efficacy) of dapagliflozin in patients with T2DM.

The primary safety objective of this study was to exclude excess CV risk (i.e., noninferiority using the primary safety variable of MACE, with a noninferiority margin of 1.3) with dapagliflozin versus placebo added to standard of care in patients with T2DM and either established CV disease, or two or more risk factors for CV disease. The primary efficacy objectives were to determine if dapagliflozin is superior to placebo for the dual efficacy

endpoints of MACE and a composite of HF hospitalization and CV death.

The Applicant submitted one study report (Study D1693C0001) in support of the two efficacy supplements for NDAs 202293 and 205649.

Trial Design

This was a randomized, double-blind, multinational, event-driven study with two treatment groups (dapagliflozin 10 mg once daily, or placebo) added to standard-of-care, with the aim to investigate the effect of dapagliflozin on CV outcomes relative to placebo in patients with T2DM and either established CV disease or at least two CV risk factors. This study is part of the ongoing CV safety assessment for dapagliflozin and was a post-marketing requirement. To fulfil an additional post-marketing requirement, the DECLARE study population was also followed to evaluate the incidence of bladder cancer.

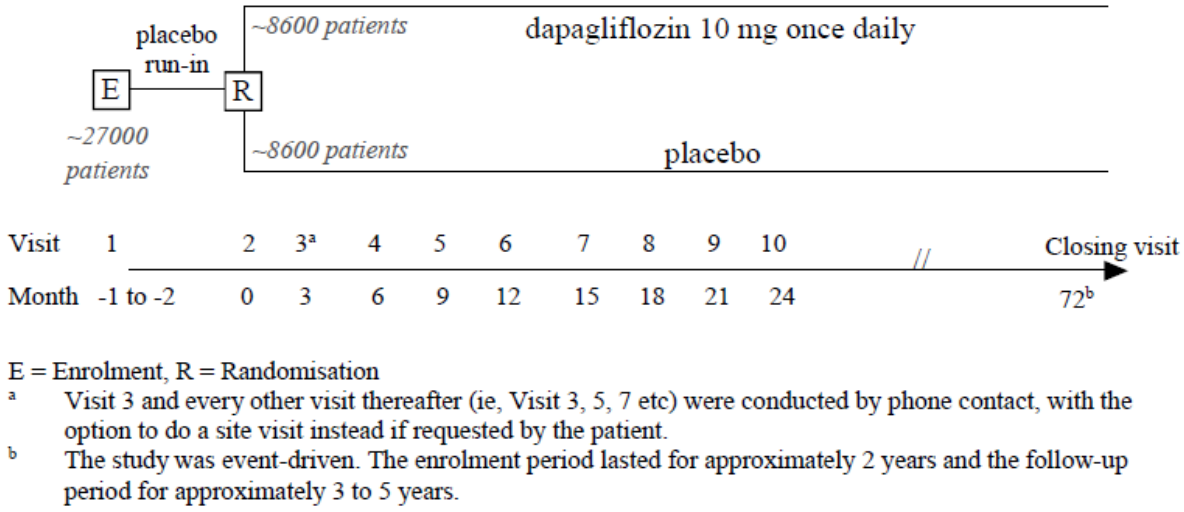
The study was conducted at 882 clinical sites in 33 countries (Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, France, Germany, United Kingdom, Hong Kong, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, Philippines, Poland, South Korea, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, United States, and Vietnam). The international coordinating investigator was Marc Sabatine, MD, MPH (Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA). The co-primary investigators (PIs) were Stephen Wiviott, MD (Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA) and Itamar Raz, MD (Diabetes Unit, Hadassah Medical Centre, Jerusalem).

Approximately 17,150 patients with a documented history of CV disease or two or more CV risk factors in addition to T2DM were planned to be randomized in a 1:1 ratio per treatment group, with a recruitment goal of approximately 30% of patients each from North America and Europe.

The study included a 4 to 8-week placebo run-in period starting at Visit 1 to identify non-adherent patients. Randomization was then performed via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) at Visit 2 in balanced blocks. Randomization was stratified by CV risk category (established CV disease or multiple risk factors without established CV disease) and baseline hematuria status (defined as a positive microscopy [≥3 RBCs] at the screening visit and/or a urine dipstick indicative of hematuria [positive or trace] at the randomization visit). To prevent unequal treatment allocation, randomization blocks were divided into four stratification groups: (1) Positive hematuria and primary prevention, (2) Positive hematuria and secondary prevention, (3) Negative hematuria and primary prevention, (4) Negative hematuria and secondary prevention. Enrollment based on disease state, geographic region, and gender was also monitored and could be capped as needed.

The trial was event-driven, with 1390 predetermined primary endpoint events needed to have 85% power to demonstrate superiority of dapagliflozin to placebo with an HR of 0.85. In general, the time-to-event was derived from the date of randomization. The anticipated trial duration was six years, including an enrollment period of three years and follow-up period of three to six years. The actual enrollment period lasted for approximately two years and the study's median follow-up time was 4.2 years. After the run-in period, patients who successfully completed the run-in and still met all the inclusion criteria and none of the exclusion criteria for the trial were randomized. Study visits occurred thereafter at three-month intervals throughout the remainder of the trial (alternating between clinical site assessments and telephone contacts). Patients were not permitted to take pioglitazone, rosiglitazone or other SLGT2 inhibitors for the duration of the study. Patients were otherwise to be treated based on the American Diabetes Association (ADA) guidelines and could have background diabetes medications adjusted at the investigators' discretion. Patients were also to be treated according to regional standards of care for CV risk factors. When the Executive Committee decided to close the trial, a Closing Visit was scheduled for all patients within 8 weeks of the start of the close-out period. Patients who prematurely discontinued treatment had an End of Treatment (EoT) visit. The trial design is shown in Figure 1 below.

Figure 1. DECLARE Trial Design



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Source: Excerpted from the DECLARE Clinical Study Report, Figure 1, p. 20

The time period during which AEs were still to be considered "on treatment" was seven (7) days for changes in lab values and vital signs, and 30 days for SAEs. Data up to 30 days after the last treatment intake was considered on treatment for the primary, secondary, and categorical exploratory endpoints. Data up to seven days after last treatment intake was considered on treatment for the continuous exploratory variables, including HbA1c and body weight.

Key Inclusion Criteria:

1. Female or male ≥40 years
2. Diagnosed with T2DM based on the following:
   - Prior documentation of T2DM AND/OR
   - Treatment with anti-hyperglycemic medications and/or diet AND/OR
   - **ADA criteria**: fasting glucose >126 mg/dL or HbA1c ≥6.5% OR 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test, or a random plasma glucose ≥200 mg/dL in patients with classic symptoms of hyperglycemia or hyperglycemic crisis. In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.
3. High risk for CV event defined as having either established CV disease and/or multiple risk factors, with the following definitions:
   - Established CV disease:
     i. Ischemic heart disease (any of the following):
        - Documented myocardial infarction
        - Percutaneous coronary intervention
        - Coronary artery bypass grafting
        - Objective findings of coronary stenosis (≥50%) in at least two coronary artery territories (i.e., left anterior descending, ramus intermedius, left circumflex, right coronary artery) involving the main vessel, a major branch, or a bypass graft

     ii. Cerebrovascular disease (any of the following):
        - Documented ischemic stroke (known transient ischemic attack, primary intracerebral hemorrhage, or subarachnoid hemorrhage do NOT qualify)
        - Carotid stenting or carotid endarterectomy
        - Peripheral arterial disease (any of the following):
          a. Peripheral arterial intervention, stenting or surgical revascularization
          b. Lower extremity amputation as a result of peripheral arterial obstructive disease
          c. Current symptoms of intermittent claudication AND ankle/brachial index (ABI) <0.90 documented in the last 12 months

   - Multiple Cardiac Risk Factors
     i. No known CV disease AND
        - Age ≥55 years in men and ≥60 in women

     ii. AND presence of at least one of the following additional risk factors
        - Dyslipidemia (at least one of the following):

a. Low-density lipoprotein cholesterol (LDL-C) >130 mg/dL within the last 12 months
b. On lipid lowering therapy prescribed by a physician for hypercholesterolemia (i.e., LDL-C >130 mg/dL for greater than 12 months. This should be verified by documentation of lab value LDL-C >130 mg/dL).

- Hypertension (at least one of the following):
  a. BP >140/90 mmHg at enrollment visit. The patient must have an elevated systolic BP (>140 mmHg) and an elevated diastolic BP (>90 mmHg) on both measurements
  b. On anti-hypertensive therapy prescribed by a physician for blood pressure lowering
- Tobacco use (5 cigarettes/day or more for at least one year at randomization)

4. Women of child-bearing potential (WOCBP) must take precautions to avoid pregnancy throughout the study and for four weeks after intake of the last treatment dose.
   - WOCBP must have a negative urine pregnancy test. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal.
   - WOCBP must be willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator.

Key Exclusion Criteria:

1. Use of the following excluded medications:
   - Current or recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for a total of two years or more during lifetime.
   - Current or recent (within 12 months) treatment with rosiglitazone
   - Previous treatment with any SGLT2 inhibitor
   - Any patient currently receiving chronic (>30 consecutive days) treatment with an oral steroid at a dose equivalent to oral prednisolone ≥10 mg (e.g. betamethasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day
2. Acute CV event, e.g. acute coronary syndrome, transient ischemic attack, stroke, any revascularization, decompensated HF, sustained ventricular tachycardia <8 weeks prior to randomization. Patients with acute CV events can be enrolled in the run-in period as long as randomization does not occur within 8 weeks of the event.
3. Systolic BP >180 or diastolic BP >100 mmHg at randomization.
4. Diagnosis of type 1 diabetes mellitus, maturity onset diabetes of the young, or secondary diabetes mellitus

5. History of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time
6. History of any other malignancy within five years (with the exception of successfully treated non-melanoma skin cancers)
7. Chronic cystitis and/or recurrent urinary tract infections (3 or more in the last year)
8. Any conditions that, in the opinion of the investigator, may render the patient unable to complete the study including but not limited to CV (New York Heart Association Class IV congestive HF, recurrent ventricular arrhythmias) or non-CV disease (e.g. active malignancy with the exception of basal cell carcinoma, cirrhosis, chronic lung disease, severe autoimmune disease) and/or a likely fatal outcome within 5 years
9. Pregnant or breastfeeding patients
10. Involvement in the planning and/or conduct of the study or other dapagliflozin studies (applies to AstraZeneca, Bristol-Myers Squibb, Hadassah and TIMI or representative staff and/or staff at the study site)
11. Previous enrollment or randomization in the present study
12. Active participation in another clinical study with an investigational product and/or investigational device
13. Individuals at risk for poor protocol or medication compliance during run-in period (reasonable compliance defined as 80% to 120%, unless a reason for non-compliance is judged acceptable by the investigator). If for any reason, the investigator believes that the patient will not tolerate or be compliant with the investigational product or study procedures, the patient should not be randomized and considered a run-in failure.
14. Patients were to be excluded during run-in and not be randomized if the following was observed from laboratory findings or observations during enrollment and run-in assessments:
    - HbA1c ≥12% or HbA1c <6.5% from the central laboratory
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN) or total bilirubin (TBL) >2.5 x ULN
    - Creatinine clearance <60 mL/min (based on the Cockroft-Gault equation)
    - Hematuria (confirmed by microscopy at Visit 1) with no explanation as judged by the investigator up to randomization. If bladder cancer is identified, patients are not eligible to participate.
    - Any reason the investigator believes the patient is not likely to be compliant with the study medication and protocol

Study Administrative Structure and Committees:

The DECLARE trial was conducted under the supervision of an Executive Committee, Steering Committee, and Data Monitoring Committee (DMC).

- Executive Committee: This committee included both academic leaders in the fields of diabetes and CV disease, and members from the Applicant. The committee was

responsible for the overall design, conduct, and supervision of the study, including protocol amendments. The Executive Committee made recommendations to the Applicant based on input from the DMC following two interim analyses of the trial data. There were 12 committee members (7 from academia and 5 from the Applicant). The Chairperson of the Executive Committee was Dr. Marc Sabatine, Division of Cardiovascular Medicine, Brigham and Women's Hospital. The other members from academia were Dr. Stephen Wiviott (Harvard Medical School), Dr. Deepak Bhatt (Brigham and Women's Hospital), Dr. Itamar Raz (Hadassah Hebrew University Hospital), Dr. Darren McGuire (University of Texas Southwestern Medical Center), Dr. Lawrence Leiter (St. Michael's Hospital, Toronto, Canada), and Dr. John Wilding (University Hospital Aintree, United Kingdom). The members from the Applicant were Arie Katz, Eva Johnsson, Ingrid Gause Nilsson, Anna Maria Langklide (all from AstraZeneca) and Danny Liaw (Bristol-Myers Squibb).

- Steering Committee: This committee was responsible for providing clinical guidance on study implementation, conduct of the study and interpretation of results. Members included all members of the Executive Committee and additional members who were PIs for the study and members who had expertise in diabetes and CV disease. There were 70 members of this committee.
- Data Monitoring Committee/Data Safety Monitoring Board: An independent DMC was responsible for monitoring patient safety and reviewing overall conduct of the trial. Based on monitoring of safety data, the DMC advised the Applicant on whether the trial should continue according to the protocol, the study protocol should be modified, or the study should be discontinued overall or in a particular subgroup. The DMC also assessed efficacy data at the interim analysis and decided if stopping guidelines were met; an independent statistical group (Stanford University, Department of Medicine, Quantitative Sciences Unit) performed the interim efficacy analyses provided to the DMC/DSMB. The first DMC review of interim analyses of MACE events took place on February 8, 2016 after 33% of events were collected. DMC members were appointed by the Applicant and the trial's academic leadership. There were 5 members of the DMC/DSMB (4 physicians and 1 biostatistician), and they were compensated as consultants to the TIMI Study Group. Based on review of the submitted meeting minutes, prior to trial database lock on September 16, 2018, the DMC met 9 times from March 29, 2013 to June 6, 2017. The DMC members were Dr. Robert Harrington (DMC Chairperson, Stanford University Medical Center), Dr. Kerry Lee (Duke Clinical Research Institute), Dr. Michael Droller (a Urologist), Dr. Jaakko Tuomilehto (University of Helsinki Department of Public Health), and Dr. Robert Nesto (Department of Cardiovascular Medicine, Lahey Clinic Medical Center).

The following additional committees were associated with the trial:

- Clinical Event Committee (CEC): The CEC was an independent, blinded committee appointed by the TIMI Study Group and approved by the Applicant, comprising 28

physician members. The CEC was appointed to centrally adjudicate all primary and secondary CV endpoints in a blinded fashion. All possible malignancies (excluding non-melanoma skin cancer), pre-defined liver enzyme elevations, and all events of potential DKA were also adjudicated. Studies in scope for DKA adjudication included all ongoing Phase 3 studies of dapagliflozin. Study investigators reported potential events via electronic case report forms (CRFs) in real time. The clinical trial database was also searched monthly for AEs or laboratory data that might indicate a potential event. After identification of a potential event, a complete package was sent to the CEC within two weeks. The CEC reviewers had a target to evaluate the complete event package within four weeks of receipt.

- Strategy and Tactics Group: This committee comprised members from the TIMI Study Group, Hadassah Medical Centre, and the Applicant, and provided operational strategy guidance for the trial.
- Joint Working Group: This committee comprised members from the TIMI Study Group, Hadassah Medical Centre, and the Applicant, and directed all aspects of study operations.

Investigational Drug Dosing:

Dapagliflozin was administered as a 10 mg once daily dose. During the run-in period, patients were given placebo in a single-blind fashion (i.e., only patients were blinded). Patients randomized to dapagliflozin initiated at the 10 mg dose. Dapagliflozin and matching placebo were identical in appearance; both were biconvex, diamond shape, green tablets 11 mm in size.

Concomitant Medications:

Patients were to be treated for diabetes with glycemic goals as recommended by the ADA and European Association for the Study of Diabetes (EASD). Adjustment of patients' diabetes medications was at the Investigators' discretion and based on local treatment guidelines and best practices. All patients were to be treated according to regional standards of care for CV risk factors (such as blood pressure, lipids, antithrombotic treatment). Concomitant medications were recorded in the eCRF at randomization. All new or changed concomitant medications associated with an AE were to be recorded in the eCRF.

Discontinuation of Investigational Product:

Patients were free to discontinue treatment at any time; the Investigators, Applicant or representatives of the Applicant could also discontinue patients' treatment at any time if deemed appropriate for safety reasons. The following specific treatment stopping criteria were established:

- Liver criteria:
  - ALT and/or AST >3 times the upper limit of normal (ULN) and concomitant TB >2 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of

the initial laboratory results)
- ALT and/or AST >8 times ULN confirmed at a repeated measurement at the central laboratory (which should be obtained within 3 days, whenever possible, following receipt of the initial laboratory results)
- ALT and/or AST >5 times ULN confirmed at the central laboratory and sustained over a period of 14 days or more

- Kidney criteria:
  - If at any time the patient's CrCl (based on Cockroft-Gault) fell below 30 mL/min calculated at the central laboratory and confirmed at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient was to be discontinued from treatment
  - If at any time the patient's CrCl (based on Cockroft-Gault) fell below 30 mL/min calculated at a local laboratory, a central laboratory CrCl was to be obtained promptly. If the CrCl was confirmed by the central laboratory and persisted at a repeated central laboratory measurement (to be obtained within 4 days, whenever possible), the patient was to be permanently discontinued from treatment
- Bladder cancer:
  - If at any time a patient was diagnosed with bladder cancer, the patient was to be discontinued from treatment
- Pregnancy:
  - In the event of pregnancy, the patient was to discontinue treatment and notify the TIMI Hotline

Temporary treatment discontinuation for any reason and any duration was permitted. Treatment could be restarted in patients who had discontinued if the Investigators determined that the benefits of restarting treatment outweighed the risks. If a patient was permanently discontinued from treatment, study assessments were to be continued until the end of the study, if the patient agreed. In addition, all events requiring adjudication in these patients were submitted to the CEC if possible.

Withdrawals:
Patients were free to completely withdraw from the study (i.e., withdraw consent) at any time. Further assessments and contacts were stopped only in those patients who withdrew consent. Alternative methods of contact were also offered in lieu of completely withdrawing, such as periodic telephone follow-up or assessment of health status via medical records, or vital status via public records in accordance with local privacy laws. Patients who agreed to modified follow-up procedures after permanently discontinuing study treatment were not considered to have withdrawn consent.

If a patient took concomitant medications that interfered with the study treatment, or had

repeated hypoglycemic episodes, study treatment could be discontinued temporarily or permanently, if necessary.

Patients who completely withdrew from the study were not replaced.

Premature Trial Termination:
The Applicant could stop the entire study for the following reasons:

- Failure to meet expected enrollment goals overall or at a particular study site
- Emergence of any safety/efficacy information that could significantly affect continuation of the trial and/or invalidate the earlier positive benefit-risk assessment
- Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial

Study Endpoints

Primary Endpoint:
The primary endpoints were time-to-first event of the composite MACE endpoint (cardiovascular death, myocardial infarction, or ischemic stroke), and time-to-first event of the composite endpoint of hospitalization for heart failure or CV death. All components of these endpoints were adjudicated.

Secondary Endpoints:

- Renal composite endpoint: confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed eGFR <15 mL/min/1.73m^2 and/or renal or CV death (time-to-first event)
- All-cause mortality

Exploratory Endpoints:

- The individual components of the primary endpoint (CV death, MI, ischemic stroke and hospitalization for heart failure) (time-to-first event)
- The composite endpoint of CV death, MI, ischemic stroke, hospitalization for heart failure, hospitalization for unstable angina pectoris, or hospitalization for coronary or non-coronary revascularization; and the additional individual components of hospitalization for unstable angina pectoris and hospitalization for coronary or non-coronary revascularization (time-to-first event)
- HbA1c
- Initiation of insulin therapy in patients not receiving insulin therapy at baseline
- Need for any of the following: an increase in dose for an oral anti-diabetes medication, a ≥25% increase in insulin dose, or the addition of new anti-diabetes medication for ≥3 months (proportion)

- Major hypoglycemia and/or hospitalization for hypoglycemia
- Development of confirmed sustained macroalbuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline
- Development of confirmed sustained albuminuria (UACR ≥300 mg/g) in subjects without macroalbuminuria at baseline (UACR ≥30 mg/g; time-to-first event)
- Regression in sustained confirmed albuminuria defined in three ways: (1) baseline microalbuminuria to normoalbuminuria, (2) Baseline macroalbuminuria to microalbuminuria, (3) the previous two factors combined (proportions)
- eGFR (sustained confirmed decrease ≥30% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation; time-to-first event)
- eGFR (sustained confirmed decrease ≥40% to sustained confirmed eGFR <60 mL/min/1.73m^2 using CKD-EPI equation; time-to-first event)
- eGFR total slope and chronic slope using CKD-EPI equation (*added to final SAP; not included in the final clinical study protocol)*
- Renal composite endpoint: confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 (using CKD-EPI equation) and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed eGFR <15 mL/min/1.73m^2 and/or renal death (time-to-first event) (*added to final SAP; not included in the final clinical study protocol)*
- Albumin to creatinine ratio (adjusted mean percent change after 1, 2, 3 and 4 years)
- Change in body weight after 1, 2, 3, and 4 years
- Proportion of patients with 5% body weight loss and 10% body weight loss after 1, 2, 3 and 4 years
- Retinal laser and/or intraocular treatment due to development of and/or deterioration in diabetic retinopathy
- Blood pressure change from baseline
- Peripheral revascularization/limb ischemic event
- Surgical amputation and related events
- Any stroke (ischemic, hemorrhagic, or undetermined)

Statistical Analysis Plan

The initial SAP (Edition 1.0) was dated November 19, 2012 and was revised several times based on feedback from the Agency. A major change to the statistical testing hierarchy was submitted in SAP Edition 6.0, dated December 17, 2015, in which the composite of heart failure hospitalization/CV death was elevated to a dual primary efficacy endpoint along with MACE, and a renal composite endpoint was added to the closed testing procedure as a secondary endpoint. The first interim analysis was reviewed by the DMC on February 8, 2016 after 33% of planned MACE events were adjudicated. The SAP was finalized on May 31, 2018 (Edition 8.0) and contained additional exploratory analyses of eGFR slope that were not included in the final CSP. The trial database was locked on September 16, 2018.

The study was event-driven, with 1390 MACE events required to have 85% power to demonstrate superiority of dapagliflozin to placebo with a HR of 0.85. The study ultimately accumulated 1559 MACE events. The Cox proportional hazards model was used to analyze the time-to-event variables and was stratified by baseline hematuria and baseline CV risk category.

There were two interim analyses performed by an independent statistical group (Stanford University) and reviewed by the DMC/DSMB. These interim analyses assessed superiority for MACE and all-cause mortality after 1/3 and 2/3 of the MACE events had occurred and used an O'Brien-Fleming alpha-spending rule. The interim analyses assessed superiority of dapagliflozin to placebo for MACE, and the study would be terminated early if clear superiority was demonstrated. The first interim analysis had a one-sided alpha level of 0.000095; the second interim analysis had a one-sided alpha level of 0.00614. This left a one-sided alpha of 0.023095 for the final analysis. At each interim analysis MACE was tested at the prespecified alpha level, and if superiority was demonstrated, all-cause mortality was then to be tested at the same alpha level. If superiority was shown for both endpoints, the DMC was to evaluate the CV data and safety data to determine whether to recommend ending the study early. Neither interim analysis presented to the DMC demonstrated superiority of dapagliflozin to placebo for MACE, and therefore the trial continued to completion. In addition to the interim efficacy analysis for MACE, an interim analysis of bladder cancer took place on February 8, 2016, after 32 bladder cancer events had been collected. There were no findings from that analysis that affected the DMC's recommendation to continue the trial.

For the final statistical testing procedure, non-inferiority of dapagliflozin compared to placebo for MACE was tested based on a one-sided alpha of 0.023095, and based on a non-inferiority margin of 1.3 per the 2008 FDA Guidance for Industry: *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. If non-inferiority was demonstrated, the full alpha was to be split between the two dual efficacy endpoints: superiority of dapagliflozin for MACE, and the composite of HF hospitalization/CV death. If either of these dual endpoints demonstrated superiority of dapagliflozin, the alpha could be recycled to the other efficacy endpoint. (b) (4)

All primary, secondary, and exploratory efficacy endpoints were tested based on the Full Analysis Set (FAS), which included all patients who have been randomized to study treatment irrespective of protocol adherence and participation in the study. Patients in the FAS were analyzed based on their randomized treatment assignment regardless of whether they received that treatment and whether an event occurred before or after treatment discontinuation.

Table 3. Confirmatory Testing Procedures Using One-sided Alpha

H1: Non-inferiority for MACE (α=0.0231)[a]	
The α splits into independent testing of the primary composites in parallel:	
H02: Superiority for MACE (α=50% of primary α)[c]	H03: Superiority for hospitalisation for heart failure or CV death (α=50% of primary α)[c]
H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death[b]	
H05: Superiority for all-cause mortality[d]	

[a] At the interim analyses, the α for superiority was replaced by 0.000095 (first interim) and 0.00614 (second interim), and no testing for non-inferiority was performed.
[b] With the exception of all-cause mortality, secondary endpoints were only tested once. The α was controlled for the overall Type I error across the primary and secondary variables and across the interims and final analysis.
[c] The α was 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalisation for heart failure or CV death.
[d] All-cause mortality was assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it was tested second following MACE. If the study had been stopped following an interim analysis, all-cause mortality would have remained as the 2nd endpoint following the test for superiority of MACE. Because the study ran to completion, all-cause mortality was tested as presented in this table.

CV Cardiovascular; eGFR Estimated glomerular filtration rate; ESRD End-stage renal disease; MACE Major adverse cardiovascular events

Source: Excerpted from the DECLARE CSR, p. 40

The following analysis sets were defined in the SAP:

- **Full Analysis Set (FAS):** All patients randomized to study treatment, irrespective of protocol adherence and continued participation in the study. The FAS was the primary analysis set for the primary and secondary endpoints, and the exploratory efficacy endpoints.
- **Safety analysis set (SAS):** All patients who received at least one dose of randomized dapagliflozin or placebo and who had data observed at any time after first randomized dose until the end of the study. Patients who were randomized to one treatment group but erroneously received the other treatment were analyzed according to their actual treatment in this set. All safety variables except the primary safety variable were analyzed using this set, which was the primary analysis set for malignancies, fractures, and amputations.
- **On-treatment analysis set (OT-SAS):** All randomized patients who received at least one dose of investigational product and who had data observed at any time after first randomized dose until the end of the study, and only observations collected *during treatment with study drug or within a certain number of days of the last dose of study drug:*
    - Primary, secondary, and categorical exploratory endpoints: 30 days

- Continuous exploratory and safety endpoints: 7 days
- SAEs: 30 days
- AEs of special interest that are not serious: 7 days

The OT-SAS was the primary analysis set for safety variables with the exception of malignancies, amputations and fractures.

The analysis sets and variables analyzed with each set are summarized in Table 4 below.

Table 4. Analysis sets used for primary and sensitivity analyses for efficacy and safety variables

Variable	Primarily analysis	Sensitivity analysis
Primary variables	FAS	On-Treatment set
Secondary variables	FAS	On-Treatment set
Exploratory Efficacy variables	FAS	On-Treatment set for selected variables
Cancer, Amputations and Fractures	Safety analysis set	On-Treatment set
Other Safety variables	On-Treatment set	Safety analysis set

Source: Excerpted from DECLARE Statistical Analysis Plan, Edition 8.0 (final), p. 21

Protocol Amendments

There were five global revisions of the clinical trial protocol after the initial protocol was finalized on November 12, 2012.

- Protocol Amendment 1 (April 5, 2013):
  - Added baseline collection of waist and hip circumference
  - Updated eCRF to reflect whether patients have undergone any urinary tract investigations between planned trial visits
  - Clarified that from the signing of informed consent to the closing visit, only adverse events that qualify as an SAE, are the reason for treatment discontinuation, are a suspected CV event, a suspected neoplasm (benign, malignant, or unspecified), a major hypoglycemic event, a fracture, a hepatic event, a renal event, or a symptom of volume depletion, should be recorded in the eCRF
  - Added a malignancy specific form to the eCRF (in addition to the SAE form) to record all possible malignancies (except for non-melanoma skin cancer)
  - Changed renal monitoring plan to retest patients with CrCl (based on Cockroft-Gault) <45 mL/min within 4 days whenever possible
- Protocol Amendment 2 (December 19, 2013):
  - Updated inclusion criteria to specify “current” tobacco use as an additional risk

factor for CV disease
- Updated exclusion criteria to specify recent (within 24 months) treatment with pioglitazone and/or use of pioglitazone for 2 years or more at any time
- Added that the proportion of patients with an HbA1c between 6.5 and 7.0% will be capped at approximately 5% of the study population.
- Added more detailed documentation of antihypertensive medications, and changes in concomitant medications associated with treatment for an AE, to the eCRF
- Added closer monitoring of renal function for patients with decreases in CrCl to <60 mL/min based on Cockroft-Gault
- Added details to the plan for assessment of hepatic laboratory abnormalities, including sampling for "Hy's law panel", for patients with confirmed AST and/or ALT >3 x ULN

- Protocol Amendment 3 (April 28, 2014):
  - Increased enrollment target to 27000 patients to reach the randomization target of 17150 due to a higher observed screen failure rate than originally estimated
  - Changed secondary prevention population enrollment goal to 33% (from initial primary prevention population enrollment goal of 33%)
  - The assumed annual event rate on placebo was specified at 2.1%
  - Added hypersensitivity reactions (serious or leading to treatment discontinuation), urinary tract infections (serious or leading to treatment discontinuation), and genital infections (serious or leading to treatment discontinuation) to the list of AESIs to be recorded in the eCRF
  - Global safety database responsibility transferred from Bristol Myers Squibb to AstraZeneca

- Protocol Amendment 4 (August 11, 2015): This protocol amendment was never in use, as it was replaced by Protocol Amendment 5 on December 23, 2015 (see below) in response to FDA feedback regarding the renal secondary endpoints
  - Changed statistical testing procedure for primary endpoint to first test if dapagliflozin is non-inferior to placebo for the MACE endpoint with an NI margin of 1.3, and if non-inferiority is met the second step would test whether dapagliflozin is superior to placebo for the MACE endpoint
  - Added three renal secondary endpoints: development of albuminuria, change in albumin-to-creatinine ratio, and ≥30% decrease in eGFR from baseline (time to onset for all)
  - Minor changes to exploratory endpoints
  - Updated protocol throughout to reflect that AstraZeneca is now the sole Sponsor of the study
  - Added DKA to CEC-adjudicated events

- Protocol Amendment 5 (December 23, 2015):
  - In response to publication of the EMPA-REG results, this amendment changed the statistical confirmatory testing procedure for the primary objective to first test if dapagliflozin is non-inferior to placebo for the MACE endpoint with an NI margin of 1.3. If non-inferiority is met the second step would test whether dapagliflozin is superior to placebo for two co-primary endpoints: MACE and the composite of heart failure hospitalization or CV death
  - Hospitalization for congestive heart failure was moved from the list of secondary endpoints and elevated to a component of the coprimary endpoints
  - In response to FDA feedback, changed proposed renal secondary endpoints to a renal composite endpoint: confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73^2) and/or renal or CV death
  - Moved the secondary endpoints of reduction of body weight from baseline and the composite endpoint of CV death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina pectoris, or hospitalization for any revascularization to exploratory endpoints
  - Removed the proposed secondary endpoints of development of albuminuria, change in albumin-to-creatinine ratio, and ≥30% decrease in eGFR from baseline (time to onset for all) and added several renal exploratory endpoints encompassing these parameters
  - Added change in body weight at 2 and 3 years, and proportion of patients with 5% body weight loss and 10% body weight loss after 2 years and 3 years
  - In response to FDA feedback, added surgical amputation and related events to list of exploratory endpoints
  - Added eCRF form to capture amputations and related events
  - Updated procedures for following up on patients with worsening renal function
  - Added additional options for sensitivity analyses including imputation of missing data

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has indicated that their study was conducted in compliance with Good Clinical Practice (GCP) rules as referenced in the International Conference on Harmonisation (ICH) guidelines (ICH E6), the U.S. Code of Federal Regulations Guidelines for Good Clinical Practice, and the Declaration of Helsinki.

The Applicant reported potential scientific misconduct at Site 5709 (Principal Investigator Jerry Cygler, Poland) on November 22, 2016 related to the SIROCCO trial for benralizumab. The Applicant reported anomalous PK data from 8 patients randomized to benralizumab and conducted a "for cause" audit of the site, which did not identify an explanation for the data in question. The Applicant also had concerns that the site had submitted redacted documentation that did not allow for identification of the cause of the anomalous results. The Applicant considered this to be a breach of Good Clinical Practice standards and audited other clinical trials being conducted at the same site, including DECLARE. No concerns were identified regarding the 30 patients randomized in the DECLARE trial at this site, but the Applicant chose to halt study activities at this site because they could not exclude the possibility that other GCP violations may have occurred. The 52 patients enrolled at this site were excluded from the Applicant's analyses for DECLARE.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements and there do not appear to be conflicts of interest that would compromise data integrity. Refer to the Financial Disclosure template in Section 13.2.

Patient Disposition

There were 882 study sites across 33 countries. Of note, in the data files submitted to this sNDA Hong Kong is coded as a separate country, such that there are 34 country codes represented in the datasets. The first study patient was enrolled on April 25, 2013; the final patient was randomized on June 30, 2015; the last on-site visit of a patient took place on September 11, 2018. Overall, 25698 patients were enrolled, 17160 patients were included in the FAS population used to assess CV safety and efficacy, and 16906 (98.5%) patients completed the study.

Of note, the ADSL dataset contains 25750 patients with a "Yes" randomization flag (i.e., 52 additional patients beyond the 25698 enrolled patients described above). These 52 patients were all enrolled at Site 5709 in Poland, which was found by the Applicant to have GCP violations during another trial. Therefore, the Applicant decided to exclude all 52 DECLARE patients enrolled at this study site (30 of whom had been randomized) prior to unblinding of the trial; these 52 patients were not included in any of the Applicant's analyses.

Of the 25698 enrolled patients, 8538 (33.2%) were not randomized. Most of these (8340, 32.5% of the enrolled population) failed inclusion or exclusion criteria, with the most common reasons being HbA1c outside of acceptable range (3757 patients, 44% of unrandomized patients) and CrCl < 60 ml/min (1824, 21% of unrandomized patients).

Overall, 98.5% of patients randomized completed the trial. As shown in Table 5, a small

percentage of patients discontinued from the trial in each treatment arm (1.3% of patients in the dapagliflozin group and 1.7% of patients in the placebo group). More patients discontinued study drug in the placebo arm (2144 or 25%) versus the dapagliflozin arm (1807 or 21.1%), with the most common reason for treatment discontinuation in both groups being "subject decision" followed by adverse events. A Kaplan-Meier plot of time-from-randomization to premature permanent discontinuation of study drug (not shown here but presented in the CSR, p.54) demonstrates that rates of study drug discontinuation were similar between arms until approximately 6 months, at which time the curves separated as more patients discontinued study drug in the placebo arm.

A small number of patients discontinued due to development of study-specific discontinuation criteria. For over 99% of randomized patients, vital status was known at the end of the trial. Of those for whom vital status was unknown (48 dapagliflozin patients and 64 placebo patients), most had withdrawn consent, while 30 patients (12 dapagliflozin patients and 18 placebo patients) were lost to follow-up despite attempts to assess vital status.

Table 5. Patient Disposition (Randomized Population)—Study D1693C00001

Disposition Event	Dapagliflozin 10mg n (%)	Placebo n (%)
Randomized	8582 (100.0)	8578 (100.0)
Completed trial	8473 (98.7)	8433 (98.3)
Discontinued from trial	109 (1.3)	145 (1.7)
Adverse event	0	0
Withdrawal of consent	97 (1.1)	127 (1.5)
Lost to follow-up	12 (0.1)	18 (0.2)
Discontinued treatment	1807 (21.1)	2144 (25.0)
Adverse event	671 (7.8)	548 (6.4)
Subject decision	825 (9.6)	1086 (12.7)
Study-specific discontinuation criteria	38 (0.4)	60 (0.7)
Liver enzyme elevation	6 (0.06)	8 (0.09)
Creatine clearance <30 mL/min	10 (0.1)	17 (0.2)
Bladder cancer	22 (0.3)	35 (0.4)
Pregnancy	0	0
Other Reason	273 (3.2)	450 (5.2)
Final Vital Status Available	8534 (99.4)	8514 (99.3)
Alive	8005 (93.3)	7944 (92.6)
Dead	529 (6.2)	570 (6.6)

Source: Derived from ADSL.xpt and ADDS.xpt datasets using JMP

Protocol Violations/Deviations

Important protocol deviations occurred in approximately 10% of patients in each treatment arm and were balanced between arms (Table 6). The majority of protocol deviations were due to patients being assigned a randomization code according to incorrect entry of stratification factors. Seventeen patients (8 assigned to dapagliflozin, 9 assigned to placebo) were randomized but never took study drug; these patients were excluded from the on-treatment analysis sets. Five patients (4 assigned to dapagliflozin, 1 assigned to placebo) received the incorrect study drug at any point during the study.

In addition to the information presented in Table 6, the ADPRODEV dataset shows that 44 patients in the placebo group and 42 patients in the dapagliflozin group had more than one important protocol deviation; a maximum number of three protocol deviations was reported for any individual subject (two patients in the placebo group and three patients in the dapagliflozin group had a total of three important protocol deviations).

Table 6. Major Protocol Deviations

Protocol Deviation Term	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Total patients with at least 1 major protocol deviation	861 (10.0)	870 (10.1)
Subject assigned a randomization code according to incorrect entry of baseline stratification factors	780 (9.1)	770 (9.0)
Unexplained hematuria at randomization	40 (0.5)	54 (0.6)
Subjects previously randomized into the study	21 (0.2)	28 (0.3)
CrCl <60 mL/min at enrollment	13 (0.2)	16 (0.2)
Subjects without established CV disease and less than 2 risk factors	12 (0.1)	15 (0.2)
Subjects with acute CV disease at randomization	10 (0.1)	10 (0.1)
Current or recent (within 24 months prior to randomization) treatment with pioglitazone and/or use of pioglitazone for a total of 2 years or more during lifetime	8 (0.1)	7 (0.1)
Subjects randomized but took no investigational product	8 (0.1)	9 (0.1)
Screening or run-in HbA1c out of range (≥12% or <6.5%)	7 (0.1)	2 (0.02)
Subjects who received incorrect investigational product, completely or at any time during the	4 (0.05)	1 (0.01)

study		
History of bladder cancer	2 (0.02)	2 (0.02)
Previous treatment with any SGLT2 inhibitor	1 (0.01)	0
Abnormal LFTs (AST or ALT >3xULN or Total bilirubin >2.5xULN at enrollment	0	1 (0.01)
Subjects with end stage renal disease at baseline	0	1 (0.01)

Source: Derived from ADPRODEV.xpt dataset using JMP and adapted from Table 11.1.2.2 in the CSR Appendix

Unblinding:

The sNDA submission did not provide details about unblinding of subjects during the trial. The Applicant submitted additional information regarding unblinding on June 28, 2019, in response to an Information Request. The Applicant reported that no members of the study team at TIMI, Hadassah, AstraZeneca, Bristol-Myers Squibb, or personnel at the study centers or clinical research organizations handling data had access to unblinded information prior to data unblinding on September 17, 2018. The DMC had access to individual treatment codes and could merge these with collected study data while the study was ongoing. Subject unblinding was permitted by personnel at study centers in medical emergencies and personnel at the AstraZeneca Patient Safety Department for purposes of periodic safety reporting and expedited reporting of SAEs. During the trial, 6 patients were unblinded by study site personnel due to medical emergencies, and 192 patients were unblinded by AstraZeneca for safety reporting purposes.

Table 7. Summary of Patient Unblinding During the DECLARE Trial

Unblinded by	Dapa 10 mg	Placebo	Total
Site-level personnel	2	4	6
AZ DES	93	99	192

Source: Applicant response to Clinical Information Request submitted on June 28, 2019, Ser 0616

Reviewer Comment: *Protocol deviations were randomly distributed across treatment arms and there were no significant imbalances between arms. These deviations are unlikely to have affected the overall conclusions of the trial. Similarly, the unblinding of patients for safety reporting purposes and medical emergencies appears reasonable, was evenly distributed across treatment arms, and was unlikely to have affected the conclusions of the trial.*

Table of Demographic Characteristics

Table 8. Baseline Demographic Characteristics (FAS Population)—Study D1693C00001

Demographic Parameter	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Sex		
Male	5411 (63.1)	5327 (62.1)
Female	3171 (36.9)	3251 (37.9)
Age, mean (years ± SD)	63.9 ± 6.8	64.0 ± 6.8
Median (years)	64	64
Min, max (years)	40, 92	40, 88
Age Group		
< 50 years	202 (2.4)	220 (2.7)
< 65 years	4631 (54.0)	4622 (53.9)
≥ 65 years	3951 (46.0)	3956 (46.1)
≥ 75 years	538 (6.3)	558 (6.5)
Race		
White	6843 (79.7)	6810 (79.4)
Black or African American	295 (3.4)	308 (3.6)
Asian	1148 (13.4)	1155 (13.5)
American Indian or Alaska Native	52 (0.6)	52 (0.6)
Native Hawaiian or Other Pacific Islander	9 (0.1)	13 (0.2)
Other	235 (2.7)	240 (2.8)
Ethnicity		
Hispanic or Latino	1298 (15.1)	1270 (14.8)
Not Hispanic or Latino	7284 (84.9)	7308 (85.2)
Region		
North America	2737 (31.9)	2731 (31.8)
United States	1938 (22.6)	1947 (22.7)
Canada	799 (9.3)	784 (9.1)
Latin America	946 (11.0)	931 (10.9)
Europe	3390 (39.5)	3390 (39.5)
Eastern Europe	2370 (27.6)	2324 (27.1)
Western Europe	1020 (11.9)	1066 (12.4)
Asia/Pacific	882 (10.3)	890 (10.4)
Middle East/Central Asia	185 (2.2)	208 (2.4)
Africa	231 (2.7)	225 (2.6)
Australia	211 (2.5)	203 (2.4)

Source: Derived from DM.xpt and ADSL.xpt datasets using JMP

Reviewer Comment: *Overall, most study subjects were white, and over half the study subjects were male. Approximately 32% of subjects were enrolled at study sites in North America; European study sites enrolled the largest proportion of patients (approximately 40%, with about two thirds of European subjects enrolled at Eastern European study sites). Black/African American, American Indian/Alaska Native, and Native Hawaiian/Pacific Islander subjects were under-represented in the trial; this is particularly noteworthy given the high prevalence of T2DM in these groups. Asian subjects, on the other hand, were relatively well-represented in this trial. The demographic characteristics of DECLARE are similar to those of the EMPA-REG OUTCOME trial and the CANVAS program. This allows for meaningful comparisons across CVOTs in the class, but may limit generalizability of trial findings to demographic groups that were under-represented.*

The Applicant also provided demographic analyses based on CV risk category (established CV disease versus multiple risk factors). The only notable finding is that an even higher proportion of patients in the established CV disease group were male: 72.1% of the total population with established CV disease were males while 27.9% were female. This is to be expected given the higher risk of CV disease in males. Otherwise demographic parameters were comparable to the overall study population when analyzed by baseline CV risk category.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9. Baseline Clinical Characteristics (FAS Population)

Baseline Characteristic	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Weight (kg), mean ± SD	90.9 ± 20.2	90.6 ± 20.5
BMI (kg/m^2), mean ± SD	32.1 ± 6.0	32.0 ± 6.1
BMI <30 kg/m^2	3432 (40.0)	3532 (41.2)
BMI ≥30 kg/m^2	5145 (60.0)	5042 (58.8)
Systolic Blood Pressure (mmHg), mean ± SD	135.1 ± 15.3	134.8 ± 15.5
Diastolic Blood Pressure (mmHg), mean ± SD	78.0 ± 9.0	77.9 ± 9.1
T2DM duration (years), mean ± SD	11.9 ± 7.7	11.9 ± 7.9
Glycemic status		
HbA1c%, mean ± SD	8.3 ± 1.2	8.3 ± 1.2
Fasting plasma glucose (mg/dL), mean ± SD	171.5 ± 56.4	170.9 ± 54.6
***Baseline HbA1c category** (%)*		
<7	773 (9.0)	774 (9.0)
≥7 to <8	3317 (38.7)	3309 (38.6)
≥8 to <9	2193 (25.6)	2327 (27.1)
≥9	2297 (26.8)	2164 (25.2)
Not reported	2 (0.02)	4 (0.05)
Renal function		
eGFR (mL/min/1.73^2) by CKD-EPI, mean ± SD	85.4 ± 15.8	85.1 ± 16.0
Baseline eGFR category		
Normal + Stage 1 CKD (≥90)	4137 (48.2)	4025 (46.9)
Stage 2 CKD (60-89)	3838 (44.7)	3894 (45.4)
Stage 3a CKD (45-59)	513 (6.0)	563 (6.6)
Stage 3b CKD (30-44)	80 (0.9)	89 (1.0)
Stage 4 (15-29)	10 (0.1)	6 (0.1)
Stage 5 (<15)	3 (0.03)	1 (0.01)
Not reported	1 (0.01)	0
***Baseline urine albumin/creatinine ratio** (mg/g)*		
<30	5819 (67.8)	5825 (67.9)
≥30 to ≤300	2017 (23.5)	2013 (23.5)
>300 to ≤1000	429 (5.0)	380 (4.4)
>1000	165 (1.9)	195 (2.3)
Not reported	152 (1.8)	165 (1.9)
Baseline hematuria status		
Positive	1230 (14.3)	1222 (14.2)
Negative	7160 (83.4)	7167 (83.6)

Not reported	192 (2.2)	189 (2.2)
Medical History		
Established CV disease	3474 (40.5)	3500 (40.8)
Multiple risk factors*	5108 (59.5)	5078 (59.1)
Heart Failure	852 (9.9)	872 (10.2)
Hypertension	7769 (90.5)	7658 (89.3)
Hyperlipidemia	6885 (80.2)	6911 (80.6)
Retinopathy	1079 (12.6)	1058 (12.3)
Nephropathy	714 (8.3)	691 (8.1)
Lower extremity amputation	50 (0.6)	56 (0.7)
Concomitant medications		
Any anti-diabetic therapy	8415 (98.1)	8420 (98.2)
Metformin	7020 (81.8)	7048 (82.2)
Sulfonylurea	3615 (42.1)	3707 (43.2)
Insulin	3566 (41.6)	3445 (40.2)
DPP4-inhibitor	1418 (16.5)	1470 (17.1)
GLP1 receptor agonist	397 (4.6)	353 (4.1)
Other anti-diabetic drug	13 (0.2)	21 (0.2)
Number of anti-diabetic therapies		
None	167 (1.9)	158 (1.8)
1 medication	2061 (24.0)	2134 (24.9)
2 medications	3800 (44.3)	3711 (43.3)
3 or more medications	2554 (29.8)	2757 (30.0)
CV Medications		
ACE inhibitor/ARB	6974 (81.3)	6970 (81.3)
Thiazide diuretic	1916 (22.3)	1857 (21.6)
Loop Diuretic	866 (10.1)	936 (10.9)
Beta blocker	4498 (52.4)	4527 (52.8)
Calcium channel blocker	2976 (34.7)	3013 (35.1)
Mineralocorticoid receptor antagonist	366 (4.3)	395 (4.6)
Acetylsalicylic acid	4753 (55.4)	4770 (55.6)
Statin/ezetimibe	6432 (74.9)	6436 (75.0)
Anticoagulant	529 (6.2)	556 (6.5)
Any antiplatelet therapy	5244 (61.1)	5239 (61.1)
Dual antiplatelet therapy	793 (9.2)	846 (9.9)

*12 patients in the dapagliflozin treatment arm and 15 patients in the placebo arm did not have documented established CVD or multiple risk factors and were assigned to the MRF group in the ADSL dataset

Source: Derived from ADSL.xpt and ADCM.xpt datasets using JMP and adapted from Tables 11.1.4.1.1 and 11.1.4.2.1 in CSR Appendix 11

Reviewer Comments: *Details of subjects' baseline heart failure history was not systematically collected or confirmed. While about 10% of patients in each treatment group reported a baseline medical history of heart failure, about 30% of patients in each treatment group had baseline echocardiograms on file. This may reflect practice patterns in different countries or regions, or may suggest that the baseline medical history collection did not capture all patients with a history of heart failure.*

It is noteworthy that although 513 patients in the dapagliflozin arm and 563 patients in the placebo arm had baseline eGFR 45-60 mL/min/1.73m^2, 48% of these actually had baseline eGFR 55-60 mL/min/1.73m^2 and only 91 patients in the dapagliflozin arm had eGFR 45-49 mL/min/1.73m^2. Thus, this eGFR category skews heavily toward the upper eGFR range and highlights the limited representation of patients with baseline renal impairment in the trial.

I also looked at concomitant medications by CV risk category: overall a higher proportion of patients with established CV disease took insulin (45.7%) compared with patients with MRF (37.5%), and a slightly lower proportion of patients with eCVD took metformin (78.1%) compared with patients with MRF (84.7%). These differences are unlikely to have affected the results of the study. The mean total daily dose of insulin at randomization was 71.5 IU, similar across the two treatment arms.

Table 10. Baseline History of Cardiovascular Disease (FAS Population)

Baseline Cardiovascular Disease	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Established CV disease	3474 (40.5)	3500 (40.8)
Ischemic heart disease	2824 (32.9)	2834 (33.0)
Cerebrovascular disease	653 (7.6)	648 (7.6)
Peripheral arterial disease	522 (6.1)	503 (5.9)
1 CV disease	2992 (34.9)	3064 (35.7)
2 CV diseases	439 (5.1)	387 (4.5)
3 CV diseases	43 (0.5)	49 (0.6)
Multiple risk factors, but without established CV disease*	5096 (59.3)	5063 (59.0)
Dyslipidemia	3738 (43.6)	3778 (44.0)
Hypertension	4686 (54.6)	4588 (53.5)
Current tobacco use	1277 (14.9)	1221 (14.2)
Left ventricular ejection fraction at baseline reported	2579 (30.1)	2623 (30.6)
<30% or severe dysfunction	61 (0.7)	65 (0.8)
30 to <45% or moderate dysfunction	257 (3.0)	288 (3.4)
45 to <55% or mild dysfunction	503 (5.9)	517 (6.0)
≥55% or normal	1758 (20.5)	1753 (20.4)

*Table 9 (Baseline Clinical Characteristics) shows 12 additional patients in the dapagliflozin group and 15 additional patients in the placebo group who were assigned to the multiple risk factor group in the ADSL dataset. Categorization of these patients as eCVD versus multiple risk factors was missing and they were all assigned to the MRF group in the ADSL dataset. These patients have been removed here.

Source: Derived from ADSL.xpt using JMP and adapted from Tables 11.1.3.3.1 and 11.1.4.1.1 in the CSR Appendix

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

During the trial, subjects were considered compliant with their investigational treatment regimen if their adherence rates, based on tablet counts, were between 80 and 120%. Overall 74.4% of enrolled subjects met this definition, balanced between treatment arms (74.8% in the dapagliflozin arm versus 74.0% in the placebo arm). Compliance was slightly higher among patients with MRF (76.9%) versus those with eCVD (70.8%). Overall higher compliance was observed in Europe and Asia, which reported 80.8% and 80.0% compliance, respectively, compared with North America and Latin America, which reported 65.9% and 67.0% compliance, respectively.

Reviewer Comment: *Treatment compliance in DECLARE was lower than that reported in the EMPA-REG OUTCOME trial, for example, which reported almost 92% compliance in each*

treatment arm. The CANVAS program did not define treatment compliance in the same way as DECLARE and EMPA-REG, and reported only the percentage of patients who discontinued the two CANVAS trials due to treatment noncompliance, making comparisons to the other CVOTs in the SLGT2 inhibitor class more difficult. Prospective electronic monitoring studies have demonstrated that in clinical practice patients take 67-85% oral hypoglycemic agent doses as prescribed.[11] As such, the DECLARE treatment compliance rate appears consistent with patient adherence rates in clinical practice. Overall, treatment compliance in DECLARE appears to be reasonable and similar between treatment arms, allowing for meaningful interpretation of the study results.

All concomitant medications were recorded in the eCRF. Anti-diabetic and anti-hypertensive concomitant medications were presented in **Table 9** above. Patients were to continue baseline anti-diabetic therapy during the trial, but investigators were told they could consider lowering the dose of insulin secretagogues or injectable insulins to reduce the risk of hypoglycemia with addition of the IP. Otherwise, patients were to be treated for diabetes as per the ADA and EASD guidelines. Patients could have adjustments to their diabetes medications at the investigators' discretion. As a cardiovascular outcome trial, DECLARE's main purpose was not to estimate efficacy of dapagliflozin with regard to HbA1c reduction, and therefore changes or additions to antidiabetic regimens were not considered "rescue therapy" per se. However, changes to diabetic regimens were recorded in the eCRF. These are discussed in the efficacy section of this review.

Table 11. CV Medication Use After Randomization: Overall and by Baseline CV Risk Category (FAS Population)

Population	Dapagliflozin 10mg n (%)	Placebo n (%)
Overall FAS	**8582 (100)**	**8578 (100)**
ACE inhibitor/ARB	7326 (85.4)	7373 (86.0)
Statin/ezetimibe	7111 (82.9)	7082 (82.6)
Any antiplatelet agent	5669 (66.1)	5658 (66.0)
Acetylsalicylic acid	5187 (60.4)	5172 (60.3)
Beta blockers	4934 (57.5)	5075 (59.2)
Calcium channel blockers	3461 (40.3)	3701 (43.1)
Diuretics-thiazides	2219 (25.9)	2277 (26.5)
Diuretics-loops	1216 (14.2)	1449 (16.9)
Dual antiplatelets	1166 (13.6)	1178 (13.7)
Anticoagulants	799 (9.3)	867 (10.1)

[11] Cramer JA. A systematic review of adherence with medications for diabetes. *Diabetes Care* 2004;27(5):1218-24

Mineralocorticoid receptor antagonists	575 (6.7)	669 (7.8)
Established CV disease	**3474 (40.5)**	**3500 (40.8)**
ACE inhibitor/ARB	3002 (86.4)	3043 (86.9)
Statin/ezetimibe	3202 (92.2)	3176 (90.7)
Any antiplatelet agent	3100 (89.2)	3097 (88.5)
Acetylsalicylic acid	2765 (79.6)	2786 (79.6)
Beta blockers	2662 (76.6)	2715 (77.6)
Calcium channel blockers	1384 (39.8)	1462 (41.8)
Diuretics-thiazides	771 (22.2)	788 (22.5)
Diuretics-loops	736 (21.2)	831 (23.7)
Dual antiplatelets	956 (27.5)	998 (28.5)
Anticoagulants	441 (12.7)	450 (12.9)
Mineralocorticoid receptor antagonists	366 (10.5)	394 (11.3)
Multiple risk factors, but without established CV disease	**5096 (59.3)**	**5063 (59.0)**
ACE inhibitor/ARB	4324 (84.7)	4330 (85.3)
Statin/ezetimibe	3909 (76.5)	3906 (76.9)
Any antiplatelet agent	2569 (50.3)	2561 (50.4)
Acetylsalicylic acid	2422 (47.4)	2386 (47.0)
Beta blockers	2272 (44.5)	2360 (46.5)
Calcium channel blockers	2077 (40.7)	2239 (2239)
Diuretics-thiazides	1448 (28.3)	1489 (29.3)
Diuretics-loops	480 (9.4)	618 (12.2)
Dual antiplatelets	210 (4.1)	180 (3.5)
Anticoagulants	358 (7.0)	417 (8.2)
Mineralocorticoid receptor antagonists	209 (4.1)	275 (5.4)

Source: Adapted from Table 11.1.4.2.2 in the CSR Appendix

Reviewer Comment: *More patients in the placebo arm initiated diuretics during the trial, which is not surprising given that patients in the dapagliflozin arm had already received an additional drug with a diuretic mechanism.*

Efficacy Results – Primary Endpoint

The final confirmatory testing hierarchy (Table 3) elevated the composite of time-to-first heart failure hospitalization or CV death to a dual primary efficacy endpoint, along with the time-to-first occurrence of 3-point MACE. If dapagliflozin were non-inferior to placebo for MACE, testing could proceed down the hierarchy to test for superiority for 3-point MACE and hospitalization for heart failure/CV death. If either of these demonstrated statistical superiority of dapagliflozin, the entire one-sided alpha could be recycled to test the other primary efficacy endpoint. Only if both dual primary efficacy endpoints were statistically significant could the

alpha be recycled to test the secondary renal composite endpoint.

MACE Endpoint

As prespecified, the Applicant performed the primary analysis using the Full Analysis Set (FAS), considering all events from date of randomization up to trial completion. Overall there were 1559 patients with 3-point MACE events collected during the trial: 756 patients (8.8%) in the dapagliflozin arm and 803 patients (9.4%) in the placebo arm. The hazard ratio (HR) based on the Cox proportional hazards model for dapagliflozin vs. placebo was 0.93 (95% CI 0.84, 1.03) (Table 12). Based on these results, the Applicant concluded that dapagliflozin is non-inferior to placebo for MACE as measured against a non-inferiority margin of 1.3. Because the upper bound of the 95% CI was greater than 1.0, the Applicant also concluded that superiority of dapagliflozin over placebo was not demonstrated. The 95% CI was based on a reduced α level of 0.0231 due to the interim analyses of the trial data that occurred after approximately one third and two thirds of the MACE events had been collected.

Table 12. Confirmatory Analysis of Endpoint Hierarchy (FAS Population)

Priority and type	Order tested	Analysis	HR dapagliflozin to placebo (CI)	p-value[a]	Statistically significant
Primary safety	First	Non-inferiority: MACE	0.93 (0.84, 1.03)	<0.001	Yes
Primary efficacy	Second	Superiority: Hospitalisation for HF/CV death	0.83 (0.73, 0.95)	0.005	Yes
		Superiority: MACE	0.93 (0.84, 1.03)	0.172	No
Secondary efficacy	Third	Superiority: Renal composite endpoint	0.76 (0.67, 0.87)	<0.001	Not tested
	Fourth	Superiority: All-cause mortality	0.93 (0.82, 1.04)	0.198	Not tested

Derived from Tables 11.2.1.1, 11.2.2.1.1, and 11.2.2.2.1
[a] 1 sided p-value presented for MACE non-inferiority, all other p-values are 2-sided
Non-inferiority for MACE was tested at α=0.0231 (1-sided). Superiority for hospitalisation for heart failure or CV death, and superiority for MACE were tested in parallel following closed testing procedure at α =0.0231 (2-sided); as the composite of hospitalisation for HF and CV death was statistically significant, the full α was recycled to test MACE at α=0.0462 (2-sided). As MACE was not significant the renal composite endpoint and all-cause mortality were not tested as part of the confirmatory testing procedure.
Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term.
CI Confidence interval; CV Cardiovascular; HF Heart failure; HR Hazard ratio; MACE Major adverse cardiovascular event (cardiovascular death, ischaemic stroke, and myocardial infarction); FAS Full analysis set

Source: Excerpted from DECLARE CSR, Table 17, p. 66

The number of patients with a 3-point MACE event shown by each component of the composite endpoint is presented in Table 13, and a forest plot of MACE and its individual components is shown in Figure 2. Of note, the concordance between investigator-reported cardiac ischemic events and adjudicated cases was approximately 90%, for ischemic stroke concordance was approximately 82%. Dapagliflozin was not superior to placebo for any of the individual MACE components.

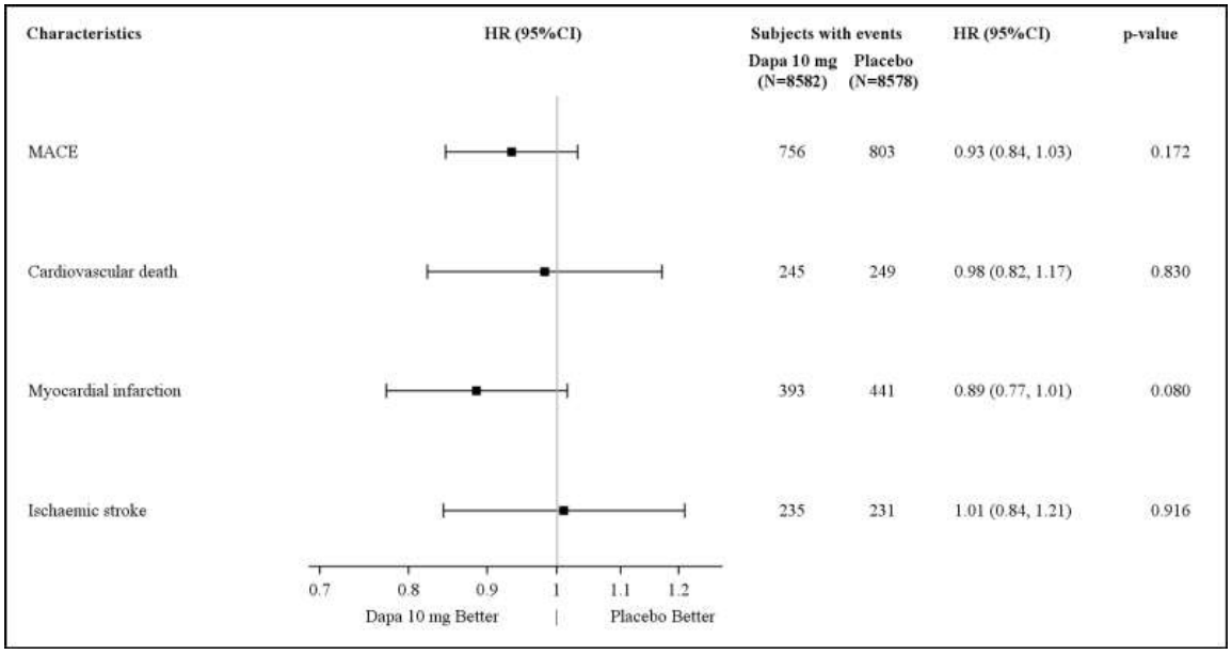
Table 13. Time from Randomization to First Occurrence of any Event of the Composite of CV Death, Myocardial Infarction, or Ischemic Stroke (FAS Population)

	Dapa 10 mg (N=8582)		Placebo (N=8578)			p-value		
Efficacy variable	Subjects with events n (%)	Event rate	Subjects with events n (%)	Event rate	Hazard ratio (CI)	[a]	[b]	[c]
Composite endpoint CV death/myocardial infarction/ ischaemic stroke	756 (8.8)	22.6	803 (9.4)	24.2	0.93 (0.84, 1.03)	<0.001	0.086	0.172
CV death	166 (1.9)		167 (1.9)					
Myocardial infarction	377 (4.4)		428 (5.0)					
Ischaemic stroke	213 (2.5)		208 (2.4)					

[a] One-sided p-value for non-inferiority test in MACE at alpha=0.0231.
[b] One-sided p-values for parallel superiority tests in MACE and hospitalisation for heart failure/CV death at alpha=0.01155, if [a] significant.
[c] Two-sided p-values for superiority. Nominal p-values for components.
[d] The number of events for the single components CV death, myocardial infarction and ischaemic stroke is the actual number of events for each component and does not add up to the number of events in the composite endpoint.
All events were adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% confidence intervals (CI) were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years. FAS Full analysis set; MACE Major adverse cardiovascular event (CV death/myocardial infarction/ischaemic stroke); N Number of subjects per treatment group

Source: Excerpted from Table 11.2.1.1 in the DECLARE CSR Appendix 11

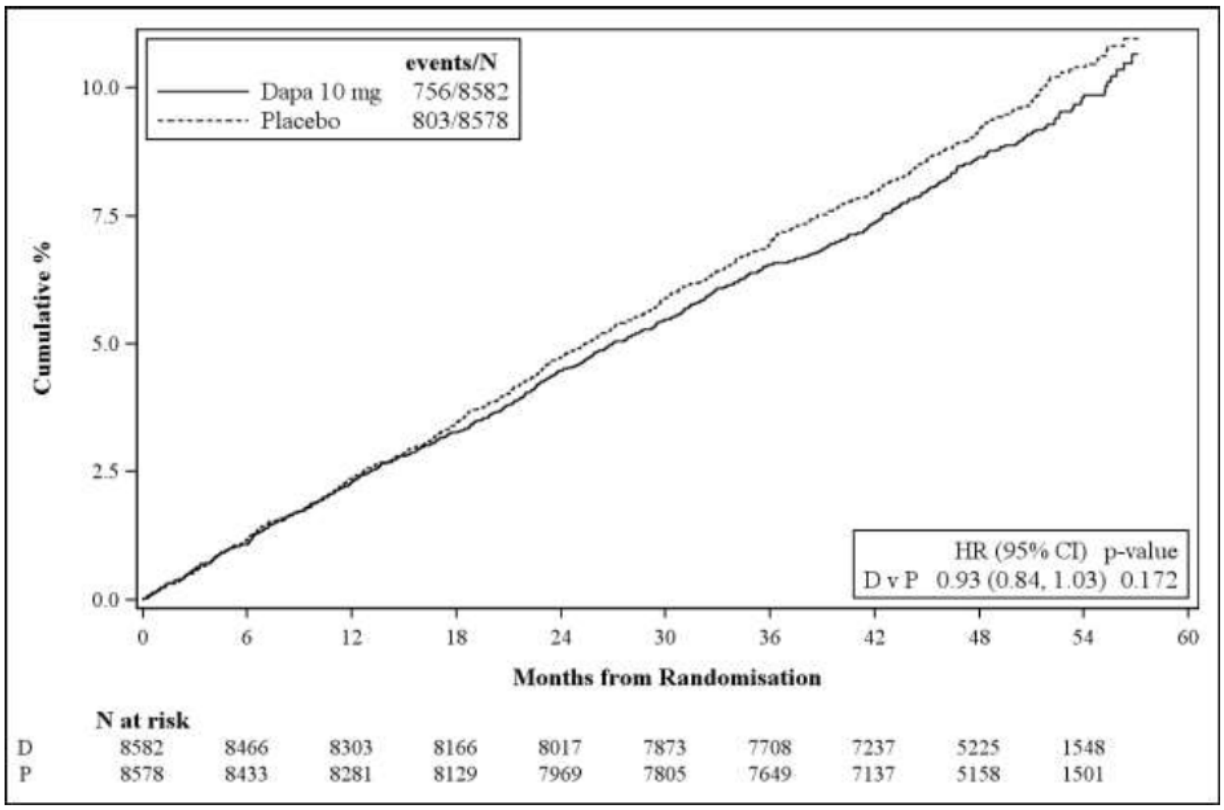
Figure 2. Forest Plot of the Composite of CV Death, MI or Ischemic Stroke (FAS Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.1.1

The Applicant's Kaplan-Meier estimation of time-to-first event of 3-point MACE is shown below in Figure 3.

Figure 3. Kaplan-Meier Plot of Adjudicated Events of the Composite of CV Death, Myocardial Infarction, and Ischemic Stroke (FAS Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.3

Reviewer Comment: *The Applicant's analysis demonstrated that dapagliflozin was non-inferior to placebo for the endpoint time-to-first MACE. These findings were confirmed by the FDA Statistical Reviewer (see Dr. Sherman Xia's review dated September 6, 2019). Dapagliflozin was also not superior to placebo for the composite MACE endpoint or any of its individual components. These results were consistent in patients with established CV disease and multiple risk factors (see discussion of Subpopulations, Section 7.1.3).*

The DECLARE results differed from both the EMPA-REG OUTCOME and CANVAS program findings. Canagliflozin and empagliflozin demonstrated superiority to placebo for the MACE endpoint in patients with established CV disease. For empagliflozin this result was driven almost entirely by the CV death component of MACE, as reflected in the final empagliflozin CV indication. For canagliflozin superiority for the overall MACE composite endpoint was observed, but no individual component demonstrated statistical superiority of canagliflozin, possibly due to too few events in each component category to achieve a statistically superior result. Possible reasons for the different results from DECLARE are the baseline patient population characteristics—i.e., only ~40% of patients enrolled in DECLARE had established CV disease—

versus some other property of dapagliflozin itself that may differ from the other two drugs in the class. The DECLARE trial also studied only one dose of dapagliflozin, while EMPA-REG and the CANVAS program both evaluated two doses of each respective drug; however, it is not clear that this would affect the final conclusions of the trial given that the higher dose of dapagliflozin was studied. Overall, the robustness of the DECLARE results are bolstered by the large number of MACE events collected (i.e., 1559 events, which exceeded the 1390 events needed to have 85% power to demonstrate superiority of dapagliflozin to placebo with an HR of 0.85) and the small amount of missing data for the trial.

Hospitalization for Heart Failure/CV Death Endpoint

The final statistical testing hierarchy specified that if non-inferiority of dapagliflozin to placebo was demonstrated for MACE, two dual primary efficacy endpoints would be tested next: superiority of dapagliflozin to placebo for MACE and the composite of hospitalization for heart failure (HHF)/CV death. If either of these dual efficacy variables was statistically significant, the full alpha could be recycled to test the other variable. As discussed above, superiority of dapagliflozin to placebo for MACE was not demonstrated; therefore, testing stopped at this point and secondary endpoints were not formally evaluated for statistical significance.

As prespecified, the Applicant performed the primary analysis using the FAS population, considering all events from date of randomization up to trial completion. Overall there were 417 patients (4.9%) in the dapagliflozin arm and 496 patients (5.8%) in the placebo arm with first occurrence of HHF/CV death: HR 0.83 (95% CI 0.73, 0.95; p=0.005). These results are shown in Table 14. The statistical significance of the composite endpoint was driven entirely by the difference in events of hospitalization for heart failure (HR 0.73; 95% CI 0.61, 0.88), while CV deaths were balanced between treatment arms.

Table 14. Time from Randomization to First Occurrence of any Event of Hospitalization for Heart Failure/CV Death (FAS Population)

Efficacy variable	Dapa 10 mg (N=8582)		Placebo (N=8578)		Hazard ratio (CI)	p-value
	Patients with events n (%)	Event rate	Patients with events n (%)	Event rate		
Composite endpoint hospitalisation for heart failure/CV death	417 (4.9)	12.2	496 (5.8)	14.7	0.83 (0.73, 0.95)	0.005[a]
Hospitalisation for heart failure	212 (2.5)		286 (3.3)			
CV death	205 (2.4)		210 (2.4)			
Single components[c]						
Hospitalisation for heart failure	212 (2.5)	6.2	286 (3.3)	8.5	0.73 (0.61, 0.88)	<0.001[b]
CV death	245 (2.9)	7.0	249 (2.9)	7.1	0.98 (0.82, 1.17)	0.830[b]

Source: Table 11.2.1.1

[a] Two-sided p-value.

[b] Nominal p-values.

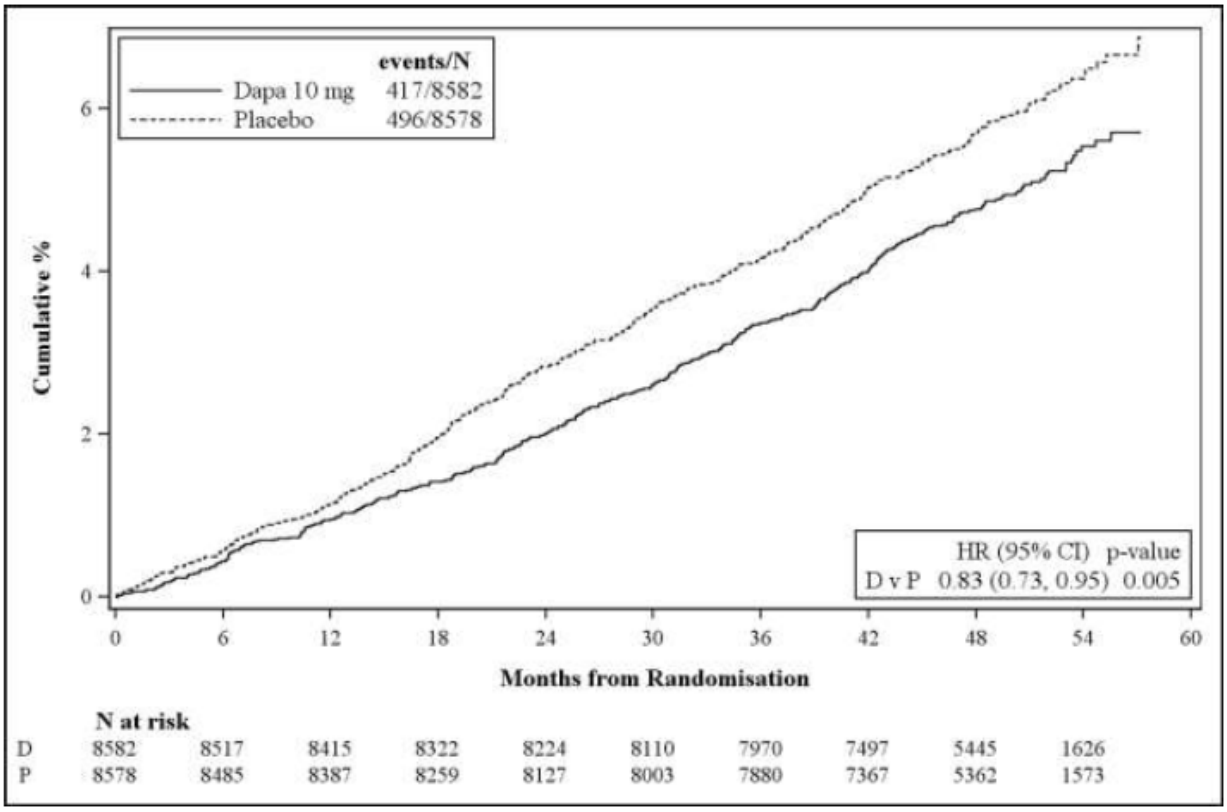
[c] Single components were analysed as exploratory variables. The number of first events for the single components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

All events were adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment as a model term. 95% CIs were calculated for the composite endpoints. Event rate displayed as event rate per 1000 subject years.

Source: Excerpted from the DECLARE CSR, Table 18, p. 68

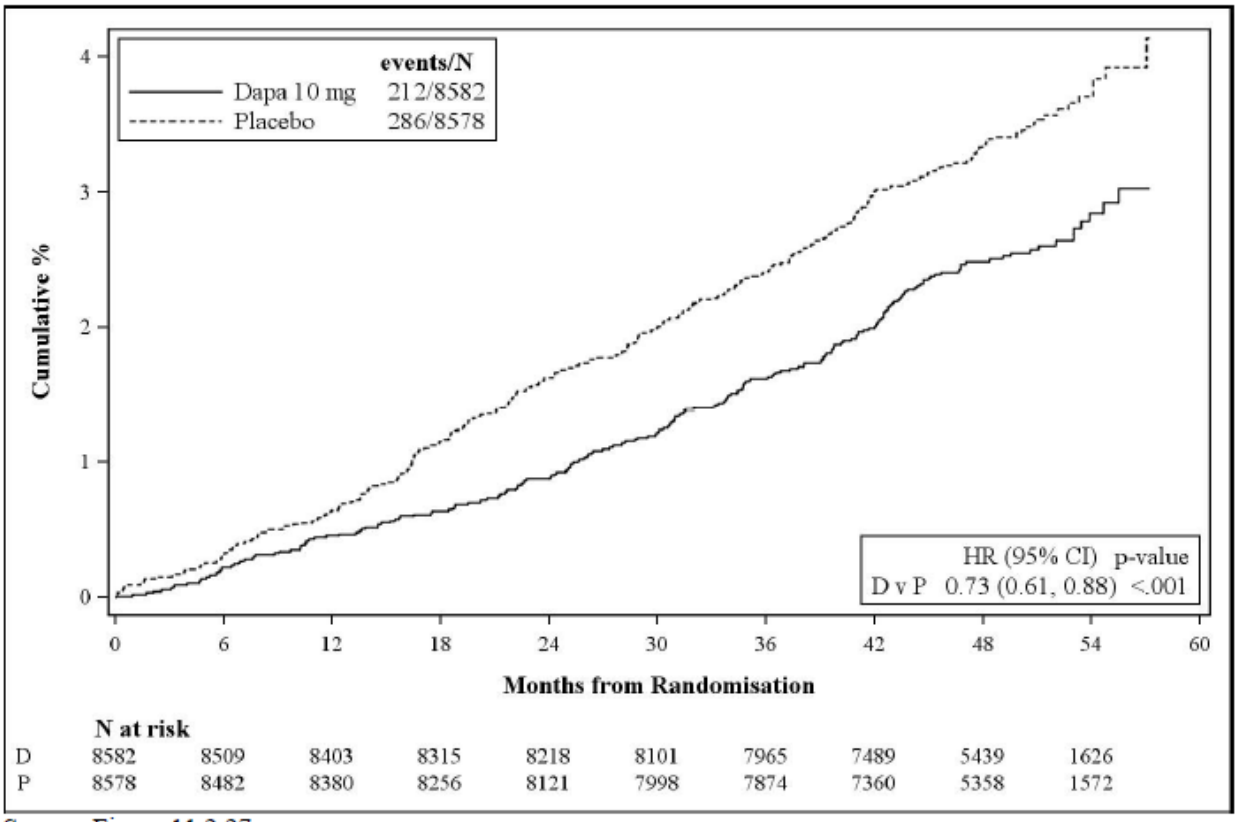
The Applicant's Kaplan-Meier estimation for the composite of HHF/CV death is shown in **Error! Not a valid bookmark self-reference.** and the Kaplan-Meier estimation for the HHF component alone is shown in Figure 5. Early and sustained separation of the curves between treatment arms is apparent.

Figure 4. Kaplan-Meier Plot of Adjudicated Events of the Composite of Hospitalization for Heart Failure or CV Death (FAS Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.9

Figure 5. Kaplan-Meier Plot of Adjudicated Event of Hospitalization for Heart Failure (FAS Population)



Source: Figure 11.2.27
N at risk is the number of patients at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. Analysis of time from randomisation to first occurrence of event or censoring.
CI Confidence interval; D Dapa 10 mg; FAS Full analysis set; HR Hazard ratio; N Number of patients per treatment group; P Placebo; v Versus

Source: Excerpted from the DECLARE CSR, Figure 6, p. 71

To assess whether patients in each treatment arm who had HHF events were treated to the same standards, we asked the Applicant to submit further details regarding concomitant diabetes (Table 15) and cardiovascular medications (Table 16) for patients who had this event. While it is unclear whether treatments were optimized at randomization or the time of the event, in this subset of the overall study population there were no obvious differences in concomitant therapies between treatment arms that would appear to affect the trial results. In addition, these are post-randomization variables that should be interpreted with caution.

Table 15. Antidiabetic Therapies at Baseline and Time of First Event in Patients with Adjudicated Heart Failure Hospitalization Events (FAS)

	Dapa 10 mg (n=212)		Placebo (n=286)	
	Baseline n (%)	At the time of event [a] n (%)	Baseline n (%)	At the time of event [a] n (%)
Metformin	146 (68.9)	135 (63.7)	217 (75.9)	199 (69.6)
Sulfonylurea	66 (31.1)	58 (27.4)	116 (40.6)	105 (36.7)
Insulin	127 (59.9)	135 (63.7)	160 (55.9)	181 (63.3)
DPP-4 inhibitor	30 (14.2)	37 (17.5)	35 (12.2)	48 (16.8)
GLP-1 receptor agonist	4 (1.9)	12 (5.7)	18 (6.3)	19 (6.6)
Other anti-diabetic drug	4 (1.9)	9 (4.2)	9 (3.1)	9 (3.1)

FAS Full analysis set; Dapa Dapagliflozin; n Number of patients; DPP-4 Dipeptidyl peptidase-4; GLP-1 Glucagon-like peptide-1; hHF Hospitalization due to heart failure

[a] Concomitant medications taken for >3 months

Source: Excerpted from Response to Information Request submitted on June 28, 2019, Seq 0616

Table 16. Cardiovascular Medications at Baseline and Time of First Event in Patients with Adjudicated Heart Failure Hospitalization Events (FAS)

	Dapa 10 mg (n=212)		Placebo (n=286)	
	Baseline n (%)	At the time of event [a] n (%)	Baseline n (%)	At the time of event [a] n (%)
ACE inhibitor/ARB	178 (84.0)	173 (81.6)	255 (89.2)	237 (82.9)
Thiazide diuretic	43 (20.3)	31 (14.6)	65 (22.7)	53 (18.5)
Loop Diuretic	91 (42.9)	116 (54.7)	122 (42.7)	164 (57.3)
Beta blocker	160 (75.5)	160 (75.5)	220 (76.9)	227 (79.4)
Calcium channel blocker	86 (40.6)	80 (37.7)	126 (44.1)	114 (39.9)
Mineralocorticoid receptor antagonist	36 (17.0)	46 (21.7)	47 (16.4)	64 (22.4)
Acetylsalicylic acid	125 (59.0)	120 (56.6)	186 (65.0)	186 (65.0)
Statin/ezetimibe	177 (83.5)	178 (84.0)	250 (87.4)	254 (88.8)
Anticoagulant	56 (26.4)	66 (31.1)	66 (23.1)	82 (28.7)
Any antiplatelet therapy	147 (69.3)	141 (66.5)	208 (72.7)	208 (72.7)
Dual antiplatelet therapy	32 (15.1)	35 (16.5)	52 (18.2)	43 (15.0)

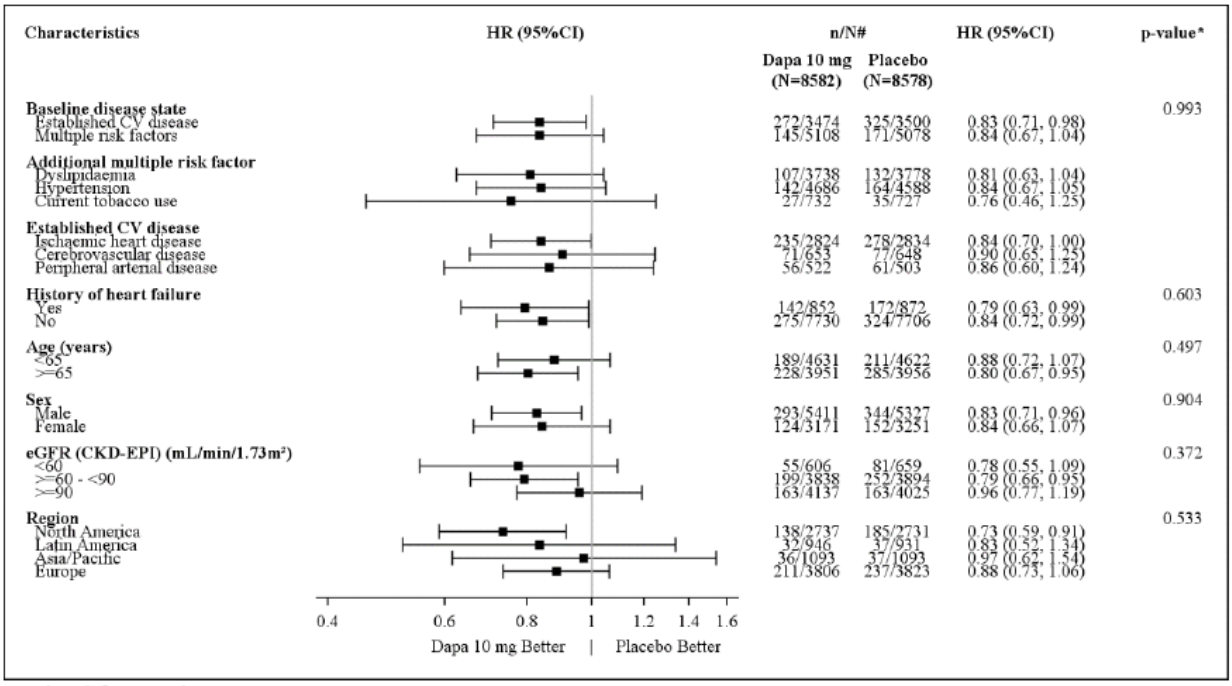
FAS Full Analysis Set; Dapa Dapagliflozin; n Number of Patients; hHF Hospitalization due to heart failure

[a] Concomitant medications taken for >3 months

Source: Excerpted from Response to Information Request submitted on June 28, 2019, Seq 0616

Subgroup analyses of the HHF/CV death endpoint demonstrated similar findings as observed in the overall population, with HR <1.0 for dapagliflozin compared to placebo across subgroup characteristics of baseline CV risk category, history of heart failure, age, sex, eGFR category, and region (Figure 6). Subgroup analyses of the HHF component alone are presented in Section 7.1.3 and are consistent with the overall composite subgroup analyses.

Figure 6. Forest Plot of the Composite of Hospitalization for Heart Failure or CV death by Subgroups (FAS)



Derived from: Figure 11.2.8
Only adjudicated events with event date on or after date of randomisation are included. * p-value for interaction
CI Confidence interval; CV Cardiovascular; FAS Full analysis set; HR Hazard ratio; N Number of patients; N# Number of patients within subgroup category; n Number of patients with event
Source: Excerpted from the DECLARE CSR, p. 78

The CEC charter specified that HF events that were urgent care visits should also be recorded. There were only 2 events in the dapagliflozin arm and 8 events in the placebo arm categorized as urgent HF visits. Overall concordance between investigator-reported hospitalizations for heart failure and adjudicated hospitalizations for heart failure was approximately 60% in this trial.

Reviewer Comments: *I considered several factors in assessing the results of the HHF/CV death endpoint, including mechanistic plausibility of this benefit, robustness of the clinical trial results, and statistical and trial conduct considerations that affect regulatory decision-making. Since the DECLARE trial did not provide substantial evidence that dapagliflozin reduces the risk of CV death, I will focus this discussion on the heart failure hospitalization component of the*

composite endpoint.

First, it is mechanistically plausible that dapagliflozin could reduce the risk for hospitalization for heart failure given its diuretic effect. There may also be other mechanisms by which SGLT2-inhibitors confer benefits to cardiac function and/or efficiency. This is an active area of basic science and clinical research, and while the evidence base remains limited, animal and human data suggest SGLT2 inhibitors may improve cardiac myocyte substrate metabolism and cardiac ion handling in addition to their hemodynamic effects.[12,13] Whether these or other unknown factors predominate, or act synergistically, to confer a heart failure benefit is unclear.

Second, although I evaluated the results of DECLARE as a stand-alone trial, it is noteworthy that consistent reductions in the risk of heart failure hospitalization have been observed across the SGLT2 inhibitor class. Both the EMPA-REG OUTCOME trial and the CANVAS program enrolled similar populations to DECLARE with regard to baseline HF history, and demonstrated similar reductions in the risk of hospitalization for heart failure. However, neither of these trials prespecified the HHF endpoint or a composite endpoint that included HHF in their statistical testing hierarchy, and the results were therefore considered exploratory. In addition, although HHF was an adjudicated event in both trials, with EMPA-REG in particular there were review concerns about the CEC charter definition of heart failure hospitalization and changes to the definition made during the trial. Recently, the CREDENCE trial evaluated superiority of canagliflozin to placebo for reducing the risk of end-stage kidney disease, doubling of serum creatinine, and renal or CV death in a population with T2DM and chronic kidney disease; this trial was terminated after the prespecified interim analysis due to overwhelming evidence of efficacy benefit for the primary renal composite endpoint. CREDENCE also demonstrated superiority of canagliflozin to placebo for the HHF/CV death composite endpoint and the HHF component alone. Components of the composite were adjudicated, and the statistical testing hierarchy preserved alpha to test these secondary efficacy endpoints, leading to an indication for canagliflozin to reduce the risk of hospitalization for heart failure in adults with T2DM and diabetic nephropathy. Thus, all three large CVOTs in the SGLT2 inhibitor class and a large canagliflozin renal outcome trial have either strongly suggested or demonstrated benefit in reducing the risk of HHF in the treatment arms compared to placebo. The available clinical trial evidence to date is therefore extremely consistent with regard to the HHF findings and bolsters the robustness of the DECLARE results.

Third, I considered whether the clinical benefit for HHF in DECLARE was demonstrated in a way that meets regulatory standards to merit an indication. One review issue is that the trial did not

[12] Bertero E, Roma LP, Ameri P, Maack C. Cardiac effects of SGLT2 inhibitors: the sodium hypothesis. *Cardiovascular Research*;114:12-18
[13] Zelniker TA, Braunwald E. Cardiac and renal effects of Sodium-Glucose C-Transporter 2 inhibitors in diabetes: *JACC* State-of-the-Art Review. *J Am Coll Cardiol* 2018;72(15):1845-55

systematically collect baseline heart failure data, including baseline ejection fraction information, and there was no plan to optimize heart failure medication or device therapy before initiation of study drug. About 10% of the study population reported a medical history of heart failure, but this was not confirmed by study personnel, and patients with New York Heart Association Class IV heart failure were excluded from the trial. Thus, the trial design excluded patients who might be expected to derive the most benefit for this endpoint. However, it is noteworthy that despite these limitations, a clear benefit emerged for this clinically significant endpoint.

Another review concern is that the Applicant changed the statistical confirmatory testing procedure for the trial in December 2015. In response to publication of the EMPA-REG OUTCOME results[14], reporting a reduced incidence of hospitalization for heart failure with empagliflozin compared with placebo, the DECLARE investigators elevated the HHF/CV death endpoint to a primary efficacy variable. Although this change was clearly made due to external scientific information, careful review of the DMC/DSMB meeting minutes and protocol amendments shows that the change in the statistical testing hierarchy occurred prior to review of any unblinded data for the first interim analysis of the DECLARE data, which took place in February 2016. In addition, the purpose of the interim analysis was to assess for superiority of dapagliflozin to placebo for the MACE endpoint, to be followed by superiority for all-cause mortality only if the MACE findings were statistically significant; heart failure events were not evaluated as part of this analysis. As such, there is no evidence to suggest that the change in the testing hierarchy occurred in response to specific knowledge about the DECLARE results, or that inappropriate access to unblinded data influenced the change to the testing hierarchy. Therefore, I conclude that the change to the statistical testing hierarchy does not represent a major review concern; the FDA statistical review team concurs with this assessment.

Finally, I assessed the CEC charter definitions for HHF and their application throughout the trial. All versions of the CEC charter used the same definition for HHF, which was consistent with recommended cardiovascular and stroke endpoint definitions for clinical trials.[15] One review concern was that the CEC charter stipulated that, to be adjudicated as an HHF event, heart failure must be the primary diagnosis for hospital admission. An initial review of ten randomly selected CEC adjudication packages identified one case that was adjudicated as an HHF, but stated HF was not the primary diagnosis for admission. In their August 5, 2019 response to an IR requesting clarification regarding this case, the Applicant stated that the patient had been admitted with osteomyelitis but was also volume-overloaded and found to have new left ventricular dysfunction on echocardiogram, requiring intravenous diuresis. The Applicant also

[14] Zinman B, Wanner C, Lachin JM et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28
[15] Hicks KA, Mahaffey KW, Mehran R, Nissen SE. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation* 2018;137:961-972

submitted an appendix document entitled "CEC Department Conventions" which they stated was used by adjudicators to "clarify and operationalize Charter definitions, particularly around complex cases".[16] The CEC Conventions document included an Appendix Heart Failure Definition, dated March 13, 2015, stating that "A Heart Failure event that occurs during a period of hospitalization will be considered to have met the hospitalization criterion in instances where heart failure was the primary reason for prolonging the hospitalization by at least 24 hours."[17] Using this appended definition, the case in question was adjudicated as a heart failure hospitalization because heart failure extended the patient's hospitalization by at least 24 hours. In order to ascertain how many such cases were included in the final HHF event count for each treatment arm, I reviewed CEC facesheet documents for all heart failure hospitalizations and identified cases in which the primary diagnosis for admission was not heart failure for the first event of HHF used in the adjudicated dataset to calculate the HHF/CV death efficacy endpoint. I identified 65/212 cases (30.1%) in the dapagliflozin arm and 94/286 cases (32.9%) in the placebo arm where heart failure was not the primary diagnosis for the hospitalization that was included as the first HHF event contributing to the primary efficacy analysis. The FDA statistical reviewer performed a sensitivity analysis excluding these events, and the results were consistent with the primary analysis (HR 0.77; 95% CI 0.62, 0.95). It is also important to note that this sensitivity analysis represents a "worst case scenario" considering that many patients who did not have HF listed as the primary diagnosis for admission for their first adjudicated HF event went on to have additional heart failure hospitalizations during the trial for which HF was the primary diagnosis for admission. As such, many of the patients excluded for the purposes of the sensitivity analysis would have ultimately been included in the primary efficacy analysis based on a subsequent hospitalization, even applying the strictest initial HHF definition. Therefore, review of the adjudicated HF cases and the additional sensitivity analysis were supportive of the conclusion that the risk of hospitalization for heart failure was reduced in the dapagliflozin arm in the studied population.

In summary, from the clinical perspective the results of the DECLARE trial provide substantial evidence that dapagliflozin reduces the risk of hospitalization for heart failure when added to standard of care T2DM treatment in the studied population. The submitted results demonstrate this benefit in a clinically and statistically robust manner that support an indication statement. I favor an indication statement that reflects this benefit in the studied population, i.e., adults with T2DM with established CV disease or multiple CV risk factors.

Data Quality and Integrity

For the efficacy data submitted to these sNDAs, the statistical review team conclude the quality

[16] Applicant response to Information Request dated August 5, 2019, NDA 202293, Seq 0627
[17] CEC Conventions Document, p. 3, submitted as an Appendix to Applicant response to Information Request dated August 5, 2019, NDA 202293, Seq 0627

of the datasets and associated documentation (reviewer guide and define files) were acceptable. I concur with this assessment.

Efficacy Results – Secondary and other relevant endpoints

(b) (4)

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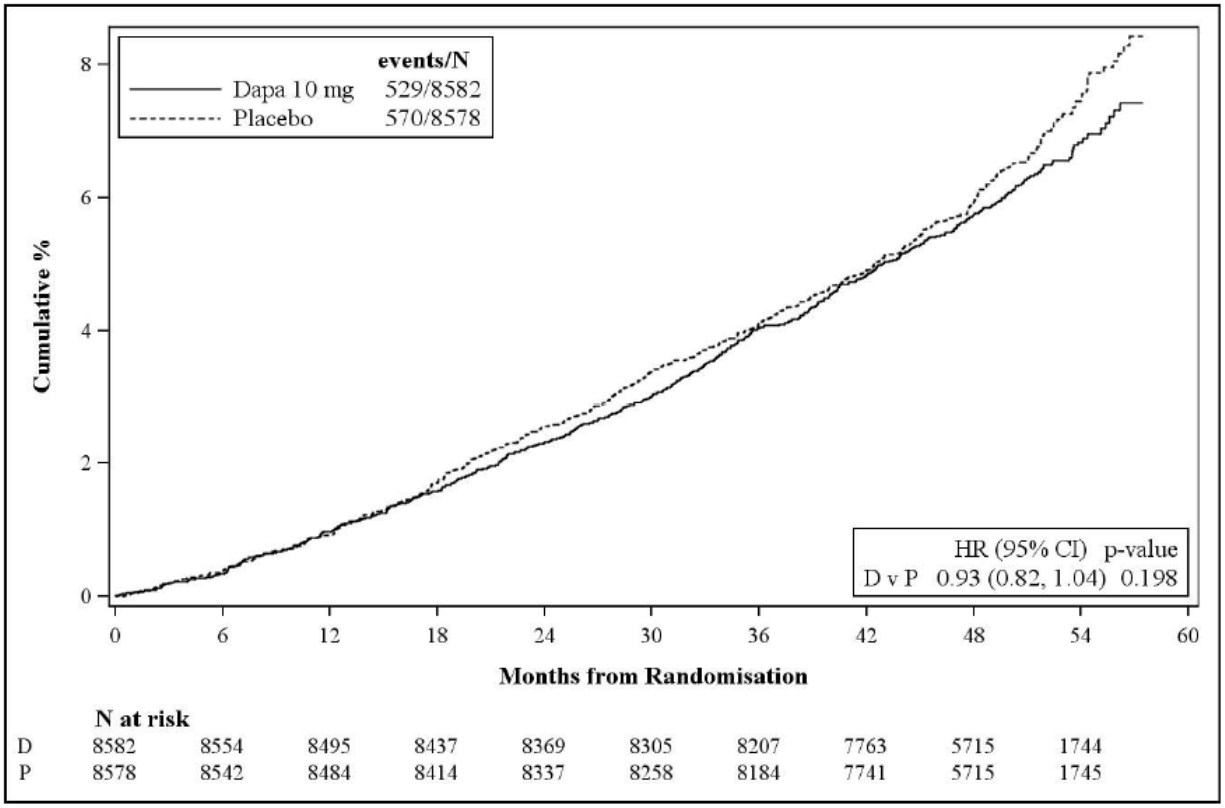
(b) (4)

Key Secondary Efficacy Endpoint: All-Cause Mortality

Deaths were adjudicated by the CEC and analysis of all-cause mortality was part of the prespecified confirmatory testing hierarchy. Analysis of this endpoint was considered exploratory due to insufficient preserved alpha to allow for formal testing. Overall, in the FAS population there were 529 deaths (6.2%; 15.1 events per 1000 patient-years) in the dapagliflozin arm and 570 deaths (6.6%; 16.4 events per 1000 patient-years) in the placebo arm (HR 0.93; 95% CI 0.82, 1.04). Therefore, although the point estimate for the HR for all-cause mortality was slightly less than 1.0, dapagliflozin was not statistically superior to placebo in reducing the risk of death from any cause when added to standard of care in the studied population. The Applicant's Kaplan-Meier analysis for all-cause mortality is shown in Figure 9.

Figure 9. Kaplan-Meier Plot of Time-to-Event of All-Cause Mortality (FAS Population)



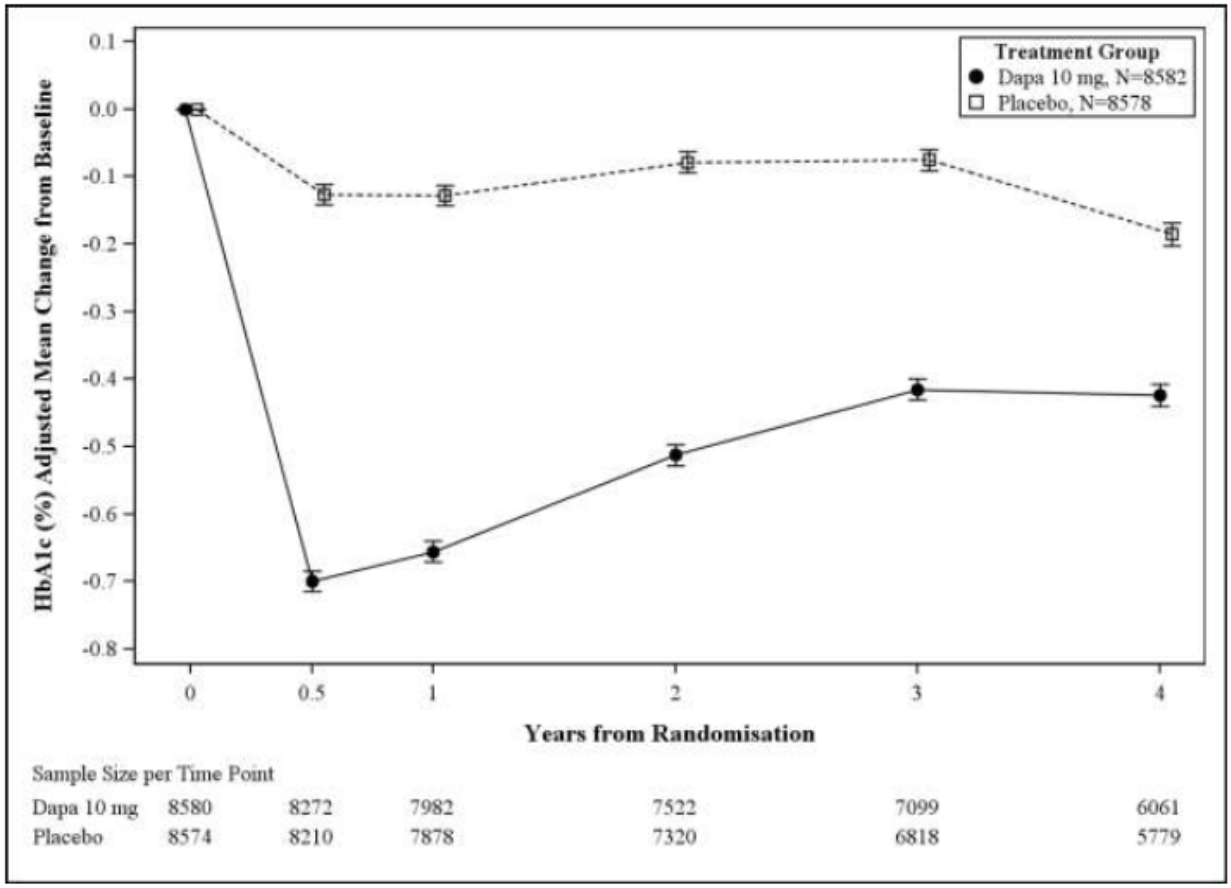
Source: Excerpted from the DECLARE CSR, Figure 15, p. 83

Exploratory Efficacy Variable: HbA1c

As a cardiovascular safety outcome trial, DECLARE did not focus on estimating the efficacy of dapagliflozin to improve glycemic control. However, information about changes to antidiabetic therapy was collected and HbA1c change was reported as an exploratory endpoint that was not included in the statistical testing hierarchy.

At baseline, HbA1c was similar between treatment arms. As shown in Figure 10 and Table 19 below, mean HbA1c was consistently lower in the dapagliflozin arm compared to placebo after randomization. The largest difference in treatment arms was observed at 6 months post-randomization, but the reduction in HbA1c with dapagliflozin remained statistically significant through Year 4 of the trial.

Figure 10. Adjusted Mean HbA1c (%) Over Time (FAS Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.44

Table 19. Repeated Measures Analysis of HbA1c (%) Change from Baseline (FAS Population)

						Analysis of covariance						
	Absolute values			Change from baseline		Adjusted change from baseline			Difference between Dapa 10 mg and Placebo			
Treatment group Time	N#	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean Diff	SE	95% CI	p-value
Dapa 10 mg												
Baseline	8580	8.30	1.220									
6 months	8272	7.57	1.122	-0.72	1.108	-0.70	0.0150	(-0.73, -0.67)	-0.57	0.0179	(-0.61, -0.54)	<0.001
1 year	7982	7.61	1.168	-0.68	1.158	-0.66	0.0151	(-0.68, -0.63)	-0.53	0.0182	(-0.56, -0.49)	<0.001
2 years	7522	7.75	1.210	-0.54	1.226	-0.51	0.0154	(-0.54, -0.48)	-0.43	0.0186	(-0.47, -0.40)	<0.001
3 years	7099	7.83	1.256	-0.45	1.320	-0.42	0.0156	(-0.45, -0.38)	-0.34	0.0191	(-0.38, -0.30)	<0.001
4 years	6061	7.80	1.271	-0.43	1.365	-0.42	0.0164	(-0.46, -0.39)	-0.24	0.0204	(-0.28, -0.20)	<0.001

Source: Excerpted from the DECLARE CSR Appendix, Table 11.2.3.3.1

Investigators were instructed to treat patients T2DM to the glycemic goals recommended by the ADA and EASD, but the difference in HbA1c between arms demonstrates that patients did not achieve equal treatment goals. As shown in Table 20, more patients in the placebo arm were initiated on insulin or had an increase in diabetes medications during the trial;

nonetheless, these changes did not offset the difference in HbA1c between treatment arms and suggest optimization of glycemic therapy was not achieved in the placebo arm.

Table 20. Changes to Concomitant Antidiabetes Medications During the Trial

Changes to antidiabetic regimen	Dapagliflozin 10mg (N=8582) n (%)	Placebo (N=8578) n (%)
Initiation of insulin regimen	606 (12.1)	1161 (22.6)
Increase in diabetes medication	3835 (44.7)	5284 (61.6)
Increase in dose for an oral diabetes medication	1118 (13.0)	1674 (19.5)
≥25% increase in insulin dose	538 (6.3)	832 (9.7)
Addition of new diabetes medication	3020 (35.2)	4313 (50.3)

Source: Adapted from Tables 11.2.3.4.2, 11.2.3.5.2 and 11.2.3.5.3 in the CSR Appendix 11

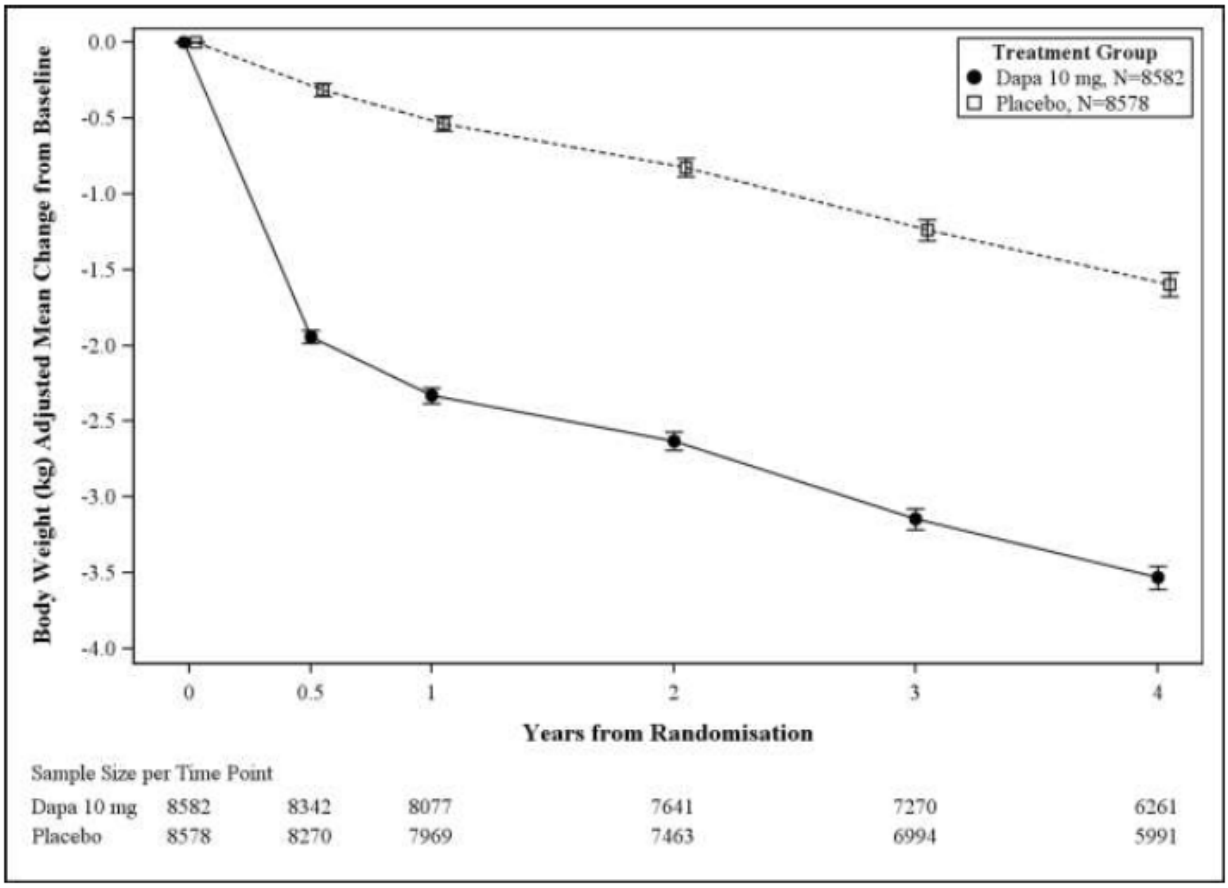
Additionally, a higher proportion of patients in the dapagliflozin arm achieved the ADA and EASD HbA1c targets early in the trial. While 9.0% of patients in each treatment arm had a baseline HbA1c <7.0%, at 1 year after randomization 30.6% of patients in the dapagliflozin arm had an HbA1c <7.0% compared with 19.3% of patients in the placebo arm, and at 2 years after randomization 26.9% of patients in the dapagliflozin arm had an HbA1c <7.0% compared with 18.7% of patients in the placebo arm. By the end of the trial, proportions of patients with HbA1c <7.0% were similar between treatment arms (28.7% in the dapagliflozin arm vs. 26.6% in the placebo arm).

***Reviewer Comment**: A similar pattern of early and sustained HbA1c reduction in the study drug arms was observed in both the EMPA-REG OUTCOME trial and the CANVAS Program. The difference in achievement of glycemic control targets between treatment arms is an important potential confounding factor in this trial and others in the class, but it is unknown to what extent this factor affected the results or conclusions of the trial.*

Exploratory Efficacy Variable: Body Weight

Body weight was reduced in the dapagliflozin arm compared with placebo, an effect that was apparent at 6 months (the first visit at which body weight was recorded after study drug initiation) and throughout the duration of the trial (Figure 11 and Table 21). These results are consistent with the findings from the registration trials for the glycemic control indication.

Figure 11. Line Graph for Body Weight Plotting Model-Adjusted Mean and Standard Error from Repeated Measures Model (FAS Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.47

Table 21. Repeated Measures Analysis of Body Weight (kg) Change from Baseline (FAS)

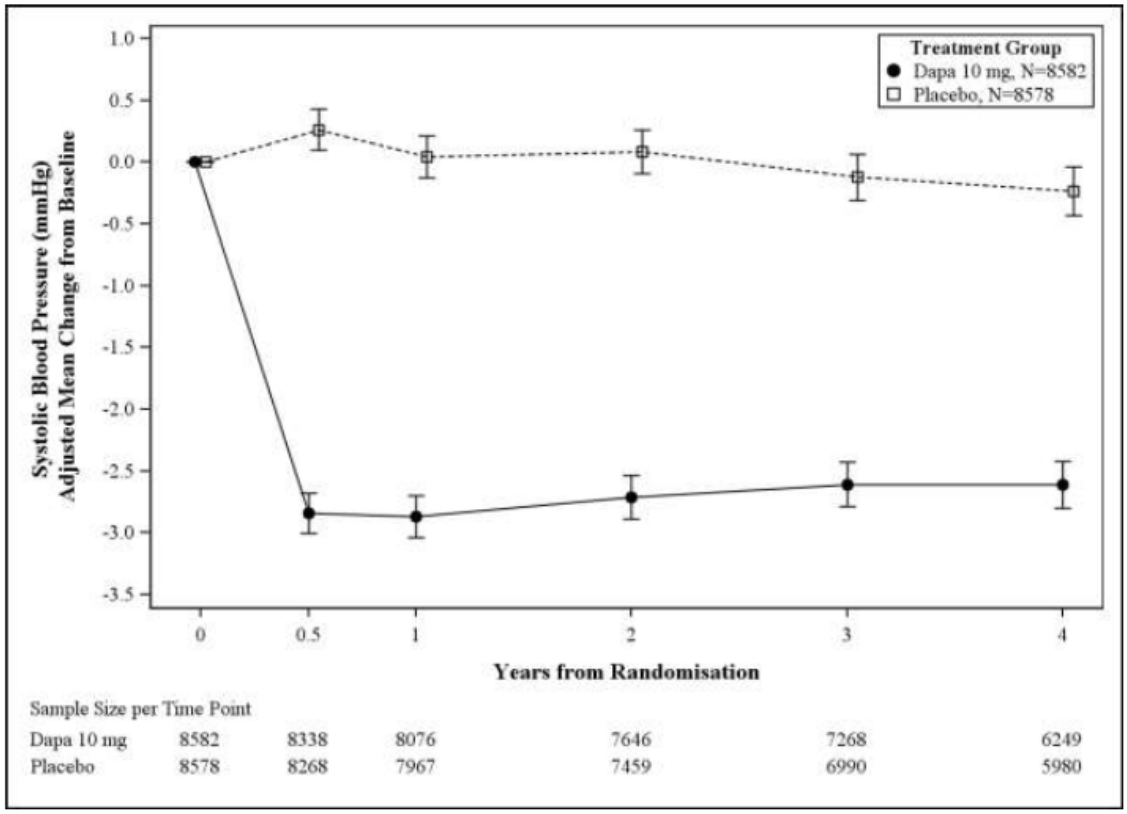
						Analysis of covariance						
	Absolute values			Change from baseline		Adjusted change from baseline			Difference between Dapa 10 mg and Placebo			
Treatment group Time	N#	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean Diff	SE	95% CI	p-value
Dapa 10 mg												
Baseline	8582	90.94	20.187									
6 months	8342	88.93	19.869	-1.95	3.094	-1.94	0.0419	(-2.02, -1.86)	-1.63	0.0464	(-1.72, -1.54)	<0.001
1 year	8077	88.41	19.698	-2.35	3.840	-2.33	0.0489	(-2.43, -2.23)	-1.79	0.0587	(-1.91, -1.68)	<0.001
2 years	7641	87.95	19.513	-2.63	4.705	-2.63	0.0595	(-2.75, -2.51)	-1.80	0.0759	(-1.95, -1.66)	<0.001
3 years	7270	87.26	19.384	-3.11	5.296	-3.14	0.0682	(-3.28, -3.01)	-1.91	0.0895	(-2.08, -1.73)	<0.001
4 years	6261	87.59	19.343	-3.53	5.897	-3.53	0.0767	(-3.68, -3.38)	-1.93	0.1027	(-2.13, -1.73)	<0.001

Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.2.3.12.1.1

Exploratory Efficacy Variable: Blood Pressure

Systolic blood pressure was reduced in the dapagliflozin arm compared with placebo (Figure 12 and Table 22). Diastolic blood pressure was slightly reduced in the dapagliflozin arm compared with placebo, but the differences were too small to be considered clinically significant (Figure 13 and Table 23).

Figure 12. Systolic Blood Pressure, Model-Adjusted Mean and Standard Error from Repeated Measures Model (FAS)



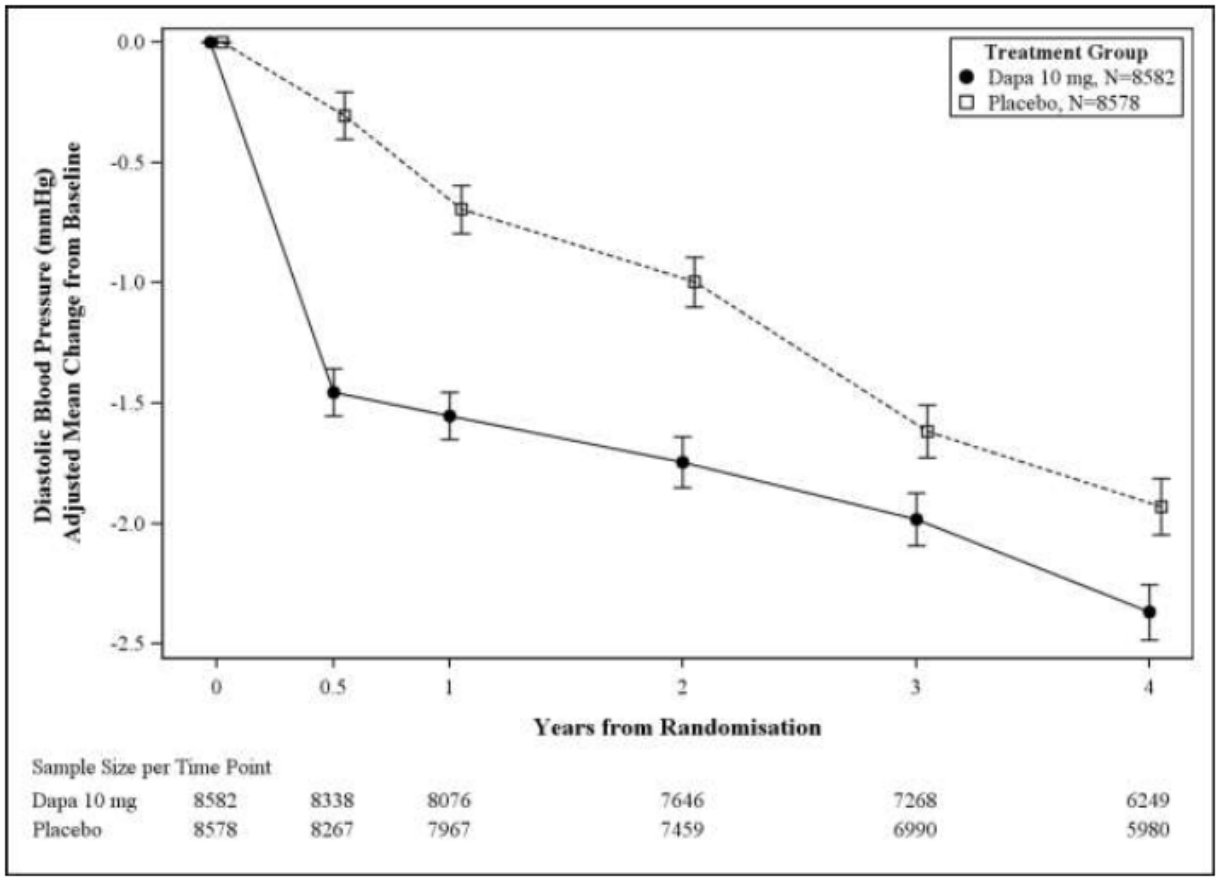
Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.49

Table 22. Repeated Measures Analysis of Systolic Blood Pressure (mmHg) Change from Baseline (FAS)

						Analysis of covariance						
	Absolute values			Change from baseline		Adjusted change from baseline			Difference between Dapa 10 mg and Placebo			
Treatment group Time	N#	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean Diff	SE	95% CI	p-value
Dapa 10 mg												
Baseline	8582	135.14	15.349									
6 months	8338	132.25	15.390	-2.89	14.569	-2.84	0.1654	(-3.17, -2.52)	-3.10	0.2031	(-3.50, -2.70)	<0.001
1 year	8076	132.23	15.573	-2.93	14.834	-2.87	0.1686	(-3.20, -2.54)	-2.91	0.2085	(-3.32, -2.50)	<0.001
2 years	7646	132.38	15.530	-2.81	15.570	-2.71	0.1759	(-3.06, -2.37)	-2.80	0.2207	(-3.23, -2.36)	<0.001
3 years	7268	132.49	15.296	-2.69	16.152	-2.61	0.1818	(-2.96, -2.25)	-2.48	0.2307	(-2.94, -2.03)	<0.001
4 years	6249	132.47	15.014	-2.53	16.221	-2.61	0.1917	(-2.99, -2.24)	-2.38	0.2464	(-2.86, -1.89)	<0.001

Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.2.3.15.1

Figure 13. Diastolic Blood Pressure, Model-Adjusted Mean and Standard Error from Repeated Measures Model (FAS)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.50

Table 23. Repeated Measures Analysis of Diastolic Blood Pressure (mmHg) Change from Baseline (FAS)

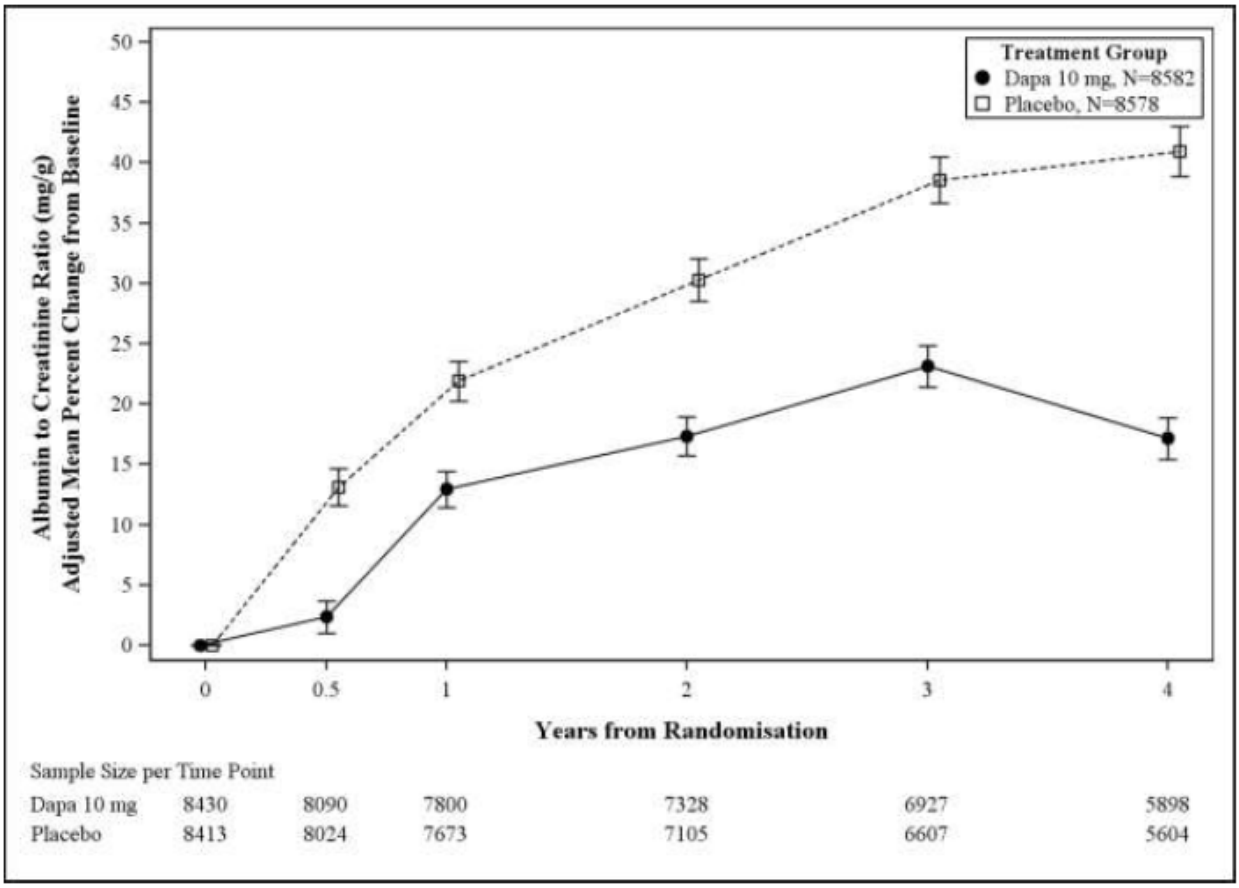
						Analysis of covariance						
	Absolute values			Change from baseline		Adjusted change from baseline			Difference between Dapa 10 mg and Placebo			
Treatment group Time	N#	Mean	SD	Mean	SD	LS Mean	SE	95% CI	LS Mean Diff	SE	95% CI	p-value
Dapa 10 mg												
Baseline	8582	78.04	9.042									
6 months	8338	76.71	9.093	-1.30	8.396	-1.46	0.0967	(-1.64, -1.27)	-1.15	0.1180	(-1.38, -0.92)	<0.001
1 year	8076	76.61	9.072	-1.39	8.783	-1.55	0.0991	(-1.75, -1.36)	-0.86	0.1220	(-1.10, -0.62)	<0.001
2 years	7646	76.43	9.218	-1.59	9.118	-1.75	0.1038	(-1.95, -1.54)	-0.75	0.1298	(-1.00, -0.49)	<0.001
3 years	7268	76.20	9.168	-1.84	9.481	-1.98	0.1080	(-2.19, -1.77)	-0.37	0.1369	(-0.63, -0.10)	0.007
4 years	6249	75.85	9.099	-2.13	9.563	-2.37	0.1134	(-2.59, -2.15)	-0.44	0.1455	(-0.72, -0.15)	0.003

Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.2.3.15.3

Exploratory Efficacy Variable: Albumin to Creatinine Ratio

In the FAS population, mean UACR increased more slowly in the dapagliflozin arm compared with placebo (Figure 14).

Figure 14. Urinary Albumin to Creatinine Ratio—Model-Adjusted Mean and Standard Error from Repeated Measures Model (FAS Population)

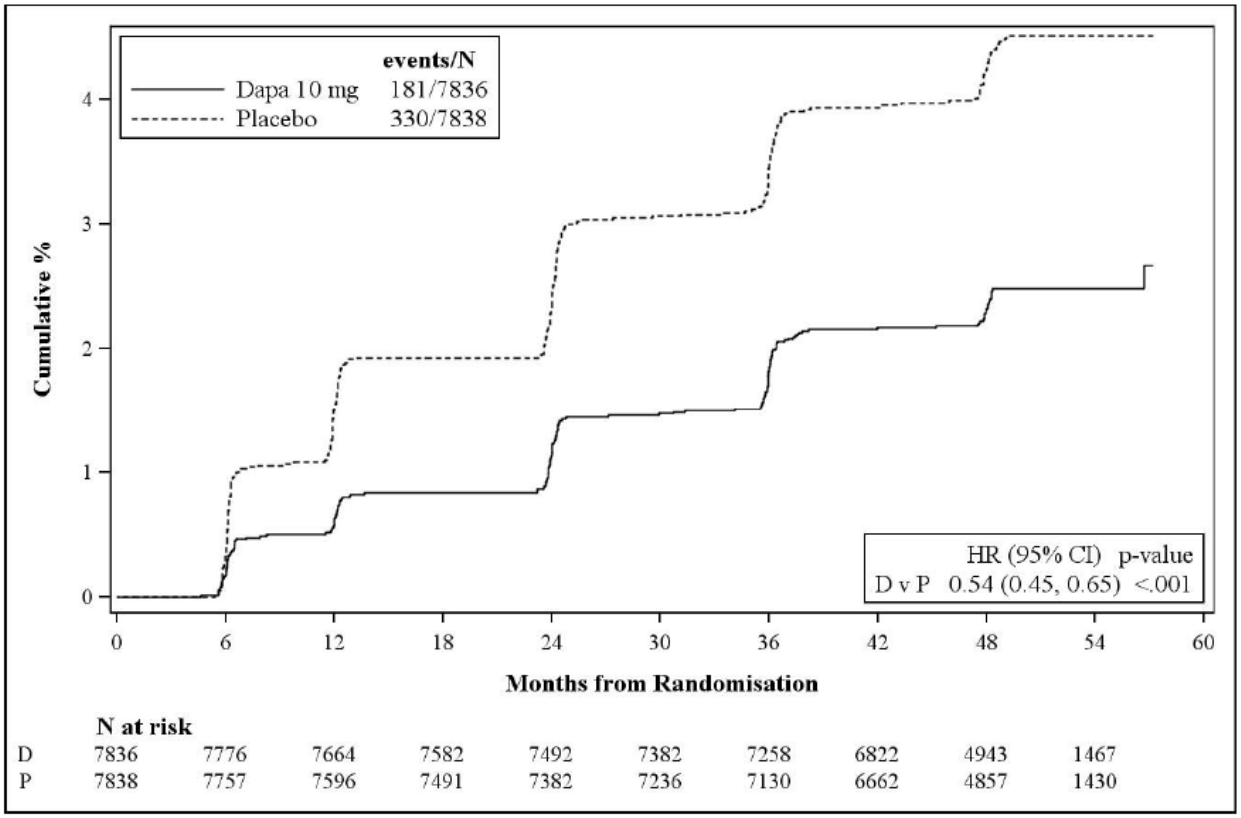


Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.46

Exploratory Efficacy Variable: New Onset Albuminuria

At baseline, the majority of the FAS population (91.3% of the overall randomized population) did not have macroalbuminuria. The incidence of new-onset macroalbuminuria (UACR >300 mg/g) was lower in the dapagliflozin arm compared with placebo: 181 patients in the dapagliflozin arm (2.3%; event rate 5.8 per 1000 patient-years) developed sustained confirmed macroalbuminuria during the trial compared with 330 patients (4.2%; event rate 10.8 per 1000 patient-years) [HR 0.54; 95% CI 0.45, 0.65]. The Applicant's Kaplan-Meier estimate of new-onset macroalbuminuria is shown in Figure 15.

Figure 15. Kaplan-Meier Plot of New-Onset Macroalbuminuria (UACR >300 mg/g)

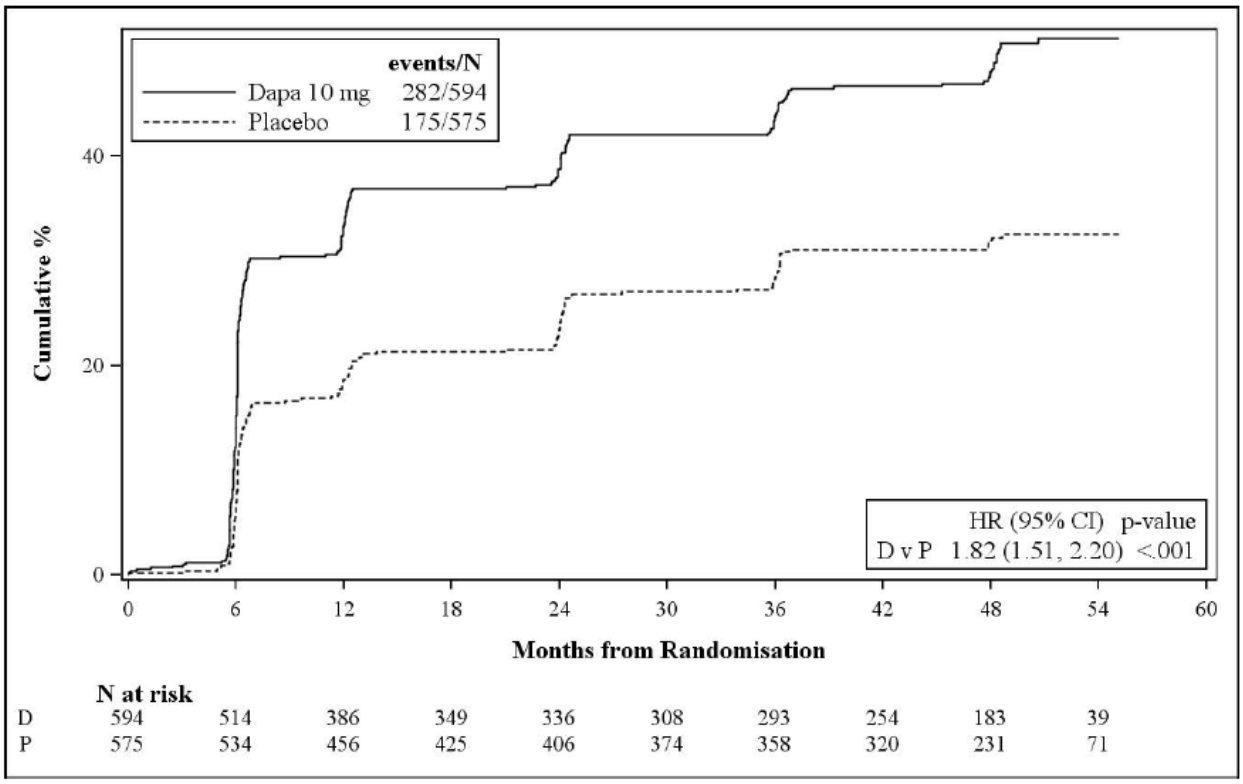


Source: Excerpted from the DECLARE CSR, Figure 17, p. 86

Exploratory Efficacy Variable: Regression in Severity of Albuminuria

At baseline 594 patients in the dapagliflozin arm and 575 patients in the placebo arm had macroalbuminuria. Of these, 282 patients in the dapagliflozin arm (47.5% of patients with baseline macroalbuminuria; event rate 193.8 per 1000 patient-years) had sustained confirmed regression of macroalbuminuria to UACR <300 mg/g compared with 175 patients in the placebo arm (30.4%; event rate 102.2 per 1000 patient-years) [HR 1.82; 95 CI 1.51, 2.2]. The Applicant's Kaplan-Meier estimate of regression of macroalbuminuria is shown in Figure 16.

Figure 16. Kaplan-Meier Plot of Time from Randomization to First Event of Regression of Macroalbuminuria



Source: Excerpted from the DECLARE CSR, Figure 18, p. 87

Reviewer Comment: *As noted by Dr. Smith in her consult review of the renal-related endpoints in this trial, changes in UACR may merely represent hemodynamic effects that are expected to be reversible after drug discontinuation.*

Other Exploratory Efficacy Variables:

(b) (4)

Table 24. Summary of Additional Exploratory Efficacy Variables in the DECLARE Trial (FAS)

Exploratory Endpoint (Time from Randomization to First Event)	Dapagliflozin (N=8582) n (%)	Placebo (N=8578) n (%)	Hazard Ratio (95% CI)
Sustained confirmed eGFR decrease ≥30% to <60 mL/min/1.73m^2	293 (3.4)	427 (5.0)	0.68 (0.58, 0.79)
Major hypoglycemia or hospitalization due to hypoglycemia	78 (0.9)	118 (1.4)	0.66 (0.49, 0.88)
Retinal laser/intraocular treatment due to diabetic retinopathy	102 (1.2)	86 (1.0)	1.18 (0.89, 1.57)
Composite of CV death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina pectoris, or hospitalization for any revascularization	1373 (16.0)	1422 (16.6)	0.96 (0.89, 1.03)
Hospitalization for unstable angina pectoris	136 (1.6)	139 (1.6)	0.98 (0.77, 1.24)
Hospitalization for any revascularization	852 (9.9)	810 (9.4)	1.05 (0.96, 1.16)
Peripheral revascularization and/or limb ischemic event	297 (3.5)	283 (3.3)	1.05 (0.89, 1.23)
Any adjudicated stroke	255 (3.0)	263 (3.1)	0.96 (0.81, 1.14)

Source: Adapted from Tables 11.2.3.10.1, 11.2.3.6.1, 11.2.3.14.1, 11.2.3.2.1, 11.2.3.2.2, 11.2.3.2.3, 11.2.3.16.1, and 11.2.3.17.1 in the DECLARE CSR Appendix 11

Dose/Dose Response

The DECLARE trial only evaluated the 10 mg dose of dapagliflozin compared with placebo. Therefore, a dose-response relationship for efficacy findings could not be assessed. The Applicant's proposed labeling in Section 2 distinguishes that the 5 mg dose should be initiated for glycemic control, and uptitrated to 10 mg as needed for additional glycemic control, while only the 10 mg dose is recommended for the (b) (4) new proposed indications (i.e., reducing the risk of heart failure hospitalization/CV death, (b) (4)

Additional Analyses Conducted on the Individual Trial

Per FDA request, the Applicant also submitted a tipping point analysis for the primary safety and dual primary efficacy endpoints to assess the robustness of the statistically significant results. The results were supportive of the conclusions from the primary analyses of the trial results.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Only data from Study D1693C00001 (DECLARE) was submitted in the respective supplements to NDAs 202293 and 205649.

7.1.1. Primary Endpoints

Primary efficacy endpoints were discussed in Section 6.

7.1.2. Secondary and Other Endpoints

Secondary and exploratory endpoints were discussed in Section 6.

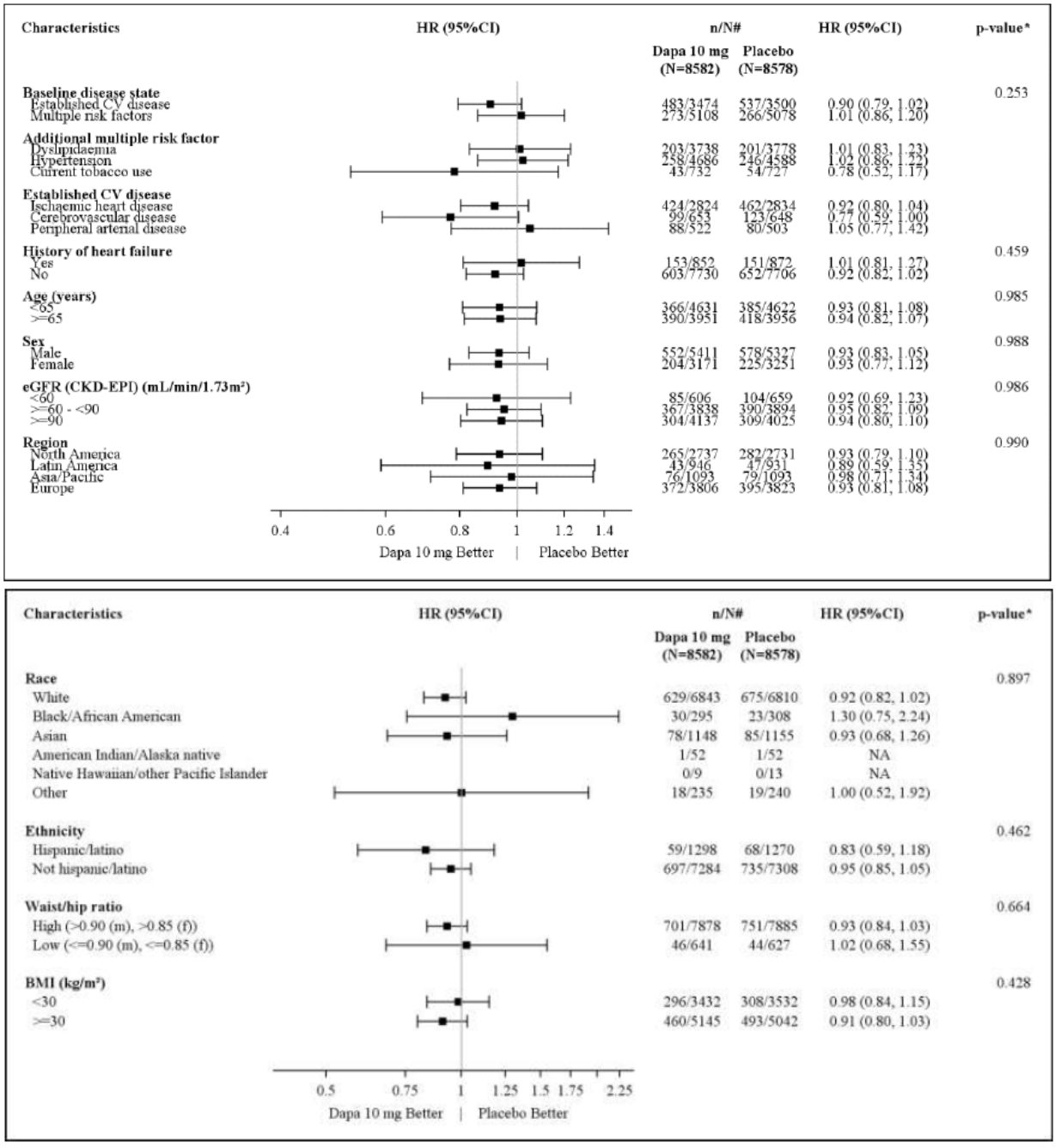
7.1.3. Subpopulations

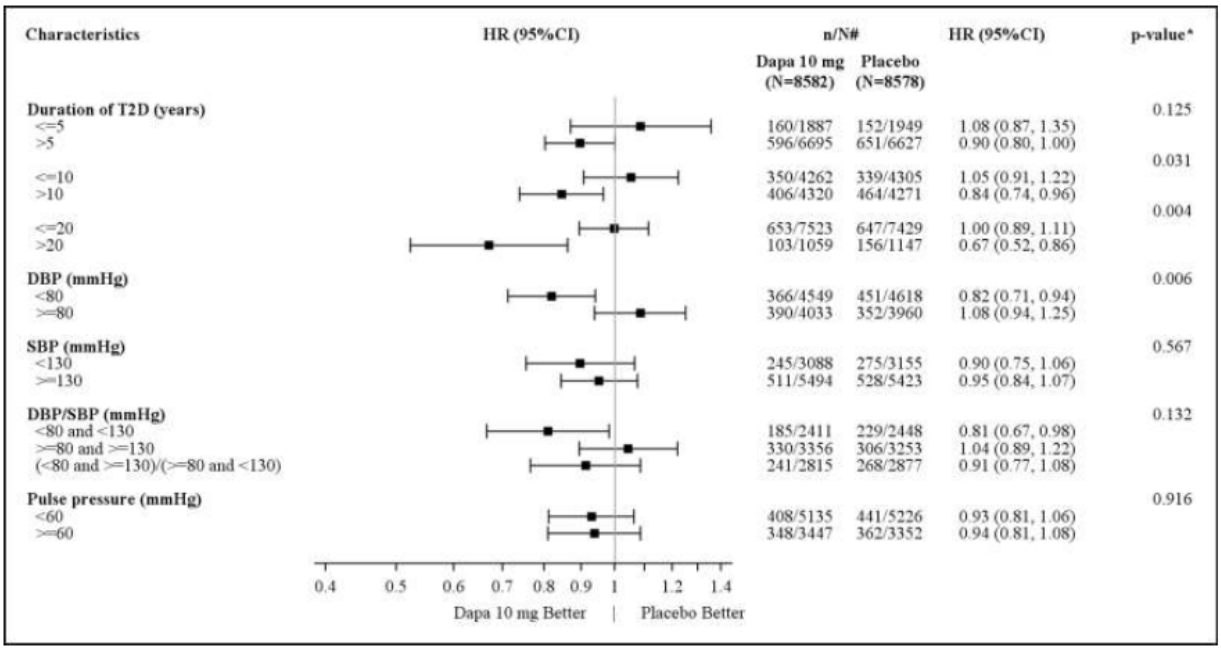
As prespecified, the Applicant performed subgroup analyses for the primary endpoints of the trial. These analyses were not adjusted for multiple comparisons and are considered exploratory. Subgroup analyses were performed for stratification factors as well as baseline demographic, diabetes-related characteristics and cancer risk factors.

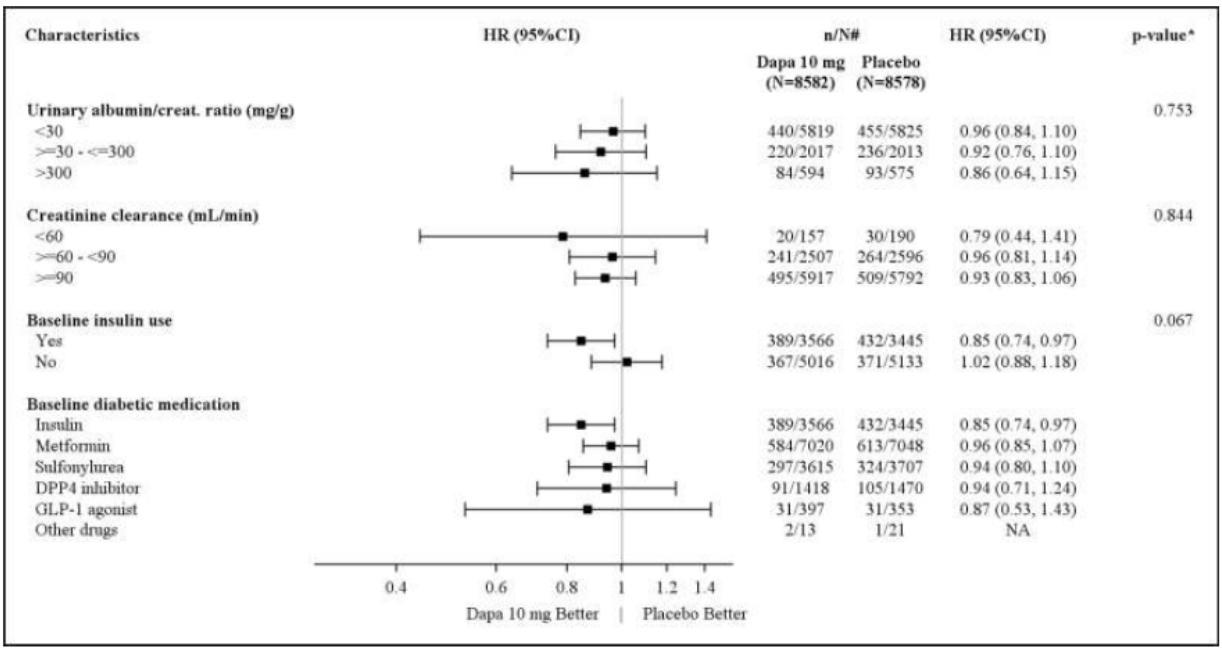
MACE

Subgroup analyses of the primary MACE endpoint were overall consistent with the overall findings of the trial. Dapagliflozin was non-inferior, but not superior, to placebo for MACE in patients with established CV disease or multiple risk factors. Other subgroup analyses by age, sex, race, ethnicity, BMI, eGFR category, and duration of diabetes were also consistent with the overall findings of the trial, with the exception of patients with baseline diabetes duration ≥10 years and baseline insulin use. In these subgroups the upper bound of the 95% CI for the HR point estimate was less than 1. It is possible that patients with more advanced diabetes (i.e., longer duration, requiring insulin) derived more benefit from the addition of dapagliflozin to standard or care, but it is difficult to draw firm conclusions from these observations due to the limitations of subgroup analyses and the possibility that these findings are due to chance.

Figure 17. Forest Plot of Hazard Ratios and 95% CI of First Occurrence of 3-point MACE by Subgroups (FAS Population)







Source: Excerpted from the DECLARE CSR, Figure 12, p. 79 and the CSR Appendix 11, Figure 11.2.2

Hospitalization for Heart Failure

Subgroup analyses of the hospitalization for heart failure component of the primary efficacy endpoint HHF/CV death were consistent with the overall findings of the trial (Table 25).

Table 25. Time from Randomization to First Occurrence of Hospitalization for Heart Failure by Subgroup (FAS Population)

	Dapa 10 mg (N=8582)			Placebo (N=8578)				p-value	
Subgroup Categories	N#	Subjects with events n(%)	Event rate	N#	Subjects with events n(%)	Event rate	Hazard ratio (95% CI)	[a]	[b]
Baseline disease state									0.302
Established CV disease	3474	151 (4.3)	11.1	3500	192 (5.5)	14.1	0.78 (0.63, 0.97)	0.025	
Multiple risk factors	5108	61 (1.2)	3.0	5078	94 (1.9)	4.6	0.64 (0.46, 0.88)	0.006	
History of heart failure									0.918
Yes	852	87 (10.2)	27.7	872	115 (13.2)	37.2	0.73 (0.55, 0.96)	0.026	
No	7730	125 (1.6)	4.0	7706	171 (2.2)	5.6	0.73 (0.58, 0.92)	0.007	
Left ventricular ejection fraction (%)									0.275
<45	318	41 (12.9)	34.4	353	63 (17.8)	52.2	0.64 (0.43, 0.95)	0.029	
≥45	2261	100 (4.4)	11.1	2270	119 (5.2)	13.2	0.84 (0.64, 1.09)	0.191	
Age (years)									0.077
<65	4631	102 (2.2)	5.5	4622	113 (2.4)	6.2	0.88 (0.68, 1.15)	0.362	
≥65	3951	110 (2.8)	7.0	3956	173 (4.4)	11.1	0.64 (0.50, 0.81)	<0.001	
Age (years)									0.726
<75	8044	183 (2.3)	5.7	8020	246 (3.1)	7.8	0.73 (0.60, 0.88)	0.001	
≥75	538	29 (5.4)	14.1	558	40 (7.2)	18.8	0.81 (0.50, 1.30)	0.377	
Sex									0.441
Male	5411	145 (2.7)	6.7	5327	201 (3.8)	9.6	0.70 (0.56, 0.86)	<0.001	
Female	3171	67 (2.1)	5.3	3251	85 (2.6)	6.6	0.81 (0.59, 1.12)	0.207	
Race									0.717
White	6843	182 (2.7)	6.6	6810	249 (3.7)	9.2	0.72 (0.59, 0.87)	<0.001	
Black or African American	295	10 (3.4)	8.6	308	16 (5.2)	13.6	0.61 (0.27, 1.34)	0.215	
Asian	1148	17 (1.5)	3.9	1155	14 (1.2)	3.1	1.24 (0.61, 2.51)	0.558	
American Indian or Alaska native	52	0	0	52	0	0	NA	NA	
Native Hawaiian or other Pacific Islander	9	0	0	13	0	0	NA	NA	
Other	235	3 (1.3)	3.3	240	7 (2.9)	7.7	NA	NA	
Ethnicity									0.388
Hispanic or latino	1298	12 (0.9)	2.4	1270	21 (1.7)	4.3	0.56 (0.28, 1.15)	0.113	
Not hispanic or latino	7284	200 (2.7)	6.9	7308	265 (3.6)	9.1	0.75 (0.62, 0.90)	0.002	
Waist/hip ratio									0.257
High (>0.90 (m), >0.85 (f))	7878	196 (2.5)	6.2	7885	271 (3.4)	8.7	0.72 (0.60, 0.86)	<0.001	
Low (≤0.90 (m), ≤0.85 (f))	641	14 (2.2)	5.5	627	12 (1.9)	4.9	1.14 (0.53, 2.47)	0.735	
BMI (kg/m^2)									0.219
<30	3432	54 (1.6)	4.0	3532	62 (1.8)	4.5	0.89 (0.62, 1.28)	0.530	
≥30	5145	158 (3.1)	7.7	5042	223 (4.4)	11.2	0.68 (0.56, 0.84)	<0.001	
eGFR (CKD-EPI) ($mL/min/1.73m^2$)									0.189
<60	606	29 (4.8)	12.3	659	48 (7.3)	19.3	0.70 (0.44, 1.12)	0.135	
≥60 - <90	3838	99 (2.6)	6.5	3894	152 (3.9)	9.9	0.65 (0.51, 0.84)	<0.001	
≥90	4137	84 (2.0)	5.1	4025	86 (2.1)	5.4	0.94 (0.69, 1.26)	0.667	
Urinary albumin/creatinine ratio (mg/g)									0.862
<30	5819	96 (1.6)	4.1	5825	128 (2.2)	5.5	0.75 (0.57, 0.97)	0.030	
≥30 - ≤300	2017	69 (3.4)	8.7	2013	100 (5.0)	12.8	0.67 (0.49, 0.91)	0.010	
>300	594	42 (7.1)	18.7	575	54 (9.4)	25.5	0.74 (0.49, 1.10)	0.140	

Region									0.172
North America	2737	89 (3.3)	7.9	2731	127 (4.7)	11.6	0.69 (0.53, 0.91)	0.008	
Latin America	946	4 (0.4)	1.1	931	14 (1.5)	4.1	0.26 (0.08, 0.80)	0.018	
Asia/Pacific	1093	21 (1.9)	5.0	1093	19 (1.7)	4.5	1.10 (0.59, 2.05)	0.757	
Europe	3806	98 (2.6)	6.4	3823	126 (3.3)	8.3	0.77 (0.59, 1.01)	0.056	
Country									0.957
Canada	799	17 (2.1)	5.1	784	26 (3.3)	8.0	0.64 (0.35, 1.18)	0.152	
United States	1938	72 (3.7)	9.1	1947	101 (5.2)	13.1	0.71 (0.52, 0.95)	0.024	

All events adjudicated and confirmed by CEC. Hazard ratio, CI and p-value calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk and haematuria with treatment and subgroup category as model terms, and also including subgroup by treatment interaction when calculating the interaction p-values. Subgroup analyses for CV risk categories only use baseline haematuria as stratification variable in the model and vice versa.
[a] p-value treatment effects within each subgroup category; [b] p-value interaction between randomised treatment and relevant subgroup;
[c] No interaction p-value for subgroups not unambiguously categorised. Event rate displayed as event rate per 1000 subject years.
CI Confidence interval; FAS Full analysis set; N Number of subjects per treatment group; N# Number of subjects within subgroup category

Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.2.3.1.4.2

Reviewer Comment: *Lower incidence of HHF was observed in patients with established CV disease and multiple risk factors, as well as by subgroup based on history of HF. However, it is difficult to interpret the subgroup results based on HF history or baseline left ventricular ejection fraction because baseline HF status was not well-characterized at the start of the trial, and baseline drug/device treatment was not specified to be optimized prior to randomization. As previously noted, 10% of the randomized population in both treatment groups is described as having a medical history of heart failure, while approximately 30% of the randomized population has available echocardiogram information. Some patients who experienced HHF events during the trial probably had undiagnosed heart failure at baseline, or baseline HF information was not adequately captured during the enrollment process. Therefore, subgroup analyses based on HF history do not provide information that would inform labeling of dapagliflozin for a HHF indication in any particular subpopulation of the DECLARE trial.*

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7.1.4. Dose and Dose-Response

There was no exploration for dose response in this trial because only the 10 mg dose of dapagliflozin was studied.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable for this efficacy supplement.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The DECLARE trial evaluated cardiovascular outcomes using only the dapagliflozin 10 mg daily dose in T2DM subjects with established cardiovascular disease or multiple risk factors. The trial excluded subjects with baseline CrCl <60 mL/min and NYHA Class IV heart failure. Trial subjects were majority White. Therefore, there are some questions about generalizability of the trial findings to other demographic populations, as well as the benefit that might be expected in patients with moderate renal impairment or advanced heart failure. In addition, there is a lack of information regarding the 5 mg dose and whether any benefit on outcomes studied in this trial could be expected at the 5 mg dose in any population or subpopulation. Some of these questions are expected to be addressed by ongoing clinical trials in patient populations with HF and CKD.

7.2.2. Other Relevant Benefits

Approval of dapagliflozin 10 mg for the reduction of hospitalization for heart failure will aid prescribers in choosing appropriate therapeutic regimens for patients.

7.3. Integrated Assessment of Effectiveness

The results of the DECLARE trial support approval of a new indication for dapagliflozin: to reduce the risk of hospitalization for heart failure in adults with T2DM and established CV disease or multiple risk factors. The Applicant's evidence of clinical effectiveness derives from one large cardiovascular outcome trial, comparing addition of dapagliflozin 10 mg daily or placebo to standard of care diabetes therapy in 17,160 randomized patients with either established CV disease or multiple CV risk factors. Evaluating time-to-first event of hospitalization for heart failure or CV death was a primary efficacy variable prespecified in the statistical analysis plan and controlled for Type 1 error via alpha spending rules. In the studied population, there were significantly fewer patients with adjudicated first events of hospitalization for heart failure in the dapagliflozin arm compared to placebo (HR 0.83; 95% CI 0.73, 0.95; p=0.005). These findings were consistent across subpopulations, including patients with and without a history or heart failure, and were robust to sensitivity analyses. Adjudicated CV deaths were balanced between treatment arms. Thus, the submitted data demonstrates substantial evidence of effectiveness of dapagliflozin in reducing the risk of hospitalization for heart failure in the studied population compared to placebo when added to standard of care T2DM treatment.

8. Review of Safety

8.1. Safety Review Approach

The safety evaluation for this sNDA was based on clinical data submitted for Study D1693C00001 (the DECLARE trial), including the CSR, analysis and tabulation datasets, and responses to multiple IRs. The safety evaluation plan for this trial included routine assessments as well as a focus on potential risks associated with the SGLT2 inhibitor class (i.e., adverse events of special interest). In addition to the adjudication committee for cardiovascular events, the Applicant established independent adjudication committees for hepatic events and diabetic ketoacidosis. As part of the safety review I confirmed the Applicant's safety analyses using the FDA reviewer tools JMP, JReview and MAED, and performed additional safety analyses where appropriate, as described in the relevant subsections.

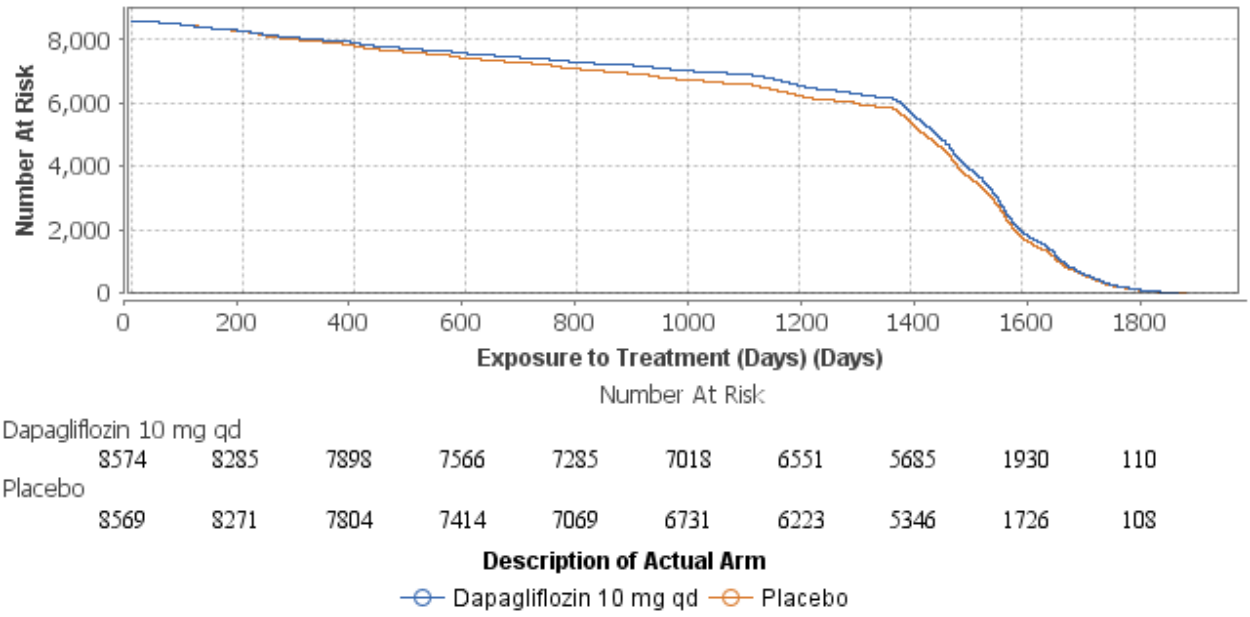
8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 17,160 patients were randomized across the two treatment groups. A total of 17,143 patients who received study drug comprise the SAS, which was the primary analysis set for malignancies, amputations, and fractures, and the OT-SAS, which was the primary analysis set for all other safety variables.

Duration of exposure ranged from 0 to 62 months. There were 30,623 patient-years of treatment exposure in the dapagliflozin arm and 29,749 patient-years of exposure in the placebo arm, with a median duration of exposure of 48 months in each arm. The mean and mediation durations of exposure to the IP were similar between treatment arms, and approximately 66% of dapagliflozin-treated subjects and 62% of placebo-treated subjects received the IP for at least 48 months (Figure 18 and Table 28).

Figure 18. Exposure Duration by Treatment Arm (Safety Population)



Source: Generated from ADSL dataset using JReview

Table 28. Duration of Exposure in DECLARE

Overall	Number (%) of subjects		
	Dapa 10 mg (N=8574)	Placebo (N=8569)	Total (N=17143)
Total number of subject years exposure (years)	30623	29749	60372
Exposure to study drug (months)			
n	8574	8569	17143
Mean	42.856	41.657	42.256
SD	14.6289	15.1854	14.9213
Median	48.100	47.830	48.000
Q1, Q3	39.930, 51.630	37.130, 51.330	38.500, 51.500
Min, Max	0.07, 61.20	0.03, 61.97	0.03, 61.97

Overall	Number (%) of subjects		
	Dapa 10 mg (N=8574)	Placebo (N=8569)	Total (N=17143)
Exposure to study drug (months) – descending cumulative (%)			
>0	8574 (100.0)	8569 (100.0)	17143 (100.0)
>1	8511 (99.3)	8519 (99.4)	17030 (99.3)
>3	8394 (97.9)	8410 (98.1)	16804 (98.0)
>6	8236 (96.1)	8214 (95.9)	16450 (96.0)
>12	7903 (92.2)	7814 (91.2)	15717 (91.7)
>18	7611 (88.8)	7474 (87.2)	15085 (88.0)
>24	7359 (85.8)	7178 (83.8)	14537 (84.8)
>30	7121 (83.1)	6855 (80.0)	13976 (81.5)
>36	6878 (80.2)	6556 (76.5)	13434 (78.4)
>42	6300 (73.5)	5984 (69.8)	12284 (71.7)
>48	4413 (51.5)	4119 (48.1)	8532 (49.8)
>54	1173 (13.7)	1075 (12.5)	2248 (13.1)
>60	38 (0.4)	37 (0.4)	75 (0.4)

Source: Excerpted from Table 11.3.1.1 in the CSR Appendix

8.2.2. Relevant characteristics of the safety population:

This submission contains a single clinical trial. The demographics and clinical characteristics of the study population were presented in Table 8 and Table 9 in Section 6.1.2 and there are no significant differences between the baseline characteristics of the FAS versus the safety population.

8.2.3. Adequacy of the safety database:

The safety database is adequate to fulfill the requirements of the PMRs. It is noteworthy that at baseline, only approximately 40% of enrolled subjects had established CVD while ~60% had multiple risk factors. This is a smaller proportion of patients with eCVD than were enrolled in the other large CVOTs in the SGLT2i class. However, this was an event-driven trial and the number of MACE events was robust and adequate to conclusively exclude an increased risk of MACE with use of this product. In addition, the analyses of the primary endpoints demonstrated similar results across baseline CVD categories.
The exclusion of patients with baseline CrCl <60 mL/min limits the generalizability of safety findings to patients with baseline renal impairment. Similarly, the over-representation of White

patients in the trial limits generalizability of findings across races, a problem common to all the large CVOTs in the diabetes space.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The quality of the overall submission was adequate. The key safety findings presented in this sNDA were reproducible and confirmed using the submitted datasets. In addition, the findings from OSI inspections of six clinical sites from the trial, selected based on higher subject enrollment and site risk rankings, supported the validity of the data.

8.3.2. Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

The Applicant defined an AE as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to the IP, whether or not it is considered causally related to the IP.

A serious adverse event (SAE) was defined as an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up) that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization of prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above

Events representing a known or possible malignancy, laboratory abnormalities fulfilling Hy's law definition (ALT/AST >3x ULN and total bilirubin >2x ULN) or overdose (defined as the accidental or intentional ingestion of any dose of the IP that is considered both excessive and medically important) were to be reported as an SAE.

AEs in the following categories were to be collected in the trial:

- SAEs
- AEs leading to discontinuation of the IP (i.e., DAEs)
- Suspected CV events
- Elective coronary and non-coronary resvascularizations
- Heart failure

- Potential diabetic ketoacidosis
- Amputation and related events
- AEs of special interest (AESIs):
    - Suspected neoplasm
    - Hepatic events
    - Major hypoglycemic events: defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behavior, and prompt recovery after glucagon administration. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal was considered sufficient evidence that the event was induced by a low blood glucose concentration
    - Fractures
    - Renal events
    - Symptoms of volume depletion
    - Hypersensitivity reactions (serious or leading to discontinuation of IP)
    - Urinary tract infections (serious or leading to discontinuation of IP)
    - Genital infections (serious or leading to discontinuation of IP)
    - Diabetic ketoacidosis (added as an AESI during the trial)
    - Pancreatitis (added as an AESI during the trial)

Any AEs recorded as unresolved at the Closing Visit were to be followed up by the investigators for as long as medically indicated.

Severity of AEs (i.e, intensity) was graded according to the following scale:

- Mild (awareness of event but easily tolerated)
- Moderate (enough discomfort to cause some interference with usual activity)
- Severe (inability to carry out usual activity)

Investigators also provided their assessment of whether there was a causal relationship between the IP and each AE.

Reviewer Comment: *The definitions and coding of AEs were acceptable. Comparisons between the verbatim terms in the CRFs and analysis datasets, and the MedDRA preferred terms (PTs) for which these AEs were coded, showed that classifications were appropriate. The Applicant used Standard MeDRA Queries (SMQs) or created Custom MedDRA Queries (CMQs) to capture AESIs. For this safety evaluation I also analyzed the safety database using Broad CMQs derived from SMQs and PTs for AESIs known to be important in the SGLT2i class overall. Results from these analyses will be presented in the relevant AESI sections.*

8.3.3. Routine Clinical Tests

In Study D1693C00001 routine clinical laboratory safety assessments, including blood and urinalysis, occurred at Visits 1 (Week -4 to -8), 2 (Day 1), 4 (Month 6), 6 (Month 12), 10 (Month 24), and end-of-treatment/Closing Visit. Fasting laboratory assessments were obtained at all the above visits except for Visit 1, which was non-fasting. Urine dipstick was also obtained for hematuria assessment at Visits 1 and 2. Investigators evaluated results for clinically significant abnormalities based on the central laboratory's reference ranges. Patients with elevations in AST or ALT greater than 3x ULN had additional testing as per the trials Algorithm on Management of Sustained Elevated Liver Safety Abnormalities. In addition, predefined levels of liver enzyme elevations underwent adjudication as part of the PMR requirements, and sustained elevations in CrCl were also handled according to predefined protocols (see the relevant sections below for details).

8.4. Safety Results

8.4.1. Deaths

Overall there were 1,098 patients in the SAS population who died, and there were numerically more deaths in the placebo arm: 529 patients (6.2%) died in the dapagliflozin arm and 569 patients (6.6%) died in the placebo arm (all-cause mortality). The largest proportion of deaths were adjudicated as CV deaths (245 patients in the dapagliflozin group and 248 patients in the placebo group). The most common causes of deaths adjudicated as non-CV deaths were malignancy (115 patients in each treatment arm), followed by infection including sepsis (48 patients in the dapagliflozin arm and 54 patients in the dapagliflozin arm). The cause of death was adjudicated as undetermined in 73 patients in the dapagliflozin arm (13.8% of deaths) and 83 patients in the placebo arm (14.6% of deaths). Overall, causes of death by adjudication classification were balanced between treatment arms.

Table 29. Summary of Deaths by Adjudication Classification (SAS)

Death	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Total number of subjects who died	**529 (6.2)**	**569 (6.6)**
CV death	245 (46.3)	248 (43.6)
Sudden cardiac death	141 (57.6)	143 (57.7)
Death due to acute myocardial infarction	28 (11.4)	36 (14.5)
Death due to stroke	28 (11.4)	28 (11.3)
Death due to heart failure	27 (11.0)	23 (9.3)
Death due to CV procedure	9 (3.7)	5 (2.0)
Death due to CV hemorrhage	1 (0.4)	1 (0.4)

Other	11 (4.5)	12 (4.8)
Non-CV death	211 (39.9)	238 (41.8)
Pulmonary	11 (5.2)	20 (8.4)
Trauma	8 (3.8)	10 (4.2)
Suicide	2 (0.9)	3 (1.3)
Hemorrhage (non-CV bleeding/stroke)	3 (1.4)	5 (2.1)
Malignancy	115 (54.5)	115 (48.3)
Renal failure	6 (2.8)	10 (4.2)
Gastrointestinal causes	2 (0.9)	1 (0.4)
Infection (including sepsis)	48 (22.7)	54 (22.7)
Inflammatory (e.g. SIRS)	1 (0.5)	0
Non-CV procedure/surgery	5 (2.4)	3 (1.3)
Prescription drug reaction or overdose	0	1 (0.4)
Neurological (non-CV)	2 (0.9)	3 (1.3)
Hepatobiliary	6 (2.8)	6 (2.5)
Pancreatic	0	1 (0.4)
Other	2 (0.9)	6 (2.5)
Undetermined deaths	73 (13.8)	83 (14.6)

Source: Derived from ADYB.xpt dataset using JMP and adapted from Table 11.3.3.1.1 in the CSR Appendix 11

Looking at deaths by system organ class (SOC), deaths occurred most commonly due to events in the "Cardiac disorders" SOC, followed by "General Disorders and administration site reactions" and "Neoplasms benign, malignant and unspecified (including cysts and polyps".

Because all deaths were adjudicated in this trial, with CV death as a component of the primary and secondary efficacy endpoints, and all-cause mortality as an additional secondary efficacy endpoint, further analyses of death have already been discussed in Section 6.

Reviewer Comment: *I reviewed randomly selected narratives and CEC adjudication packages for fatal events. A few cases did not provide enough detail to confirm the cause of death, or the cause of death appeared to be multifactorial. There were also a few cases for which the cause of death was taken from the death certificate in the absence of additional confirmatory information from the case narratives (for example, in the cases of two deaths in the placebo arm and one death in the dapagliflozin arm that were adjudicated as "renal deaths", there was only a death certificate available without additional narrative details).*

With regard to causes of death that were "undetermined" in this trial, 13.8% (73/529) and 14.6% (83/569) deaths in the dapagliflozin and placebo arms, respectively, fell into this category. This proportion of undetermined deaths was similar to that observed in the CANVAS program; a significantly higher proportion of deaths were considered "not assessable" in the EMPA-REG OUTCOME trial (approximately 40%). Unlike the EMPA-REG OUTCOME trial and

CANVAS program, the DECLARE trial did not consider "undetermined" deaths as CV deaths for the purpose of calculating the primary efficacy variables. Undetermined deaths were only included in the analysis of all-cause mortality and were balanced between treatment arms; these undetermined deaths did not affect the conclusions of the trial. I reviewed randomly selected adjudication packages for undetermined deaths and found that there were either multiple factors contributing to these deaths or an absence of any information to allow for determination of the cause of death. I also noted that several cases adjudicated as undetermined deaths had been sent for re-review by the CEC during consistency checks of the trial data, with the charter definitions of CV death vs. undetermined death accompanying the request for additional review of the cases. As a result, some cases that had been initially adjudicated as CV deaths were re-adjudicated as undetermined deaths. My review of these cases supported the final adjudication results; i.e., that these were undetermined deaths due to an absence of any information that could confirm that these were CV deaths.

In summary, from a clinical perspective my conclusion is that the adjudications of causes of death were reasonable in this trial, and the definitions in the CEC charter were consistently applied.

8.4.2. Serious Adverse Events

In the SAS population, 3205 (37.4%) of patients in the dapagliflozin arm and 3418 (39.9%) of patients in the placebo arm experienced at least one SAE during the trial. The number of patients experiencing any SAE in either treatment group by SOC is presented in Table 30, in descending order based on incidence in the dapagliflozin arm.

Table 30. Frequency of Patients with SAEs by SOC and Treatment Arm (OT-SAS Population)*

System Organ Class	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Cardiac disorders	1045 (12.2)	1108 (12.9)
Infections and infestations	610 (7.1)	692 (8.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	484 (5.6)	473 (5.5)
Nervous system disorders	430 (5.0)	412 (4.8)
Injury, poisoning and procedural complications	295 (3.4)	275 (3.2)
Vascular disorders	268 (3.1)	254 (3.0)
Musculoskeletal and connective tissue disorders	234 (2.7)	236 (2.8)
General disorders and administration site conditions	222 (2.6)	225 (2.6)
Gastrointestinal disorders	214 (2.5)	224 (2.6)
Metabolism and nutrition disorders	189 (2.2)	258 (3.0)
Respiratory, thoracic and mediastinal disorders	180 (2.1)	232 (2.7)
Renal and urinary disorders	144 (1.7)	225 (2.6)
Hepatobiliary disorders	87 (1.0)	110 (1.3)
Skin and subcutaneous tissue disorders	70 (0.8)	62 (0.7)
Reproductive system and breast disorders	66 (0.8)	65 (0.8)
Eye disorders	50 (0.6)	56 (0.7)
Blood and lymphatic system disorders	47 (0.5)	49 (0.6)
Psychiatric disorders	28 (0.3)	46 (0.5)
Investigations	26 (0.3)	25 (0.3)
Ear and labyrinth disorders	20 (0.2)	29 (0.3)
Endocrine disorders	10 (0.1)	12 (0.1)
Product issues	10 (0.1)	4 (0.0)
Immune system disorders	8 (0.1)	12 (0.2)
Congenital, familial and genetic disorders	5 (0.1)	1 (0.0)
Surgical and medical procedures	0	0

*Because some patients experienced more than one SAE during the trial, the total number of subjects in each column is greater than the number experiencing at least one SAE stated above
Source: Derived from ADSL and ADAE datasets using JReview

Looking at SAEs by HLT, Table 31 presents SAEs that occurred in ≥1% of patients in either treatment arm.

Table 31. Frequency of Patients with SAEs by HLT and Treatment Arm (OT-SAS Population)

High Level Term	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Ischaemic coronary artery disorders	656 (7.7)	662 (7.7)
Heart failures NEC	238 (2.8)	323 (3.8)
Central nervous system haemorrhages and cerebrovascular accidents	236 (2.8)	227 (2.6)
Lower respiratory tract and lung infections	184 (2.1)	224 (2.6)
Supraventricular arrythmias	123 (1.4)	165 (1.9)
Coronary artery disorders NEC	116 (1.4)	101 (1.2)
Bacterial infections NEC	109 (1.3)	132 (1.5)
Peripheral vasoconstriction, necrosis and vascular insufficiency	107 (1.2)	105 (1.2)
Pain and discomfort NEC	105 (1.2)	99 (1.2)
Osteoarthropathies	100 (1.2)	78 (0.9)
Limb fractures and dislocations	94 (1.1)	97 (1.1)
Sepsis, bacteraemia, viraemia, and fungaemia NEC	93 (1.1)	93 (1.1)
Renal failure and impairment	80 (0.9)	134 (1.6)

Source: Derived from ADSL and ADAE datasets using JReview

In general, looking at SAEs by SOC shows only a few SOCs with small numerical imbalances unfavorable to dapagliflozin (e.g., nervous system disorders and vascular disorders). Drilling down to dictionary derived terms within each SOC reveals a few imbalances discussed below.

Cardiac Disorders

Numerically more patients in the dapagliflozin arm had the SAEs with the PTs "acute myocardial infarction" (228 dapagliflozin vs. 195 placebo), "coronary artery disease" (94 vs. 69), "cardiac arrest" (24 vs. 19), and "ventricular tachycardia" (19 vs. 11). SAEs that occurred more commonly in the placebo group included "cardiac failure" (120 dapagliflozin vs. 165 placebo), "atrial fibrillation" (94 vs. 121), "cardiac failure congestive" (89 vs. 122), and "cardiac failure acute" (16 vs. 26).

General Disorders and Administrative Site Conditions

Numerically more patients in the dapagliflozin arm had SAEs with the PTs "chest pain" (27 dapagliflozin vs. 15 placebo) and "sudden death" (19 vs. 17).

Infections and Infestations

Numerically fewer patients in the dapagliflozin arm had SAEs with the PTs "urinary tract infection" (37 dapagliflozin vs. 51 placebo), "osteomyelitis" (21 vs. 30), and "gangrene" (18 vs. 24).

Metabolism and Nutrition Disorders

Numerically more patients in the dapagliflozin arm had SAEs with the PTs "hypovolemia" (8 dapagliflozin vs. 4 placebo) and "diabetic ketoacidosis" (22 vs. 17). Numerically fewer patients in the dapagliflozin arm had SAEs with the PTs "hypoglycemia" (61 dapagliflozin vs. 73 placebo), "hyperglycemia" (27 vs. 46), "diabetic metabolic decompensation" (12 vs. 24), and "diabetes mellitus inadequate control" (11 vs. 24).

Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)

Numerically more patients in the dapagliflozin arm had SAEs with the PT "prostate cancer" (62 dapagliflozin vs. 53 placebo), "pancreatic carcinoma" (9 vs. 6), and "malignant melanoma in situ" (6 vs. 3). Notably, numerically fewer patients in the dapagliflozin arm had SAEs with the PT "bladder cancer" (11 dapagliflozin vs. 22 placebo). Malignancies were adjudicated during the trial and are discussed in detail in Section 8.5 (Submission-Specific Safety Issues).

Nervous System Disorders

The numerical imbalance observed at the SOC level is accounted for by numerically more patients in the dapagliflozin arm with SAEs with the PTs "cerebrovascular accident" (89 dapagliflozin vs. 71 placebo), "ischaemic stroke" (85 vs. 79), and "transient ischemic attack" (63 vs. 46).

Renal and Urinary Disorders

Notably, numerically fewer patients in the dapagliflozin arm had SAEs with the PT "acute kidney injury" (67 dapagliflozin vs. 101 placebo), "renal failure" (5 vs. 12), "haematuria" (4 vs. 13), "ureterolithiasis" (3 vs. 16), and "renal impairment" (2 vs. 11). Within this SOC there were no imbalances in SAEs that were unfavorable to dapagliflozin in any PT.

Reproductive System and Breast Disorders

While SAEs in this SOC were balanced between treatment arms, numerically more patients in the dapagliflozin arm had SAEs with the PT "acquired phimosis" (10 dapagliflozin vs. 1 placebo).

Skin and Subcutaneous Tissue Disorders

Numerically more patients in the dapagliflozin arm had SAEs with the PT "diabetic foot" (33 dapagliflozin vs. 27 placebo).

Vascular Disorders

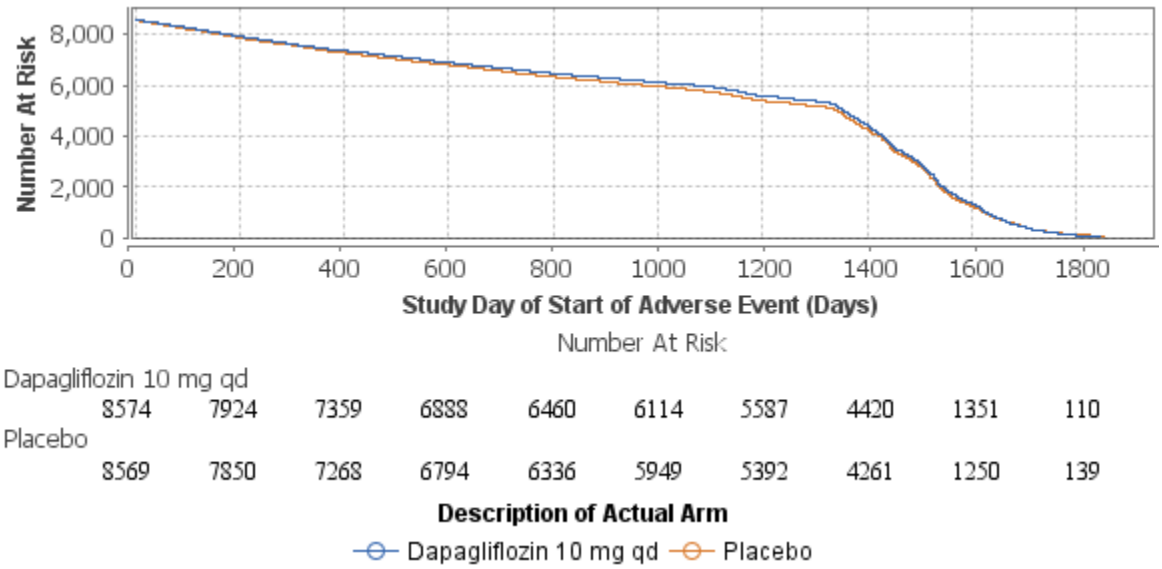
The numerical imbalance observed at the SOC level is accounted for by numerically more patients in the dapagliflozin arm with SAEs with the PTs "peripheral vascular disorder" (31 dapagliflozin vs. 16 placebo), "hypotension" (26 vs. 11), "peripheral artery stenosis" (21 vs. 17), and "deep vein thrombosis" (14 vs. 10).

Reviewer Comment: *My analysis of SAEs using JReview yielded identical numbers of events to those submitted by the Applicant in the CSR.*

Overall, with the exception of diabetic ketoacidosis (discussed in Submission-Specific Safety Issues, Section 8.5), review of SAEs in the DECLARE trial did not reveal any unexpected imbalances unfavorable to dapagliflozin, and was largely consistent with the information presented in the approved labeling. Notably, some SAEs were observed to have unexpected imbalances favorable to dapagliflozin, such as bladder cancer, acute kidney injury, and major hypoglycemia; these issues are discussed in more detail in the relevant subsections of Section 8.5.

Figure 19 presents an analysis of the time to first SAE by treatment arm, with no apparent difference between treatment arms. This analysis yielded the same pattern when looking at time to SAE by age category (<65 years vs. ≥65 years) and by gender.

Figure 19. Kaplan Meier Analysis of Time to SAE by Treatment Arm (Safety Population)



Source: Generated from ADSL and ADAE datasets using JReview

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 32 presents a summary of dropout and/or discontinuations due to AEs, presented by SOC with the most common PTs within each SOC. Overall more patients discontinued the study drug due to adverse events in the dapagliflozin arm compared with the placebo arm: 693 (8.1%) and 592 (6.9%) patients, respectively. Of these, 255 (3.0%) patients in the dapagliflozin arm and 303 (3.5%) patients in the placebo arm discontinued study drug due to an SAE. Not surprisingly, more patients in the dapagliflozin arm discontinued treatment due to daytime or nighttime

polyuria, genitourinary tract infections, and other genital conditions associated with pruritus and inflammation.

Table 32. Summary of Common Adverse Events Leading to Dropout and/or Discontinuation (Safety Population)

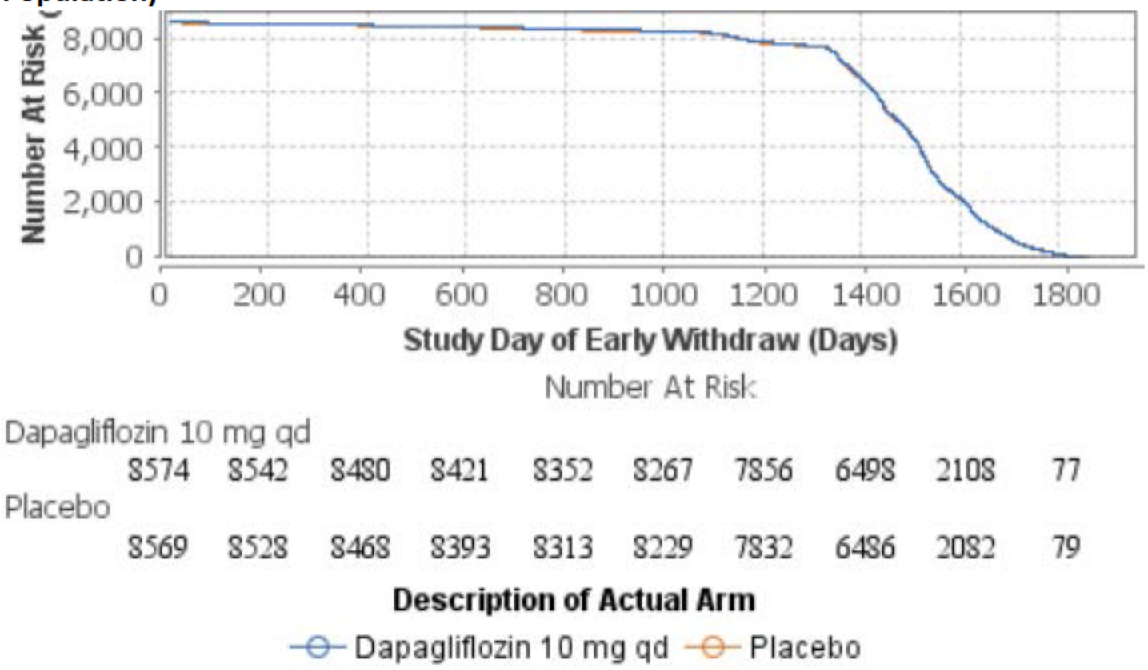
Adverse Event Leading to Discontinuation SOC/MedDRA PT	Dapagliflozin 10mg (n=693) n (%)	Placebo (n=592) n (%)
Infections and infestations	144 (20.8)	71 (12.0)
Urinary tract infection	42 (6.0)	22 (3.7)
Fungal infection	13 (1.9)	2 (0.3)
Vulvovaginal candidiasis	8 (1.2)	2 (0.3)
Vulvovaginal mycotic infection	8 (1.2)	0
Vulvovaginitis	7 (1.0)	1 (0.2)
Genital infection fungal	5 (0.7)	1 (0.2)
Balanitis candida	4 (0.6)	0
Genital candidiasis	4 (0.6)	0
Urethritis	4 (0.6)	0
Renal and urinary disorders	111 (16.0)	91 (15.4)
Pollakiuria	20 (2.9)	13 (2.2)
Renal impairment	16 (2.3)	16 (2.7)
Polyuria	15 (2.3)	1 (0.2)
Dysuria	10 (1.4)	0
Renal failure	9 (1.3)	7 (1.2)
Acute kidney injury	8 (1.2)	19 (3.2)
Nocturia	4 (0.6)	0
Urinary incontinence	4 (0.6)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	109 (15.7)	122 (20.6)
Bladder cancer	11 (1.6)	21 (3.5)
Transitional cell carcinoma	7 (1.0)	6 (1.0)
Prostate cancer	6 (0.9)	2 (0.3)
Breast cancer female	4 (0.6)	2 (0.3)
Hepatocellular carcinoma	4 (0.6)	1 (0.2)
Reproductive system and breast disorders	65 (9.4)	7 (1.2)
Balanoposthitis	27 (3.9)	2 (0.3)
Vulvovaginal pruritis	14 (2.0)	1 (0.2)
Pruritus genital	8 (1.2)	0
Nervous system disorders	40 (5.8)	55 (9.3)
Cerebrovascular accident	10 (1.4)	10 (1.7)
Dizziness	7 (1.0)	4 (0.7)

Ischaemic stroke	3 (0.4)	8 (1.4)
Investigations	36 (5.2)	27 (4.6)
Weight decreased	12 (1.7)	2 (0.3)
Blood creatinine increased	7 (1.0)	3 (0.5)
Glomerular filtration rate decreased	7 (1.0)	2 (0.3)
Cardiac disorders	34 (4.9)	41 (6.9)
Acute myocardial infarction	9 (1.3)	14 (2.4)
Cardiac failure	5 (0.7)	4 (0.7)
Cardiac failure congestive	4 (0.6)	2 (0.3)
Coronary artery disease	4 (0.6)	2 (0.3)
Metabolism and nutrition disorders	33 (4.8)	42 (7.1)
Type 1 diabetes mellitus	6 (0.9)	3 (0.5)
Hypoglycaemia	5 (0.7)	6 (1.0)
Gastrointestinal disorders	28 (4.0)	45 (7.6)
Constipation	5 (0.7)	4 (0.7)
Diarrhoea	5 (0.7)	15 (2.5)
Skin and subcutaneous tissue disorders	25 (3.6)	18 (3.0)
Rash	4 (0.6)	3 (0.5)
Pruritus	3 (0.4)	6 (1.0)
General disorders and administration site conditions	14 (2.0)	11 (1.9)
Musculoskeletal and connective tissue disorders	13 (1.9)	14 (2.4)
Vascular disorders	13 (1.9)	5 (0.8)
Respiratory, thoracic and mediastinal disorders	10 (1.4)	14 (2.4)
Psychiatric disorders	6 (0.9)	5 (0.8)
Hepatobiliary disorders	5 (0.7)	14 (2.4)
Blood and lymphatic system disorders	4 (0.6)	4 (0.7)
Immune system disorders	3 (0.4)	1 (0.2)
Injury, poisoning and procedural complications	3 (0.4)	4 (0.7)
Eye disorders	2 (0.3)	2 (0.3)
Ear and labyrinth disorders	0	0

Source: Derived from ADDS dataset and adapted from Table 11.3.3.3.1 in the CSR Appendix 11

Figure 20 presents an analysis of the time to early withdrawal from the trial by treatment arm, with no apparent difference between treatment arms. This analysis yielded the same pattern when looking at the following subgroups: age category (<65 years vs. ≥65 years), gender, ethnicity (Hispanic or Latino vs. Not Hispanic or Latino), and race (for race categories that had a sufficient number of enrolled subjects to perform a meaningful analysis).

Figure 20. Kaplan-Meier Analysis of Early Withdrawal from the DECLARE trial (Safety Population)



Source: Generated from ADSL and ADDS datasets using JReview

8.4.4. Significant Adverse Events

The International Council for Harmonization (ICH) E3 defines other significant adverse events as marked hematological and other laboratory abnormalities that led to an intervention, including withdrawal of drug treatment, dose reduction or significant additional concomitant therapy. Adverse events meeting this definition are primarily discussed in Section 8.5 (Analysis of Submission-Specific Safety Issues).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A summary of TEAEs reported in at least 10 subjects with a higher proportion in the dapagliflozin arm during the double-blind treatment period is presented in Table 33.

Table 33. Summary of Common Treatment-Emergent Adverse Events (Safety Population)

TEAE MedDRA Preferred Term	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Total subjects with TEAE	**5160 (60.2)**	**5109 (59.6)**
Urinary tract infection	515 (6.0)	470 (5.5)
Acute myocardial infarction	230 (2.7)	201 (2.3)

Haematuria	220 (2.6)	202 (2.4)
Dizziness	122 (1.4)	87 (1.0)
Coronary artery disease	121 (1.4)	94 (1.1)
Benign prostatic hyperplasia	104 (1.2)	94 (1.1)
Arthralgia	100 (1.2)	94 (1.1)
Balanoposthitis	89 (1.0)	23 (0.3)
Pollakiuria	88 (1.0)	47 (0.5)
Ischaemic stroke	86 (1.0)	81 (0.9)
Transient ischaemic attack	82 (1.0)	68 (0.8)
Fungal infection	78 (0.9)	25 (0.3)
Influenza	77 (0.9)	56 (0.7)
Hypotension	73 (0.9)	54 (0.6)
Headache	70 (0.8)	57 (0.7)
Constipation	68 (0.8)	60 (0.7)
Fatigue	68 (0.8)	49 (0.6)
Diabetic neuropathy	65 (0.8)	53 (0.6)
Musculoskeletal pain	65 (0.8)	39 (0.5)
Cystitis	63 (0.7)	55 (0.6)
Dysuria	58 (0.7)	35 (0.4)
Gastrooesophageal reflux disease	57 (0.7)	43 (0.5)
Chest pain	56 (0.7)	48 (0.6)
Musculoskeletal chest pain	56 (0.7)	49 (0.6)
Gastroenteritis	52 (0.6)	43 (0.5)
Polyuria	51 (0.6)	18 (0.2)
Vulvovaginal pruritus	50 (0.6)	8 (0.1)
Large intestine polyp	48 (0.6)	44 (0.5)
Vulvovaginal candidiasis	47 (0.5)	9 (0.1)
Ankle fracture	45 (0.5)	24 (0.3)
Insomnia	45 (0.5)	28 (0.3)
Arthritis	35 (0.4)	29 (0.3)
Vulvovaginal mycotic infection	35 (0.4)	12 (0.1)
Intervertebral disc protrusion	34 (0.4)	25 (0.3)
Peripheral artery stenosis	31 (0.4)	22 (0.3)
Urinary retention	31 (0.4)	29 (0.3)
Pruritus genital	30 (0.3)	4 (0.0)
Vaginal infection	30 (0.3)	11 (0.1)
Weight decreased	30 (0.3)	20 (0.2)
Pharyngitis	29 (0.3)	21 (0.2)
Squamous cell carcinoma	29 (0.3)	20 (0.2)
Spinal osteoarthritis	27 (0.3)	16 (0.2)

Intermittent claudication	26 (0.3)	19 (0.2)
Actinic keratosis	25 (0.3)	11 (0.1)
Cardiac arrest	25 (0.3)	19 (0.2)
Diabetic ketoacidosis	25 (0.3)	19 (0.2)
Genital infection fungal	25 (0.3)	9 (0.1)
Urinary incontinence	25 (0.3)	18 (0.2)
Deep vein thrombosis	24 (0.3)	18 (0.2)
Hand fracture	24 (0.3)	15 (0.2)
Inguinal hernia	24 (0.3)	19 (0.2)
Acquired phimosis	23 (0.3)	8 (0.1)
Micturition urgency	23 (0.3)	7 (0.1)
Palpitations	23 (0.3)	19 (0.2)
Creatinine renal clearance decreased	22 (0.3)	19 (0.2)
Epistaxis	22 (0.3)	16 (0.2)
Spinal compression fracture	19 (0.2)	10 (0.1)
Vulvovaginitis	19 (0.2)	2 (0.0)
Dry mouth	17 (0.2)	5 (0.1)
Hypercholesterolaemia	17 (0.2)	6 (0.1)
Tendon rupture	17 (0.2)	11 (0.1)
Dermatitis	16 (0.2)	11 (0.1)
Erectile dysfunction	16 (0.2)	10 (0.1)
Liver function test increased	16 (0.2)	8 (0.1)
Oropharyngeal pain	16 (0.2)	11 (0.1)
Tachycardia	16 (0.2)	10 (0.1)
Upper limb fracture	16 (0.2)	10 (0.1)
Atrioventricular block complete	15 (0.2)	12 (0.1)
Diverticulum	15 (0.2)	11 (0.1)
Pneumonia aspiration	15 (0.2)	6 (0.1)
Postoperative wound infection	15 (0.2)	8 (0.1)
Sinus congestion	15 (0.2)	9 (0.1)
Supraventricular tachycardia	15 (0.2)	8 (0.1)
Atrioventricular block second degree	14 (0.2)	8 (0.1)
Calculus urinary	14 (0.2)	9 (0.1)
Candida infection	14 (0.2)	9 (0.1)
Dental caries	14 (0.2)	6 (0.1)
Dysphagia	14 (0.2)	11 (0.1)
Nocturia	14 (0.2)	9 (0.1)
Rhinitis allergic	14 (0.2)	10 (0.1)
Skin abrasion	14 (0.2)	9 (0.1)
Tibia fracture	14 (0.2)	9 (0.1)

Tonsillitis	14 (0.2)	7 (0.1)
Balanitis candida	13 (0.2)	1 (0.0)
Pancreatitis acute	13 (0.2)	12 (0.1)
Polycythaemia	13 (0.2)	2 (0.0)
Genital infection	11 (0.1)	2 (0.0)
Oral candidiasis	11 (0.1)	3 (0.0)
Duodenal ulcer	10 (0.1)	3 (0.0)
Genital candidiasis	10 (0.1)	1 (0.0)
Sinus tachycardia	10 (0.1)	4 (0.0)

Source: Derived from DM and AE datasets using JReview

Reviewer Comment: *The patterns and types of TEAEs observed in the DECLARE trial are consistent with the information presented in the approved labeling.*

8.4.6. Laboratory Findings

The Applicant provided descriptive statistics for electrolytes, hematology parameters, uric acid, and lipid parameters. Laboratory findings related to hepatic function and renal function are discussed under Adverse Events of Special Interest, and in the efficacy section related to renal effects of dapagliflozin. Bicarbonate findings are discussed under DKA in the AESI section.

Electrolytes:

Electrolytes were collected at the Randomization, End-of-Treatment, and Closing Visits. The Applicant presented the number of patients in each treatment group with possibly clinically significant electrolyte abnormalities, for the SAS and OT-SAS populations, shown below in Table 34.

Table 34. Summary of Patients with Possibly Clinically Significant Electrolyte Abnormalities (Safety Population)

	Number (%) of subjects			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Sodium (mmol/L) [a]				
Number of subjects with any post-baseline value	7317	6583	7181	6358
<120	2 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
<130	15 (0.2)	10 (0.2)	31 (0.4)	26 (0.4)
>150	4 (<0.1)	3 (<0.1)	1 (<0.1)	0
Potassium (mmol/L) [a]				
Number of subjects with any post-baseline value	7316	6583	7180	6357
≤2.5	0	0	2 (<0.1)	2 (<0.1)
≥6.0	53 (0.7)	45 (0.7)	78 (1.1)	67 (1.1)
Calcium (µmol/L) [b]				
Number of subjects with baseline values and any post-baseline value	7249	6519	7085	6267
≥0.25 from ULN and ≥0.125 from baseline	8 (0.1)	5 (<0.1)	6 (<0.1)	3 (<0.1)
Calcium (µmol/L) [a]				
Number of subjects with any post-baseline value	7317	6584	7183	6361
<1.875	6 (<0.1)	5 (<0.1)	7 (<0.1)	3 (<0.1)
Magnesium (mmol/l) [a]				
Number of subjects with any post-baseline value	7318	6584	7182	6361
<0.5	24 (0.3)	19 (0.3)	67 (0.9)	60 (0.9)
>2.0	0	0	0	0
Phosphorus (mmol/L) [c]				
Number of subjects with any post-baseline value and age 17 to 65	4482	4070	4369	3895
≤0.58	3 (<0.1)	2 (<0.1)	5 (0.1)	4 (0.1)
≥1.81	9 (0.2)	9 (0.2)	12 (0.3)	8 (0.2)
Number of subjects with any post-baseline value and age ≥66	2835	2513	2814	2467
≤0.68	9 (0.3)	7 (0.3)	20 (0.7)	16 (0.6)
≥1.65	26 (0.9)	22 (0.9)	29 (1.0)	20 (0.8)

Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.3.4.1

Reviewer Comment: *While the Applicant's findings do not present any concerning data that would affect labeling, the Applicant did not present the mean change from baseline to last-value-on-treatment for several laboratory parameters. We requested this information in an IR and the results are presented below in Table 35. There were no concerning or unexpected findings.*

Table 35. Summary of Mean Change from Baseline for Selected Laboratory Parameters (SAS Population)

			Baseline		Last value on treatment		Change from baseline	
Lab test (unit)	Treatment	Patients Analyzed (n)	Mean	SD	Mean	SD	Mean	SD
Sodium (mEq/L)	Dapa 10 mg	6523	139.708	2.5645	140.386	2.5881	0.678	2.8729
	Placebo	6267	139.688	2.5795	139.963	2.7661	0.274	2.9123
Potassium (mEq/L)	Dapa 10 mg	6516	4.437	0.4377	4.531	0.4516	0.095	0.4770
	Placebo	6258	4.448	0.4393	4.583	0.4659	0.135	0.4777
Magnesium (mg/dL)	Dapa 10 mg	6521	1.831	0.2526	2.012	0.2294	0.181	0.2414
	Placebo	6268	1.835	0.2494	1.851	0.2400	0.016	0.2380
Calcium (mg/dL)	Dapa 10 mg	6521	9.573	0.4314	9.554	0.4214	-0.019	0.4393
	Placebo	6267	9.579	0.4326	9.556	0.4197	-0.022	0.4437
Phosphate (mg/dL)	Dapa 10 mg	6520	3.551	0.5411	3.636	0.5427	0.085	0.5687
	Placebo	6270	3.550	0.5366	3.558	0.5521	0.008	0.5556
Haemoglobin (g/dL)	Dapa 10 mg	7700	13.900	1.3635	14.382	1.5517	0.481	1.1885
	Placebo	7606	13.883	1.3998	13.541	1.5018	-0.342	1.1575
Haematocrit (%)	Dapa 10 mg	7700	42.177	4.0323	44.796	4.6817	2.619	3.6254
	Placebo	7606	42.139	4.1261	41.950	4.5396	-0.189	3.5116
LDL Cholesterol (mg/dL)	Dapa 10 mg	7658	87.524	35.1497	84.766	36.9523	-2.759	33.4159
	Placebo	7582	87.637	35.6246	82.826	36.6979	-4.812	32.6434

Only central lab values are included for summary statistics for changes from baseline.
Only measurements within 7 days of the last dose of study drug are included in on-treatment analysis.
Baseline is defined as the last result prior to randomization. N is defined as the number of subjects with baseline and a post-baseline value for the laboratory parameter of interest. Dapa dapagliflozin; SAS safety analysis set; SD standard deviation

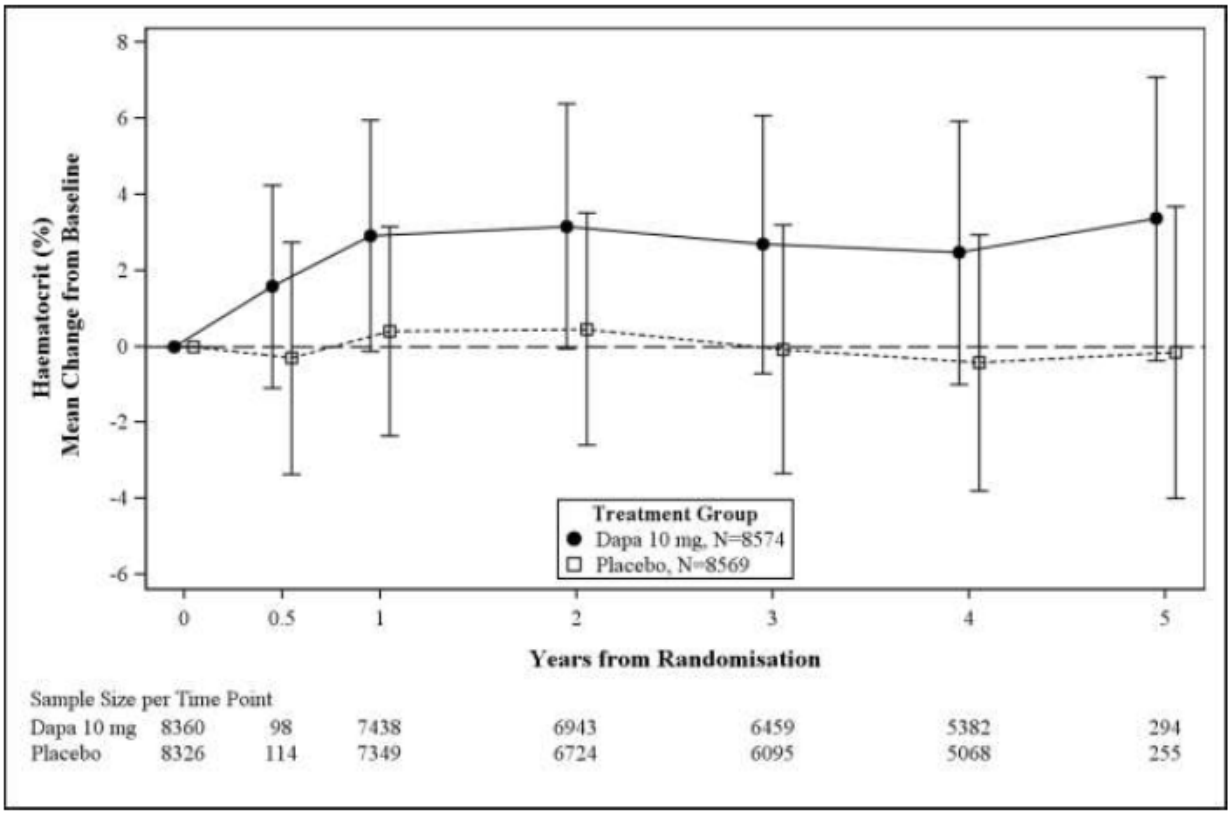
Source: Applicant response to Information Request submitted on July 25, 2019, Seq 0622

Hematology:

The current labeling for dapagliflozin describes the changes in hematocrit observed during the original development program, in which small increases in hemoglobin/hematocrit were observed in the dapagliflozin treatment arms versus comparators. These increases did not result differences in clinically significant events such as thromboembolic or vascular events.

In the DECLARE trial, hematology parameters were collected at randomization, and subsequent Visits at Months 12, 24, 36, 48, 60, End-of-Treatment, and Closing Visits. Figure 21 presents the mean hematocrit over time in the trial. Consistent with previous observations and the information presented in Table 35, hematocrit increased slightly in the dapagliflozin arm compared with placebo.

Figure 21. Mean (± SD) Change in Hematocrit Over Time in DECLARE (Safety Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.3.17.17.1

Table 36 presents the number of subjects with abnormal hematology findings. More subjects in the dapagliflozin arm had hematocrit >55% at any time during the trial compared with the placebo arm. The number of patients with hematocrit >60% at any time during the trial was small, and appears balanced between treatment arms.

Table 36. Number of Subjects with Abnormalities in Hematology Parameters (Safety Population)

	Number (%) of subjects			
	Dapa 10 mg		Placebo	
	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
HAEMATOLOGY				
Haematocrit (Vol) [a]				
Number of subjects with any post-baseline value	8204	7904	8135	7833
<0.20	0	0	2 (<0.1)	2 (<0.1)
>0.55	187 (2.3)	183 (2.3)	50 (0.6)	47 (0.6)
>0.60	13 (0.2)	13 (0.2)	11 (0.1)	11 (0.1)
Haemoglobin (g/L) [a]				
Number of subjects with any post-baseline value	8204	7904	8135	7833
<60	0	0	1 (<0.1)	1 (<0.1)
>180	100 (1.2)	99 (1.3)	32 (0.4)	31 (0.4)
>200	3 (<0.1)	3 (<0.1)	3 (<0.1)	3 (<0.1)

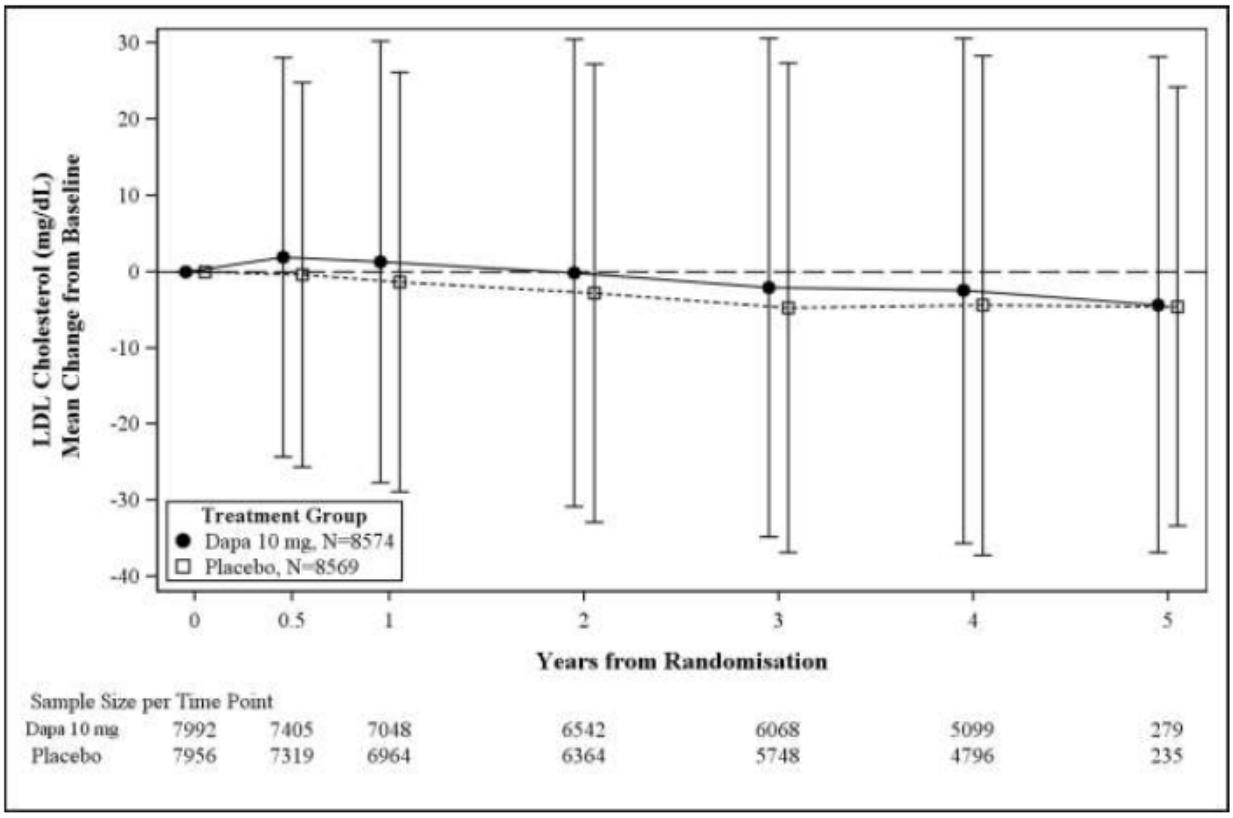
Source: Excerpted from the DECLARE CSR Appendix 11, Table 11.3.4.1

Reviewer Comment: *These findings are consistent with the approved dapagliflozin labeling. See the discussion of clinical consequences of increased hematocrit in Section 8.5.14 for further analyses.*

Lipid Measurements:

Lipid measurements (LDL-C, HDL, TG, and total cholesterol) were collected at randomization, and subsequent visits at Months 6, 12, 24, 36, 48, 60, End-of-Treatment, and Closing Visits. There were no clinically significant differences in lipid parameters between treatment groups. LCL declined slightly in both treatment arms, as shown in Figure 22.

Figure 22. Mean (± SD) LDL-C Over Time in the DECLARE Trial (Safety Population)



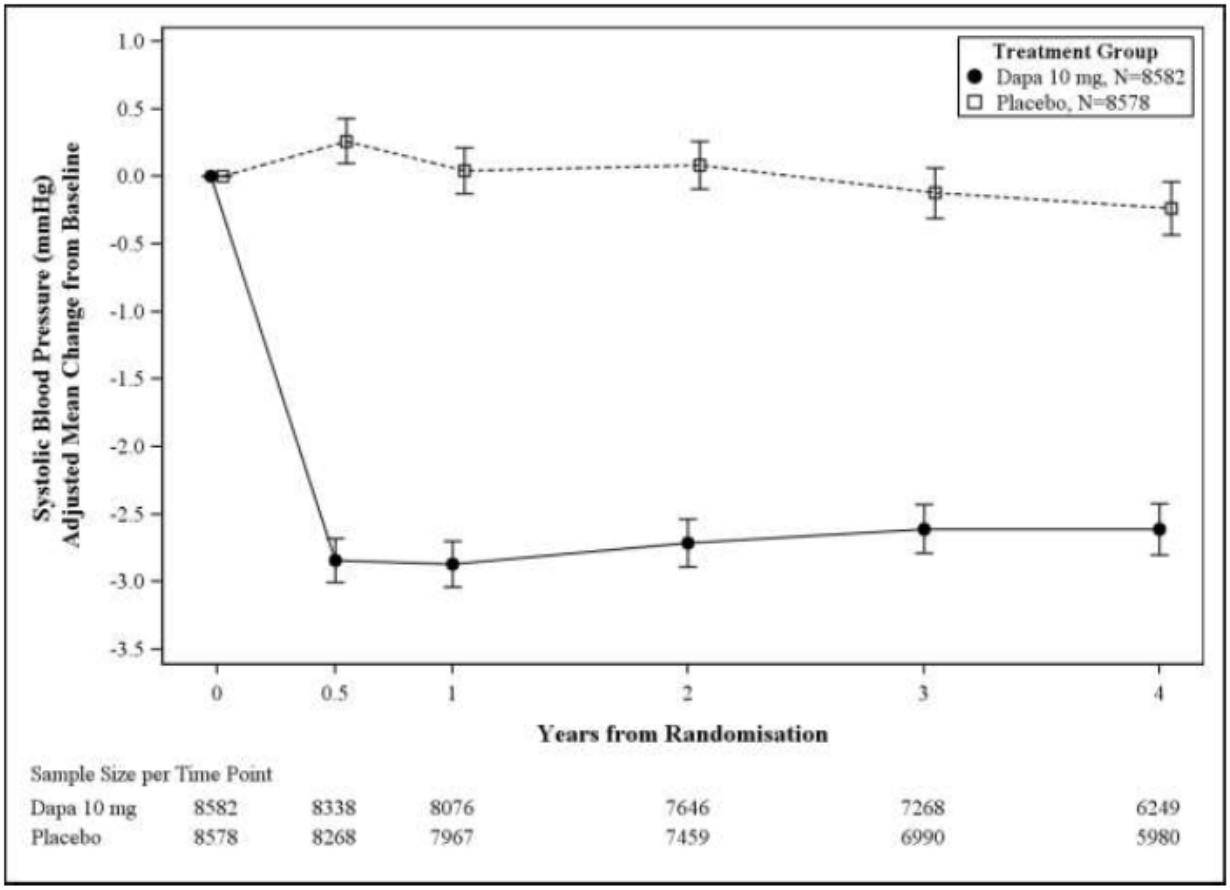
Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.3.17.17.15

Reviewer Comment*: Increased LDL-C is a labeled Warning and Precaution in the approved dapagliflozin label. Labeling negotiations are ongoing at the time of filing of this review, but the DECLARE findings could support removal of this W&P.*

8.4.7. Vital Signs

Systolic and diastolic blood pressure, pulse, and body weight were assessed at the enrollment visit, randomization visit, and Months 6, 12, 18, 24, End-of-Treatment, and Closing Visits. Baseline vital signs were similar between treatment groups. A decrease in systolic blood pressure (SBP) in the dapagliflozin arm was observed at the first post-randomization visit (Month 6) and was sustained for the rest of the trial (Figure 23). SBP remained unchanged in the placebo arm during the trial. There were no changes in pulse.

Figure 23. Adjusted Mean (± SE) Systolic Blood Pressure (mmHG) MMRM Results Over Time in DECLARE (Safety Population)



Source: Excerpted from the DECLARE CSR Appendix 11, Figure 11.2.49

Reviewer Comment: *The decrease in SBP observed in DECLARE is comparable in direction and magnitude to the decreases in SBP observed in the CANVAS program and EMPA-REG OUTCOME trial.*

8.4.8. Electrocardiograms (ECGs)

Routine ECGs were not collected during this trial at study visits. However, during the original dapagliflozin review cycle under NDA 202293 the clinical reviewer noted that there were limited differences between ECG recordings at baseline and at subsequent visits, and there were no clinically relevant rhythm differences observed.

8.4.9. QT

During the original NDA review, the Applicant's thorough QT study (D1690C00001)

demonstrated that no clinically meaningful differences in QTc intervals were observed between placebo and dapagliflozin 20 mg or 150 mg doses in healthy male subjects.

8.4.10. Immunogenicity

Immunogenicity was not assessed during this trial.

8.5. Analysis of Submission-Specific Safety Issues

The adverse events of special interest (AESI) collected were malignancies, hepatic events, major hypoglycemic events, fractures, renal events, symptoms suggestive of volume depletion, hypersensitivity reactions, urinary tract infections (UTIs), genital infections, Fournier's gangrene, amputations and diabetic ketoacidosis (DKA). Only SAEs and DAEs were collected for hypersensitivity reactions, UTIs, and genital infections.

The safety variables adjudicated by CECs were potential malignancies, hepatic events, amputations, and potential DKA events. Suspected events were identified monthly via querying the eCRF data fields for trigger terms. Clinical packages were then collected and sent to the CEC for each potential event, within a goal of two weeks. The CEC reviewers aimed to evaluate the packages within 4 weeks.

In the CSR the Applicant presented the following proportions of subjects experiencing the above AESIs:

Table 37. Summary of AESIs in DECLARE (Safety Population)

AESI	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Bladder Cancer*	26 (0.3)	45 (0.5)
Breast Cancer*	36 (0.4)	35 (0.4)
Prostate Cancer*†	73 (1.4)	63 (1.2)
Any malignancy*‡	481 (5.6)	486 (5.7)
Hepatic Events*	21 (0.2)	31 (0.4)
Major Hypoglycemic Events	58 (0.7)	83 (1.0)
Fractures‡	457 (5.3)	440 (5.1)
Renal Events	422 (4.9)	526 (6.1)
Symptoms Suggestive of Volume Depletion	213 (2.5)	207 (2.4)
Hypersensitivity Reactions	32 (0.4)	36 (0.4)
Diabetic Ketoacidosis*§	27 (0.3)	12 (0.1)
Amputations‡	123 (1.4)	113 (1.3)
Urinary Tract Infections	127 (1.5)	133 (1.6)

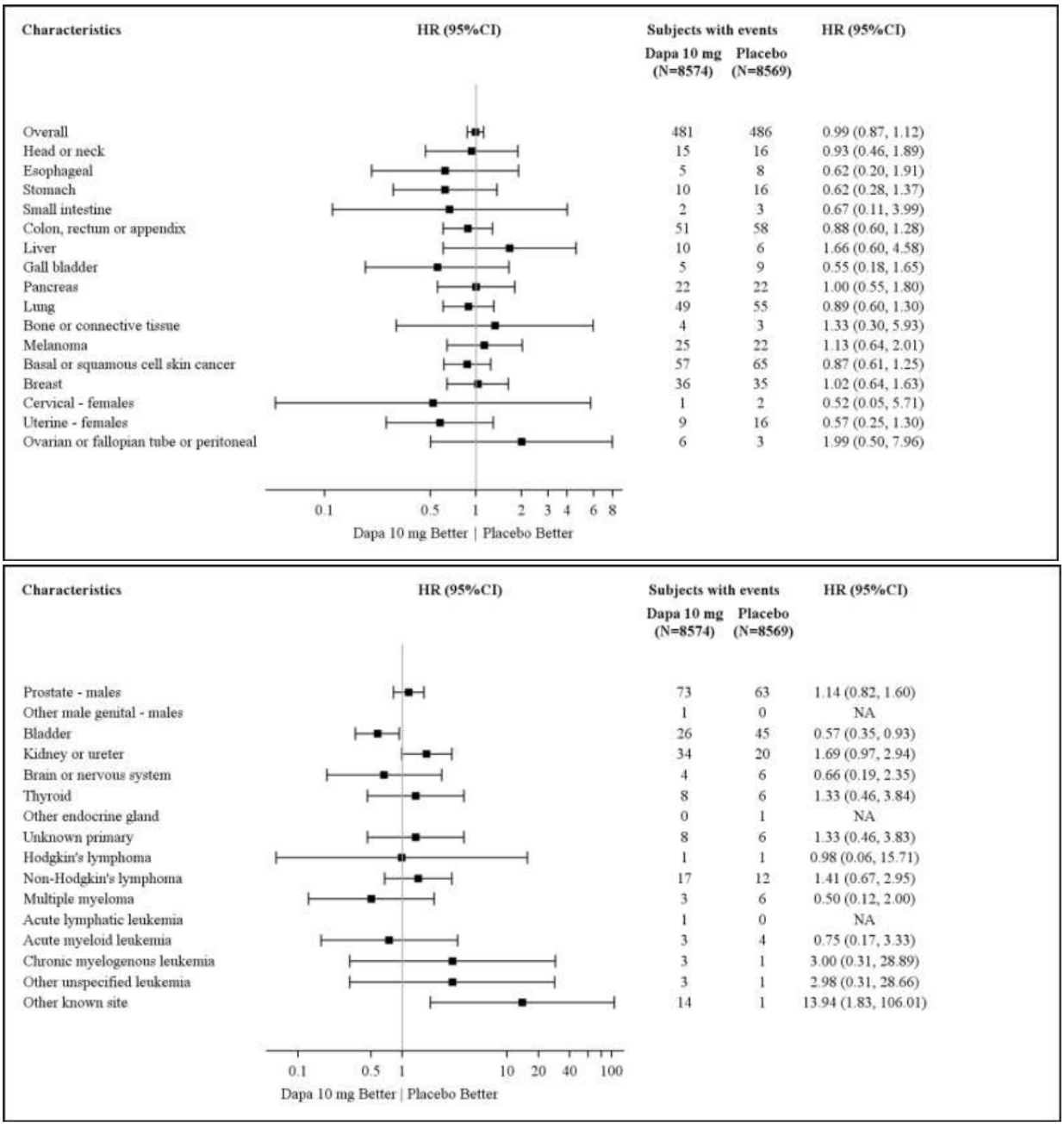
Genital Infections	76 (0.9)	9 (0.1)
Fournier's gangrene‡	1 (0.02)	5 (0.06)

*Adjudicated events
†Percentage of patients calculated based on denominator of male patients only
‡Number of patients based on the SAS population instead of the OT-SAS population, as was prespecified in the protocol. See Table 4 for analysis set definitions.
§Events presented in this table were adjudicated as "definite" or "probable" DKA
Source: Adapted from DECLARE CSR, p. 100-122

8.5.1. Malignancies

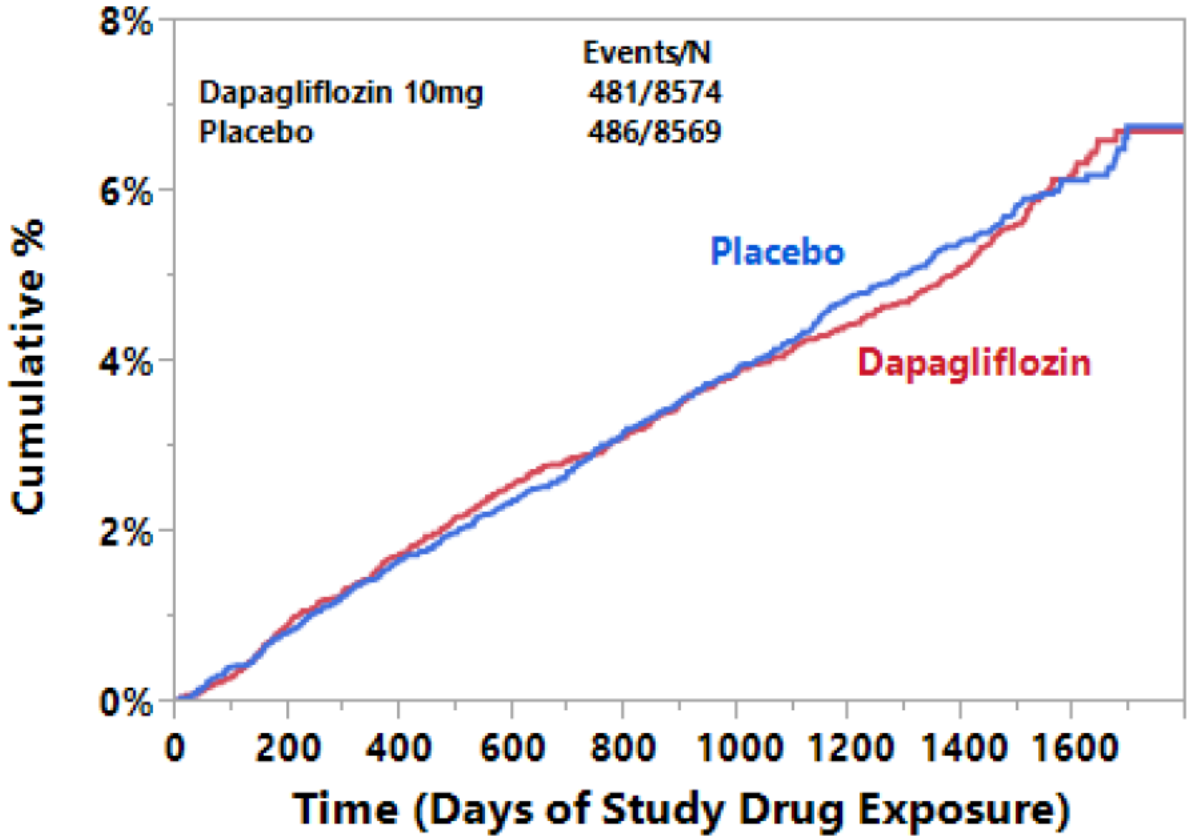
Overall, malignancies were balanced between treatment arms, with 481 subjects with adjudicated malignancy events in the dapagliflozin arm and 486 subjects in the placebo arm (HR 0.99, 95% CI 0.87, 1.12). The incidence rates of malignancy were 14.32 events per 1000 patient-years in the dapagliflozin arm and 14.52 events per 1000 patient-years in the placebo arm. A forest plot of malignancies by location is shown below in Figure 24, and a Kaplan-Meier plot of adjudicated malignancies is shown in Figure 25.

Figure 24. Forest Plot of Malignancies by Location (SAS population)



Source: Excerpted from Figure 11.3.18.1 in the CSR Appendix 11

Figure 25. Kaplan-Meier Plot of Time to First Adjudicated Malignancy (SAS population)



N at risk									
Dapa 10 mg	8574	8451	8325	8203	8093	7952	7516	6193	1961
Placebo	8569	8453	8315	8195	8064	7921	7466	6138	1913

Source: Generated from ADYB.xpt and ADSL.xpt datasets using JMP

Reviewer Comment: *The number of malignancy events at any given location was small for most anatomic sites, resulting in wide 95% confidence intervals that reflect lack of precision of the HRs. It is therefore possible that reported HRs greater than 1 are due to chance findings (e.g., for chronic myelogenous leukemia and other unspecified leukemia).*

8.5.1.1 Bladder Cancer

During the dapagliflozin NDA reviews, imbalances in bladder cancer, breast cancer, and prostate cancer were identified without a clear mechanism to establish causality. Evaluating breast and bladder cancer incidence was a component of PMR 2121-5 that DECLARE was designed to fulfil. In addition, PMR 2121-6 required that DECLARE patients be followed up beyond completion of the collection of the prespecified number of MACE events until a total of

66 bladder cancer events were collected, to provide 80% power to rule out a relative risk of 2.0 associated with dapagliflozin use. As it happened, at the time the trial had collected enough MACE events to evaluate the CV risk of dapagliflozin, the trial had also collected 71 adjudicated bladder cancer events. As such, the DECLARE findings were submitted to fulfil PMRs 2121-5 and 2121-6 simultaneously.

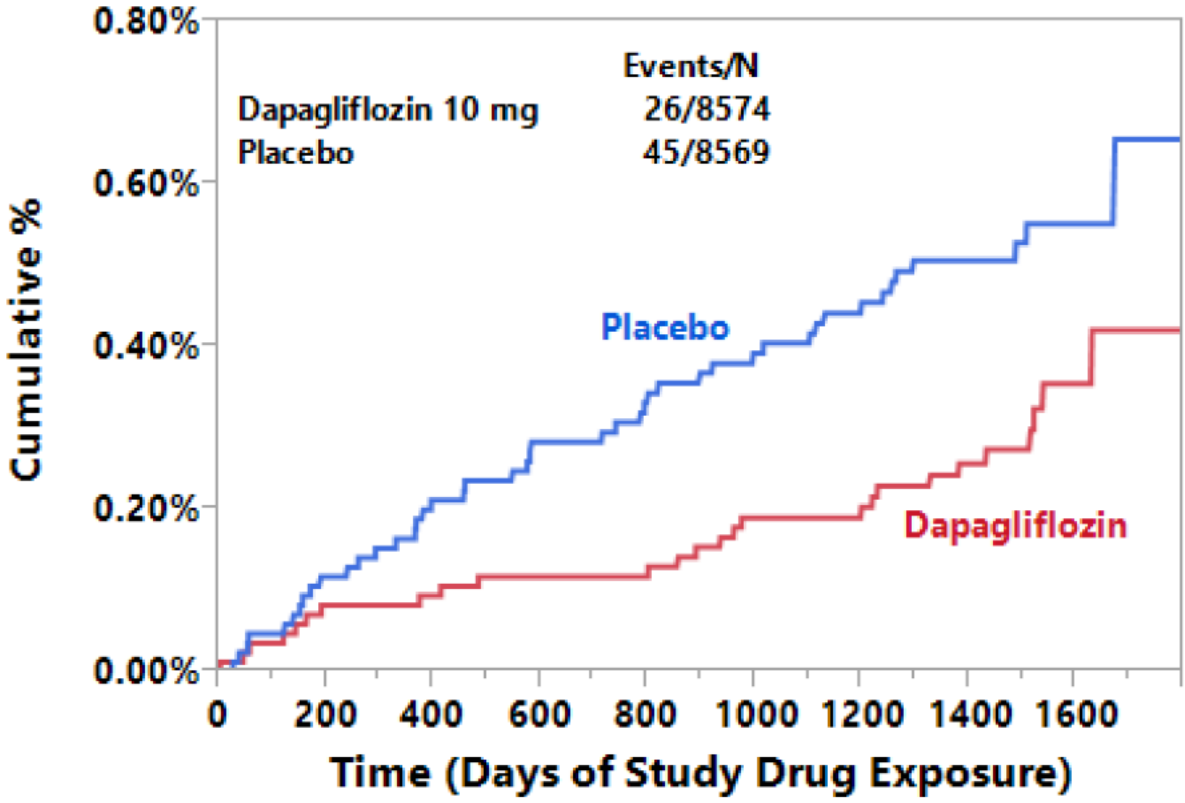
There were 26 adjudicated events of bladder cancer in the dapagliflozin arm, and 45 adjudicated events of bladder cancer in the placebo arm (HR 0.57; 95% CI 0.35, 0.93; p=0.024). Incidence rates by treatment arm and baseline hematuria status are presented in Table 38. A Kaplan-Meier plot of time to adjudicated bladder cancer events by treatment arm is presented in Figure 26.

Table 38. Adjudicated Bladder Cancer Events (SAS population)

	Dapa 10 mg (N=8574)				Placebo (N=8569)				
Bladder Cancer Event	Number of subjects at risk	Subjects with events	Subject years in study	Incidence rate (IR/1000 SY)	Number of subjects at risk	Subjects with events	Subject years in study	Incidence rate (IR/1000 SY)	Dapa 10 mg vs Placebo incidence rate ratio [a] (95% CI)
Overall	8574	26	34374	0.76	8569	45	34177	1.32	0.58 (0.34, 0.95)
Baseline haematuria									
Positive	1228	5	4821	1.04	1219	12	4737	2.53	0.41 (0.11, 1.26)
Negative	7156	19	28797	0.66	7163	32	28715	1.11	0.59 (0.32, 1.08)

Source: Table 11.3.2.2.1.6 in the CSR Appendix 11

Figure 26. Kaplan-Meier Plot Time-to-First Adjudicated Bladder Cancer (SAS population)



N at risk									
Dapa 10 mg	8574	8524	8452	8376	8302	8196	7773	6444	2080
Placebo	8569	8512	8427	8330	8250	8144	7728	6389	2028

Source: Generated from ADYB.xpt and ADSL.xpt datasets using JMP

Reviewer Comment: *Based on the above data from the DECLARE population, the Applicant has proposed removing Bladder Cancer from the* ***Warnings and Precautions*** *section of the USPI. The Applicant has fulfilled the requirements of PMR 2121-6 and excluded an unacceptable increased risk of bladder cancer in the studied population; I concur with removal of this Warning and Precaution from the label.*

8.5.1.2 Breast Cancer

The event rate of breast cancer was overall low in the DECLARE trial, and adjudicated cases of breast cancer were balanced between treatment arms.

Table 39. Adjudicated Breast Cancer Events

Event	Dapa 10 mg (N=8574) Subjects with events n (%)	Dapa 10 mg (N=8574) Event rate	Placebo (N=8569) Subjects with events n (%)	Placebo (N=8569) Event rate	Hazard ratio (95% CI)	p-value
Adjudicated breast cancer	36 (0.4)	1.0	35 (0.4)	1.0	1.02 (0.64, 1.63)	0.921

Source: Excerpted from Table 11.3.2.2.1.13 in the CSR Appendix 11

Reviewer Comment: *I was able to confirm the Applicant's analysis and Kaplan-Meier plot for adjudicated breast cancer events using JMP (plot not shown here). My conclusion from review of this data is the addition of dapagliflozin to standard of care in the studied population does not increase the incidence of breast cancer.*

8.5.1.3 Prostate Cancer

The event rate of prostate cancer was overall low in the DECLARE trial, and adjudicated cases of prostate cancer were balanced between treatment arms.

Table 40. Adjudicated Prostate Cancer Events

Event	Dapa 10 mg (N=5405) Subjects with events n (%)	Dapa 10 mg (N=5405) Event rate	Placebo (N=5323) Subjects with events n (%)	Placebo (N=5323) Event rate	Hazard ratio (95% CI)	p-value
Adjudicated prostate cancer	73 (1.4)	3.4	63 (1.2)	3.0	1.14 (0.82, 1.60)	0.437

Source: Excerpted from Table 11.3.2.2.1.14 in the CSR Appendix 11

Reviewer Comment: *I was able to confirm the Applicant's analysis and Kaplan-Meier plot for adjudicated prostate cancer events using JMP (plot not shown here). My conclusion from review of this data is the addition of dapagliflozin to standard of care in the studied male population does not increase the incidence of prostate cancer.*

8.5.2. Hepatic Events

During the initial dapagliflozin review cycle, there was a case of biochemical Hy's law, defined as serum ALT ≥3x ULN with serum total bilirubin ≥2x ULN, in a patient who had been exposed to dapagliflozin 2.5 mg. While it was unclear if this was truly a DILI case, and there were mixed opinions on the case from expert hepatologists, ultimately the etiology of the patient's liver function test abnormalities was determined to be most likely autoimmune in origin. However, given the hepatic safety concern raised during the review the evaluation of liver toxicity in DECLARE was part of the PMR requirement, and was also a Post-Authorisation Measure (PAM) in Europe.

Criteria for identification of potential liver injury cases to be sent for adjudication were as follows (from the DECLARE Event Reporting Manual):

- AST and/or ALT >3X ULN and TB >1.5X ULN (within 14 days of the AST and/or ALT elevation)
- AST and/or ALT > 5x ULN
- Hepatic disorders SMQ AEs/SAEs in subjects who prematurely discontinued study treatment due to any AE/SAE
- Hepatic disorders SMQ AEs/SAEs in any subject who died
- Additional specific hepatic terms that always require adjudication:
    - Acute liver failure
    - Hepatic failure
    - Hepatitis
    - Hepatitis acute
    - Hepatitis fulminant
    - Hepatitis toxic
    - Hepatitis autoimmune
    - Hepatocellular injury
    - Hepatotoxicity
    - Hy's law case
    - Mixed liver injury
    - Subacute hepatic failure
    - Liver transplant
    - Hepatic encephalopathy
    - Portal hypertension
    - Cirrhosis
    - Biliary cirrhosis

Assessment of possible hepatic events was performed by the Hepatic Adjudication Committee (HAC). HAC members adjudicated events based on the following Clinical Assessment of Causality scale for Drug-Induced Liver Injury (DILI):

Table 41. Clinical Assessment of Causality Scale for Hepatic Events

Causal Relationship	Likelihood	Description
Definite	> 95%	The evidence for the study drug causing the injury is beyond a reasonable doubt
Highly Likely	75 - 95%	The evidence for the study drug causing the injury is clear and convincing but not definite
Probable	50 - 74%	The preponderance of the evidence supports the link between the study drug and the liver injury
Possible	25 - 49%	The evidence for the study drug causing the injury is equivocal but present
Unlikely	< 25%	There is evidence that an etiological factor other than the study drug caused the injury is clear

[a] Rockey D.C., et al. for the US Drug-Induced Liver Injury Network. Causality Assessment in Drug-Induced Liver Injury Using a Structured Expert Opinion Process: Comparison to the Roussel-Uclaf Causality Assessment Method. HEPATOLOGY 2010;51:2117-2126

Source: Excerpted from DECLARE CEC Charter, page 31

Table 42 presents a summary of the adjudicated hepatic events in the DECLARE trial. As pre-specified, hepatic events from the OT-SAS population are presented, which includes hepatic events that occurred after the first dose of study drug to 30 days after last dose of study drug or the Closing Visit, whichever came first. Overall, there were 88 events in 82 patients sent for adjudication in the dapagliflozin arm, and 93 events in 87 subjects sent for adjudication in the placebo arm.

Table 42. Summary of Adjudicated Hepatic Events (Safety Population)

Hepatic events sent for adjudication	Dapagliflozin 10mg (N=88) n (%)	Placebo (N=93) n (%)
Adjudicated as excluded or not assessable*	67 (76.1)	62 (66.7)
Adjudicated events assigned a causality	**21 (23.9)**	**31 (33.3)**
Definite	**0**	**0**
Highly likely	**0**	**0**
Probable	**0**	**1 (1.1)**
Possible	**3 (3.4)**	**6 (6.5)**
Unlikely	**18 (20.5)**	**24 (25.8)**
Events adjudicated by severity		
Events assigned a severity	86 (97.7)	92 (98.9)
Events adjudicated as not applicable and/or no liver injury	2 (2.3)	1 (1.1)
Events adjudicated as **probable** by severity	0	1 (1.1)
AST or ALT >3x ULN, usually transient and reversible by adaptation	0	1 (1.1)
AST or ALT >3x ULN and TB >2x ULN, after or concurrent, indicating early functional loss	0	0

Serious	0	0
Acute liver failure	0	0
Fatal or requiring transplantation	0	0
Events adjudicated as **possible** by severity	3 (3.4)	6 (6.5)
AST or ALT >3x ULN, usually transient and reversible by adaptation	3 (3.4)	5 (5.4)
AST or ALT >3x ULN and TB >2x ULN, after or concurrent, indicating early functional loss	0	0
Serious	0	1 (1.1)
Acute liver failure	0	0
AST or ALT >3x ULN, usually transient and reversible by adaptation	0	0
Events adjudicated as **unlikely** by severity	18 (20.5)	24 (25.8)
AST or ALT >3x ULN, usually transient and reversible by adaptation	10 (11.4)	13 (14.0)
AST or ALT >3x ULN and TB >2x ULN, after or concurrent, indicating early functional loss	0	0
Serious	8 (9.0)	11 (11.8)
Acute liver failure	0	0
Fatal or requiring transplantation	0	0
Events adjudicated as **excluded** by severity	66 (75.0)	60 (64.5)
Not applicable and/or no liver injury	2 (1.9)	1 (1.1)
AST or ALT >3x ULN, usually transient and reversible by adaptation	4 (4.5)	3 (3.2)
AST or ALT >3x ULN and TB >2x ULN, after or concurrent, indicating early functional loss	0	2 (2.2)
Serious	35 (39.8)	30 (32.3)
Acute liver failure	2 (2.3)	3 (3.2)
Fatal or requiring transplantation	23 (26.1)	21 (22.6)
Events adjudicated as **not assessable** by severity	1 (1.0)	2 (2.2)
Not applicable and/or no liver injury	0	0
AST or ALT >3x ULN, usually transient and reversible by adaptation	1 (1.0)	2 (2.2)
AST or ALT >3x ULN and TB >2x ULN, after or concurrent, indicating early functional loss	0	0
Serious	0	0
Acute liver failure	0	0
Fatal or requiring transplantation	0	0

*****Cases were excluded if there was a definite and documented alternative cause for the abnormality. Cases were not assessable if critical data was missing that interfered with a fair assessment.

Source: Adapted from Table 11.3.2.2.2.1 in the CSR Appendix 11 and Table 26 in the CSR, p.105

Reviewer Comment*: I reviewed selected adjudication packages and case narratives for hepatic events, with a focus on the cases that were fatal or required transplantation, and did not identify any concerns with the adjudication findings. My conclusion from review of these data is that the addition of dapagliflozin to standard of care in the studied population did not increase the incidence of hepatic events.*

8.5.3. Major Hypoglycemic Events

Major hypoglycemia was defined as an event during which the patient experienced symptoms of severe impairment in consciousness or behavior, required external assistance, required intervention to treat the hypoglycemia, and symptoms promptly resolved following the intervention. These events were captured from the eCRF if all four of the above criteria were checked off as "Yes". Documentation of a low blood glucose value was not required to meet the definition of major hypoglycemia in this trial. Review of the exploratory efficacy endpoint major hypoglycemia and/or hypoglycemia requiring hospitalization was already discussed in Section 6.

Table 43 summarizes the features of the major hypoglycemic events reported in the trial. Overall there were more patients with events in the placebo arm, and this pattern was maintained across categories of baseline diabetes medications. Not surprisingly, patients taking concomitant insulin at baseline tended to have more major hypoglycemic events.

Table 43. Summary of Major Hypoglycemic Events (Safety Population)

Major Hypoglycemic Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least 1 major hypoglycemic event	**58 (0.7)**	**83 (1.0)**
Total number of events	**72**	**97**
Event rate per 1000 subject-years	**1.9**	**2.8**
Subjects with at least 1 major hypoglycemic event by baseline diabetes medication		
Insulin	46/3562 (1.3)	60/3439 (1.7)
Metformin	43/7014 (0.6)	59/7042 (0.8)
Sulfonylurea	14/3613 (0.4)	28/3706 (0.8)
DPP4 inhibitor	7/1417 (0.5)	8/1470 (0.5)
GLP-1 agonist	3/387 (0.8)	5/352 (1.4)
Other drugs	3/351 (0.9)	1/373 (0.3)
Number of major hypoglycemic events by baseline diabetes medication		
Insulin	60	73
Metformin	54	66
Sulfonylurea	15	29
DPP4 inhibitor	7	8
GLP-1 agonist	3	5
Other drugs	4	1

Source: Adapted from Tables 11.3.2.2.9.1 and 11.3.2.2.9.2 in the CSR Appendix

For the safety review of hypoglycemic events, I performed a broad customized MedDRA query (CMQ) of the ADAE dataset using the MedDRA Adverse Events Diagnosis Tool (MAED) to search for the following preferred terms: "Hyperinsulinaemia", "Hyperinsulinism", "Hypoglycaemia", "Hypoglycaemia unawareness", "Hypoglycaemic coma", "Hypoglycaemic encephalopathy", "Hypoglycaemic seizure", "Hypoglycaemic unconsciousness", "Neuroglycopenia", and "Shock hypoglycaemic". This CMQ identified 192 patients (2.2% of the safety population) who experienced 259 events in the dapagliflozin arm, and 231 patients (2.7%) who experienced 306 events in the placebo arm (RR 0.831, 95% CI 0.69, 1.00; p=0.055). While recognizing that this is an exploratory analysis, the results support the Applicant's analyses demonstrating that dapagliflozin use was not associated with an increased incidence of hypoglycemia. Of the events identified in the CMQ, 86 events were coded as SAEs in the dapagliflozin arm (with 46 of the SAEs coded as "severe") and 106 events were coded as SAEs in the placebo arm (with 59 of the events coded as "severe").

To explore hypoglycemic events by baseline HbA1c, I used JReview to examine hypoglycemic events requiring external assistance, associated with impairment in consciousness, and requiring any intervention in the ADHS dataset (Major Hypoglycemic events dataset). Looking at each of these variables for the baseline HbA1c categories of ≤7%, 7 to 9%, and ≥9% yielded the same patterns of findings as already described (i.e., any observed imbalances in between treatment arms were favorable to dapagliflozin).

Reviewer Comment: *My analysis of hypoglycemia identified more patients and events than the Applicant's analysis, most likely due to the Applicant's more narrow definition of "major hypoglycemia" requiring that all four elements of the definition be checked off as "Yes" on the eCRF to capture the event. However, my analysis yielded similar conclusions to that of the Applicant, i.e., that the addition of dapagliflozin to standard of care in the studied population did not increase the incidence of hypoglycemia. Noteworthy patterns included the observations that the proportion of patients reported as experiencing major hypoglycemia was low overall, but approximately one third of the hypoglycemia events I identified were coded as SAEs in each treatment arm. This likely reflects that investigators tended to record more serious events and did not rigorously record mild events due to the design of the eCRF; other unknown factors may also have contributed to this observation.*

8.5.4. Fractures

Increased fracture incidence rates were observed in the CANVAS trial with canagliflozin treatment compared with placebo, though not in the CANVAS-R trial, despite the similar populations in these two trials that together comprised the CANVAS program. Increased incidence of fracture was also not observed in the EMPA-REG OUTCOME trial. However, because of the CANVAS findings, fracture was an AESI for the DECLARE trial; bone fracture evaluation was a U.S. PMR for this trial, and a PAM in the EU.

Overall fracture events were balanced between treatment arms. Table 44 summarizes the fracture events, common fracture locations, and fracture locations of particular clinical interest in the DECLARE trial. There were more spinal compression fractures in the dapagliflozin arm compared with placebo (22 vs. 13) but more hip fractures in the placebo arm (14 dapagliflozin vs. 20 placebo). Looking at fracture locations considered to be "osteoporotic fractures", there were more events in the placebo arm (180) compared with the dapagliflozin arm (154). However, the Applicant did not collect baseline data regarding osteoporosis history in the study population, making their categorization of fracture events as "osteoporotic" difficult to confirm.

Table 44. Summary of Fracture Events (Safety Population)

Fracture Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least 1 fracture event	**457 (5.3)**	**440 (5.1)**
Event rate per 1000 subject-years	**13.6**	**13.2**
Rib fracture	60 (0.7)	72 (0.8)
Foot fracture	57 (0.7)	57 (0.7)
Ankle fracture	49 (0.6)	31 (0.4)
Radius fracture*	28 (0.3)	30 (0.4)
Hand fracture	28 (0.3)	17 (0.2)
Humerus fracture*	26 (0.3)	42 (0.5)
Wrist fracture*	26 (0.3)	29 (0.3)
Spinal compression fracture*	22 (0.3)	13 (0.2)
Hip fracture*	14 (0.2)	20 (0.2)
Spinal fracture*	9 (0.1)	8 (0.09)
Lumbar vertebral fracture*	8 (0.09)	10 (0.1)
Thoracic vertebral fracture*	8 (0.09)	9 (0.1)
Cervical vertebral fracture*	4 (0.04)	5 (0.06)
Upper limb fracture	22 (0.3)	13 (0.2)
Facial bones fracture	21 (0.2)	16 (0.2)
Femur fracture	18 (0.2)	19 (0.2)
Tibia fracture	17 (0.2)	12 (0.1)
Lower limb fracture	13 (0.2)	17 (0.2)
Pathological fracture	7 (0.08)	2 (0.02)
Scapula fracture	6 (0.07)	3 (0.04)
Femoral neck fracture*	5 (0.06)	9 (0.1)
Pelvic fracture*	4 (0.04)	5 (0.06)
Acetabulum fracture*	4 (0.04)	2 (0.02)

*Coded as osteoporotic fractures by the Applicant
Source: Adapted from Tables 11.3.2.2.3.1 and 11.3.2.2.3.4 in the CSR Appendix 11

My broad CMQ search of the ADAE dataset using MAED yielded nearly identical results to the Applicant's. Of note, formal bone density testing was not part of this trial; however, the median follow-up period of 4.2 years appears reasonable to detect a difference in fracture incidence between treatment arms, if such a difference were present.

The Applicant also presented analyses of fractures by the following subgroups: age, sex, baseline renal function, and osteoporotic fractures. These analyses are summarized in Table 45. There were no concerning differences in fracture SAEs or DAEs between treatment arms when analyzed by subgroup. As expected, a higher proportion of females had a fracture event

compared with males in the DECLARE trial and a higher proportion of patients ≥65 year had a fracture compared with those <65 years. A slightly higher proportion of patients with baseline eGFR <60 mL/min/1.73^2 had fractures compared with patients with baseline eGFR ≥60 mL/min/1.73m^2.

Table 45. Subgroup Analyses of Fracture Events (Safety Population)

Subgroup Characteristic	Dapagliflozin 10mg (N=8574) n/N (%)	Placebo (N=8569) n/N (%)
Age group		
<65 years	205/4626 (4.4)	200/4619 (4.3)
≥65 years	252/3948 (6.4)	240/3950 (6.1)
Sex		
Male	230/5405 (4.3)	226/5323 (4.2)
Female	227/3169 (7.2)	214/3246 (6.6)
Baseline eGFR (mL/min/1.73m^2)		
<60	38/604 (6.3)	39/658 (5.9)
60-89	205/3836 (5.3)	204/3890 (5.2)
≥90	214/4133 (5.2)	197/4021 (4.9)

Source: Adapted from Table 11.3.2.2.3.5 in the CSR Appendix 11

Reviewer Comment: *These data support the conclusion that the addition of dapagliflozin to standard of care in the studied population did not increase the overall incidence of bone fractures. However, it is notable that there were more upper extremity fractures in the dapagliflozin arm compared with the placebo arm, a pattern of fracture imbalance that was also observed in the CANVAS program and the EMPA-REG OUTCOME trial. The reason(s) for this observation is unclear at this time.*

8.5.5. Renal Events

During the initial dapagliflozin review, there was an imbalance in events of renal impairment/failure unfavorable to dapagliflozin, although there were few SAEs in this category. There have also been postmarketing reports of acute kidney injury (AKI) associated with SGLT2 inhibitors, including dapagliflozin. In 2016, FDA strengthened the existing **Warning and Precautions** statement regarding the risk of AKI for dapagliflozin and canagliflozin (*FDA Drug Safety Communication; June 14, 2016*), and AKI is a labeled warning across the SGLT2 inhibitor class. Evaluating nephrotoxicity/AKI in the DECLARE population was a U.S. PMR and evaluating renal impairment/failure was an EU PAM.

Table 46 summarizes the renal events in the DECLARE trial in the OT-SAS population (includes renal events that occurred after the first dose of study drug to 30 days [for SAEs] or 7 days [for non-SAEs] or the Closing Visit, whichever came first), overall and by preferred term from the Applicant's narrow SMQ.

Table 46. Summary of Renal Events in DECLARE (Safety Population)

Renal Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least 1 renal event	**422 (4.9)**	**526 (6.1)**
Event rate per 1000 subject-years	**14.0**	**18.0**
Acute kidney injury	125 (1.5)	175 (2.0)
Renal impairment	108 (1.3)	136 (1.6)
Chronic kidney disease	70 (0.8)	92 (1.1)
Renal failure	61 (0.7)	77 (0.9)
Blood creatinine increased	32 (0.4)	36 (0.4)
Glomerular filtration rate decreased	28 (0.3)	33 (0.4)
Creatinine renal clearance decreased	22 (0.3)	19 (0.2)
Urine flow decreased	5 (0.06)	2 (0.02)
End stage renal disease	1 (0.01)	4 (0.05)
Oliguria	3 (0.03)	2 (0.02)
Creatinine renal clearance abnormal	2 (0.02)	0
Hypertensive nephropathy	2 (0.02)	0
Renal function test abnormal	1 (0.01)	6 (0.07)
Tubulointerstitial nephritis	0	1 (0.01)
Azotaemia	0	1 (0.01)
Prerenal failure	1 (0.01)	1 (0.01)
Ischaemic nephropathy	0	1 (0.01)
Myeloma cast nephropathy	0	1 (0.01)

Subjects with events in more than one category are counted in each category. Subjects with multiple events in the same category are counted only once in that category.
Source: Adapted from Tables 11.3.2.2.8.1 and 11.3.2.2.8.2 in the CSR Appendix 11 and derived from ADAE dataset using JMP and JReview analyses

To further explore renal events in this trial, I used MAED to search the ADAE dataset with broad Custom MedDRA Queries (CMQs) for AKI and a combined CMQ of AKI/Chronic Renal Failure (see Appendix 13.3 for the complete list of PTs for each broad CMQ). For AKI, this broad CMQ search strategy yielded 575 patients (6.7%) with 750 events in the dapagliflozin arm and 745 patients (8.7%) with 1030 events in the placebo arm (0.77, 95% CI 0.70, 0.86; p=0.000001). For AKI/CRF the broad CMQ search yielded 698 patients (8.1%) with 939 events in the dapagliflozin arm and 892 patients (10.4%) with 1292 events in the placebo arm (RR 0.78, 95% CI 0.71, 0.86;

p=0.00000032). I also searched additional broad CMQs for AKI and AKI/CRF by using JReview to combine the ADAE and ADLB datasets and search for laboratory results consistent with these AE categories. While including laboratory abnormalities in the CMQ generated additional events, the analyses were consistent in favoring dapagliflozin, with fewer patients experiencing events compared with placebo (details of these analyses are not presented here since they did not generate any different findings or conclusions from the analyses already described). Therefore, various exploratory analyses using broad CMQs for renal events generated similar patterns favoring dapagliflozin when compared with the Applicant's narrow SMQ for renal events.

Table 47 summarized subgroup analyses of renal events by age, sex, baseline eGFR, and baseline UACR, based on the PTs in the Applicant's narrow SMQ. Not surprisingly, across both treatment groups higher proportions of subjects who were ≥65 years or who had baseline renal impairment or albuminuria experienced renal events during the trial compared with subjects <65 years or with baseline normal renal function or normo-albuminuria. Nonetheless, a higher proportion of patients in the placebo arm had events across the subgroup analyses. The Applicant also provided analyses of renal events based on baseline diuretic use, baseline ACEi/ARB use, diabetes duration >5 years, and baseline blood pressure (not shown in the table below). These analyses did not reveal any unexpected findings: a higher proportion of patients who used diuretics or ACEi/ARBs at baseline had renal events, but any imbalances observed between treatment arms favored the dapagliflozin arm. Similarly, patients with poorly controlled blood pressure or longer diabetes duration had more renal events, but patients in the dapagliflozin arm consistently had fewer events compared with the placebo arm.

Table 47. Subgroup Analyses of Renal Events (Safety Population)

Subgroup Characteristic	Dapagliflozin 10mg (N=8574) n/N (%)	Placebo (N=8569) n/N (%)
Age group		
<65 years	176/4626 (3.8)	215/4619 (4.7)
≥65 years	246/3948 (6.2)	311/3950 (7.9)
Baseline eGFR (mL/min/1.73m^2)		
<60	122/604 (20.2)	138/658 (21.0)
60-89	229/3836 (6.0)	287/3890 (7.4)
≥90	71/4133 (1.7)	101/4021 (2.5)
Baseline UACR		
<30	211/5817 (3.6)	262/5824 (4.5)
≥30 to ≤300	133/2016 (6.6)	169/2011 (8.4)
>300	67/592 (11.3)	85/574 (14.8)

Source: Adapted from Table 11.3.2.2.8.3 in the CSR Appendix 11

Given the importance of this AESI for the SGLT2 inhibitor class and the specific concern for AKI events in the post-market setting, I also analyzed AKI events by baseline eGFR category (Table 48). As expected, a larger proportion of patients with baseline renal impairment had AKI events and AKI SAEs in both treatment arms, reflecting that patients with baseline renal impairment are at greater risk of AKI. However, the pattern of AKI events and relative risk calculations were consistent across baseline renal function categories: imbalances in AKI events were favorable to dapagliflozin throughout eGFR categories, both looking at events overall and AKI SAEs. Of note, no AKI events were reported in patients with baseline eGFR <30 ml/min/1.73m^2, likely because there were so few patients in this eGFR category at baseline by design (13 patients in the dapagliflozin arm and 7 patients in the placebo arm).

Table 48. AKI events by baseline eGFR in DECLARE (Safety Population)

Baseline eGFR Category (mL/min/1.73m^2)	Dapagliflozin 10mg n/N* (%)	Placebo n/N (%)	Relative Risk
All baseline eGFRs			
All subjects with AKI events	125/8574 (1.5)	175/8569 (2.0)	0.7
Serious AKI events	67/8574 (0.8)	101/8569 (1.2)	0.7
Normal (≥90)			
All subjects with AKI events	34/4133 (0.8)	43/4021 (1.1)	0.8
Serious AKI events	16/4133 (0.4)	21/4021 (5.2)	0.7
Mild impairment (60-89)			
All subjects with AKI events	64/3836 (1.7)	88/3890 (2.3)	0.7
Serious AKI events	37/3836 (1.0)	58/3890 (1.5)	0.6
Moderate to severe impairment (<60)†			
All subjects with AKI events	27/604 (4.5)	44/658 (6.7)	0.7
Serious AKI events	14/604 (2.3)	22/658 (3.3)	0.7

*1 dapagliflozin subject was missing a baseline eGFR. Therefore, summing the Ns for the eGFR subcategories yields a total N=8373 instead of 8574 (dapagliflozin Safety Population total N)
†All AKI events in this eGFR category occurred in patients with baseline eGFR 30-59 mL/min/1.73m^2
Source: Derived from ADAE and ADSL datasets using JReview

Reviewer Comment: *Addition of dapagliflozin to standard of care did not increase the incidence of renal events in the studied population. On the contrary, multiple analyses yielded consistent findings confirming that there were more renal events, including AKI events and serious AKI events, in the placebo arm compared with the dapagliflozin arm.* (b) (4) [redacted]

8.5.6. Symptoms Suggestive of Volume Depletion

In the original dapagliflozin clinical development program an imbalance in AEs suggestive of volume depletion was observed. However, the number of events was small overall and there were very few SAEs, such that this potential safety signal could not be fully characterized. Therefore, evaluating serious events related to volume depletion in DECLARE was a U.S. PMR. The Applicant used a prespecified list of PTs to capture events consistent with volume depletion. Table 49 summarizes the Applicant's analysis. There was no imbalance in events between treatment arms. There were 81 subjects (0.9%) with SAEs in this category in the dapagliflozin arm and 70 subjects (0.8%) with SAEs in this category in the placebo arm. Five patients in the dapagliflozin arm and 3 patients in the placebo arm discontinued study drug due to an AE suggestive of volume depletion.

Table 49. Summary of Events of Symptoms Suggestive of Volume Depletions in DECLARE (Safety Population)

Volume Depletion Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least 1 event suggestive of volume depletion	**213 (2.5)**	**207 (2.4)**
Event rate per 1000 subject-years	**7.0**	**7.0**
SAEs	**81 (0.9)**	**70 (0.8)**
Hypotension	73 (0.9)	54 (0.6)
Syncope	58 (0.7)	62 (0.7)
Dehydration	54 (0.6)	56 (0.7)
Hypovolemia	26 (0.3)	26 (0.3)
Orthostatic hypotension	15 (0.2)	21 (0.2)
Urine flow decreased	5 (0.06)	2 (0.02)
Circulatory collapse	2 (0.02)	2 (0.02)
Shock	0	2 (0.02)
Hypovolemic shock	1 (0.01)	2 (0.02)
Blood pressure decreased	1 (0.01)	1 (0.01)

Source: Adapted from Table 11.3.2.2.4.1 in the CSR Appendix 11

I also searched the ADAE dataset using a broad CMQ in MAED (see Appendix 13.3 for the complete list of PTs). While this broad search strategy identified more events, the findings were consistent with the Applicant's analysis. This CMQ identified 384 patients (4.5%) with 514 events suggestive of volume depletion in the dapagliflozin arm and 438 patients (5.1%) with 621 events in the placebo arm (RR 0.88, 95% CI 0.77, 1.002; p=0.054).

The Applicant presented subgroup analyses of events suggestive of volume depletion by age, baseline eGFR, baseline diuretic use, baseline blood pressure, and baseline ACEi/ARB use. Not surprisingly, across both treatment groups higher proportions of subjects who were ≥65 years, had baseline renal impairment, or used diuretics at baseline had events suggestive of volume depletion. However, events were balanced between treatment arms within each subgroup category. Of note, among patients with baseline eGFR <60 mL/min/1.73m2, there were 19/604 (3.1%) patients with SAEs in this category of events in the dapagliflozin arm and 13/658 (2.0%) patients with SAEs in the placebo arm.

Table 50. Summary of Events of Symptoms Suggestive of Volume Depletions in DECLARE by Subgroup (Safety Population)

Subgroup Characteristic	Dapagliflozin 10mg (N=8574) n/N (%)	Placebo (N=8569) n/N (%)
Age group		
<65 years	96/4626 (2.1)	86/4619 (1.9)
≥65 years	117/3948 (3.0)	121/3950 (3.1)
Baseline eGFR (mL/min/1.73m^2)		
<60	35/604 (5.8)	30/658 (4.6)
60-89	115/3836 (3.0)	115/3890 (3.0)
≥90	63/4133 (1.5)	62/4021 (1.5)
Baseline Diuretic Use		
Yes	114/3482 (3.3)	106/3472 (3.1)
No	99/5092 (1.9)	101/5097 (2.0)
Baseline ACEi/ARB Use		
Yes	176/6968 (2.5)	177/6964 (2.5)
No	37/1606 (2.3)	30/1605 (1.9)

Source: Adapted from Table 11.3.2.2.4.3 in the CSR Appendix 11

Reviewer Comment: *Addition of dapagliflozin to standard of care did not increase the incidence of events suggestive of volume depletion in the studied population. The approved labeling already describes risks related to volume depletion and subgroups most at risk of these events.*

8.5.7. Hypersensitivity Reactions

Serious hypersensitivity reactions in patients treated with dapagliflozin have been reported post-marketing. Evaluating serious hypersensitivity reactions in DECLARE was a PMR. Only SAEs and DAEs were collected for this category of events. As shown in Table 37, hypersensitivity reaction events were balanced between treatment arms. Of the events collected using the Applicant's narrow SMQ for hypersensitivity, there were 15 subjects who had hypersensitivity

events classified as SAEs during the trial in the dapagliflozin arm, and 26 subjects who had a hypersensitivity SAE in the placebo arm. Narratives of the cases in which anaphylactic shock or anaphylaxis occurred are summarized below.

Table 51. Summary of Anaphylactic Reactions (Safety Population)

Subject ID	Treatment Arm	Synopsis of Narrative
(b) (6)	Placebo	62 yo F admitted with cardiac arrest secondary to anaphylactic shock that ensued immediately after 1 dose of intravenous **ceftazidime**. Patient was intubated and maintained on a ventilator, but ultimately contracted hospital-associated pneumonia and expired.
(b) (6)	Dapagliflozin	63 yo M presented for elective transurethral resection of the prostate for symptomatic prostatic hypertrophy, who received 1 dose of intravenous **piperacillin/tazobactam** post-operatively and immediately developed signs and symptoms of anaphylaxis (hypotension, itching, cough, and shortness of breath). Patient was treated with IV epinephrine infusion in the ICU and ultimately fully recovered.
(b) (6)	Placebo	66 yo F who woke up with swollen tongue, face, and hands, and noted shortness of breath, treated in the Emergency Department with epinephrine and hydrocortisone with full resolution. **Cause of reaction never identified**.
(b) (6)	Dapagliflozin	40 yo M who underwent elective circumcision, complicated by severe post-operative swelling. Patient took oral **cephalexin** and 30 minutes later developed full body hives. On paramedic evaluation he was hypotensive and complained of chest pain. Treated with epinephrine and antihistamines and fully recovered.
(b) (6)	Placebo	63 yo F with multiple known drug allergies who received **penicillin** challenge in immunology clinic, and several hours later developed diaphoresis, whole body itching and rash. Treated with steroids and antihistamines for delayed drug reaction and fully recovered.
(b) (6)	Placebo	67 yo M undergoing surgery for septic arthritis of the knee, induced with **rocuronium**, and received **cephazolin**, immediately after which he developed signs and symptoms of anaphylaxis requiring intubation for laryngeal edema. Patient fully recovered.
(b) (6)	Dapagliflozin	72 yo M who received **iodine** injection for angiography to evaluate lower extremity claudication, and immediately developed red face, itching, hypotension. Patient fully

		recovered.
(b) (6)	Placebo	63 yo M who received IV **amiodarone** for paroxysmal supraventricular tachycardia, followed immediately by feeling hot, redness on the chest and abdomen, lightheadedness, and shortness of breath. Treated with epinephrine and oxygen and fully recovered.
(b) (6)	Dapagliflozin	73 yo F who had signs and symptoms of anaphylaxis after administration of **rocuronium** as part of anesthesia induction for CABG. Treated with intubation, epinephrine, and steroids and fully recovered.
(b) (6)	Placebo	66 yo M with a history of urticaria who developed rash, angioedema, and dyspnea with no clear cause identified, ultimately attributed to **lisinopril**. Patient fully recovered from the event.
(b) (6)	Placebo	69 yo F who developed facial and throat swelling, shortness of breath while at home, treated with epinephrine. Reaction ultimately attributed to **losartan**.
(b) (6)	Placebo	61 yo M who took **cefaclor** after receiving a suture for a finger laceration, and rapidly developed weakness, whole body itching, and dyspnea. Treated with steroids and epinephrine and fully recovered.

Reviewer Comment: *There is no evidence from review of these data that dapagliflozin is associated with an increased risk of serious hypersensitivity reactions when added to standard of care in the studied population. All but one of the cases of anaphylaxis above had a clearly identifiable precipitating factor, usually a medication other than the IP, and there were more cases of anaphylaxis in the placebo arm (8 cases) compared with the dapagliflozin arm (4 cases).*

8.5.8. Diabetic Ketoacidosis (DKA)

DKA and euglycemic DKA have been associated with dapagliflozin treatment in post-marketing reports. A safety labeling change for the SGLT2 inhibitor class alerting prescribers to the potential risks of ketoacidosis and urinary tract infections was issued on December 4, 2015. Evaluation of DKA in DECLARE was a PAM in the EU. Potential DKA events were adjudicated by an independent DKA Adjudication Committee comprised entirely of endocrinologists, selected by the TIMI Study Group CEC Department. The DKA Adjudication Charter governs assessment of potential DKA events for multiple completed and ongoing studies evaluating dapagliflozin's effect on various outcomes, including the dedicated ongoing dapagliflozin heart failure and chronic kidney disease trials.

A prespecified list of MedDRA PTs was used to identify potential DKA events to be referred for adjudication. I reviewed the list of PTs provided by the Applicant and found them to be appropriate for identification of potential cases. Identification of potential events prompted completion of the relevant DKA-specific eCRF sections and preparation of a dossier for evaluation by the CEC. The main analysis of DKA was performed in the OT-SAS population. In total, there were 71 and 73 patients with potential DKA events sent for adjudication in the dapagliflozin and placebo arms, respectively. The DKA diagnostic criteria employed for the adjudication process were as follows:

Definite DKA: An event in a clinical setting consistent with DKA (history, symptoms, and physical exam) and the absence of a more likely alternative diagnosis thought to be the primary cause of presentation, with the following biochemical data:

- Ketonemia ≥3.0 mmol/L and/or significant ketonuria (more than 2+ on standard urine sticks) and
- At least one of the following criteria suggesting high anion gap metabolic acidosis:
    - Arterial or venous pH ≤7.3
    - Serum bicarbonate ≤18 mEq/L
    - Anion gap [$Na – (Cl + HCO_3)$] > 10

Probable DKA: An event that does not meet strict criteria for define DKA due to incomplete biochemical workup, but the clinical setting is consistent with DKA (history, symptoms, and physical exam) and the absence of alternative diagnoses thought to be the primary cause of presentation. Probable will be indicated when it is judged by the adjudicators to be the most likely clinical diagnosis taking into account available data. For example:

- Evidence of elevated ketone bodies (blood or urine) with suspected acidosis, but without documented metrics for metabolic acidosis
- Evidence of anion-gap metabolic acidosis with a lactate <2 mmol/L and with suspected, but without documented metrics for elevated total ketone bodies

Possible DKA: Reported as DKA, but inadequate source documents to confirm or refute are available.

Not DKA: Does not meet diagnostic criteria for definite or probable DKA, and has adequate source documents to refute an investigator reported diagnosis of DKA.

Events that met criteria for definite or probably DKA were then classified in terms of:

1. Degree of acidemia
    a. Mild –pH 7.25 – 7.30 and/or serum bicarbonate 15-18 mEq/L
    b. Moderate –pH 7.00 – 7.24 and/or serum bicarbonate 10 - <15 mEq/L
    c. Severe –pH < 7.00 and/or serum bicarbonate < 10 mEq/L

2. Symptomatic or asymptomatic based on the presence of nausea, vomiting, abdominal pain, confusion, change in breathing pattern, unusual fatigue or sleepiness
3. Highest Blood Glucose Value recorded
    a. High blood glucose > 14 mmol/l (> 250 mg/dL)
    b. Intermediate glucose 11 -14 mmol/l (200-250 mg/dL)
    c. Euglycemic <11 mmol/l (< 200 mg/dL)

Adjudicators determined that 27 patients in the dapagliflozin arm and 12 patients in the placebo arm had definite or probable DKA events (total of 29 events in the dapagliflozin arm and 12 events in the placebo arm). Of these, there were 20 patients in the dapagliflozin arm and 7 patients in the placebo arm adjudicated as having definite DKA events. Most patients with definite or probable DKA events in both treatment arms were classified as having SAEs (25 patients in the dapagliflozin arm vs. 11 in the placebo arm). Three patients in the dapagliflozin arm and 1 patient in the placebo arm had DKA events that led to drug discontinuation. Overall the adjudicated incidence rates of definite or probable DKA were 0.9 per 1000 patient-years in the dapagliflozin arm (27/8574 [0.3%]) and 0.4 per 1000 patient-years in the placebo arm (12/8569 [0.1%]). The timing of DKA events did not reveal any time period during which patients appeared to be at higher risk of events.

Three patients with DKA events in the dapagliflozin arm had T1DM by investigator report, and one additional patient was determined to have T1DM after review of the adjudication package. No patients in the placebo group with DKA events were determined to have T1DM.

There was one case of euglycemic DKA in the dapagliflozin arm, and no euglycemic DKA cases reported in the placebo arm. However, review of the adjudication package and case narratives revealed that one patient adjudicated as having DKA in the placebo arm in fact had a normal blood glucose value concurrent with the DKA event. Therefore, one patient in each treatment arm had euglycemic DKA.

The most common contributing factors to development of DKA were infection, missed insulin doses, dehydration and poor oral intake. Most patients with adjudicated DKA events in the dapagliflozin arm were using insulin therapy at the time of the event (22 out of 27 patients), and all patients in the placebo group with adjudicated DKA events took insulin. Overall, 6 patients in the dapagliflozin arm and 3 patients in the placebo group who had definite or probable DKA events died during the same hospitalization during which DKA was diagnosed. All patients who died in conjunction with their DKA event had T2DM. I reviewed the narratives and adjudication packages of these events, summarized below in Table 52.

Table 52. Summary of Patients with Definite or Probable DKA Events Leading to Death (Safety Population)

Subject ID	Treatment Arm	Synopsis of Narrative
(b) (6)	Dapagliflozin	67 yo F with **pancreatic adenocarcinoma** diagnosed 2 months prior to death. Dapagliflozin was stopped 13 days before death and chemotherapy was started 8 days before death. Patient was found unconscious at home, hypotensive, hypothermic, in ketoacidosis. She expired in the hospital the next day after a cardiac arrest. Adjudicated cause of death was malignancy.
(b) (6)	Dapagliflozin	73 yo F w/ nausea and 2 episodes of vomiting 4 days prior to DKA event, started on Augmentin by private physician. Patient stopped dapagliflozin 3 days prior to DKA onset. Nasuea/vomiting continued and she presented to the ER with weakness and shortness of breath, found to be in DKA and to be pancytopenic (diagnosed as **myelodysplastic syndrome**). On the day of admission patient had altered mental status and was intubated, then went into asystole and could not be resuscitated. Adjudicated cause of death was DKA.
(b) (6)	Dapagliflozin	61 yo F w/ 4 days of fever and vomiting who was admitted to the hospital unconscious and found to be in DKA, also with aspiration pneumonia. Diagnosed with **Legionella sepsis** based on positive urinary antigen, and anoxic encephalopathy. Patient's neurologic status did not improve, care was withdrawn, and she expired after 4 days in the ICU. Adjudicated cause of death was infection (sepsis).
(b) (6)	Dapagliflozin	72 yo F admitted with low back pain, found to have an **ST-elevation MI** and to be in DKA. She had multiple post-cath complications including emboli to both legs, ischemic colitis, and retroperitoneal hematoma. She ultimately developed sepsis thought due to colitis and expired. Adjudicated cause of death was CV death due to STEMI.
(b) (6)	Dapagliflozin	62 yo F w/ fever and altered consciousness, found to have **acute encephalitis** and DKA. No prior hx of DKA. Adjudicated cause of death was infection (sepsis).
(b) (6)	Dapagliflozin	53 yo M w/ shortness of breath, found to have **inferolateral NSTEMI,** suspected **pneumonia** on chest x-ray, heart failure, and DKA. Patient expired within hours. Adjudicated cause of death was CV death due to acute MI with concurrent HF, DKA and pneumonia.
(b) (6)	Placebo	81 yo M admitted w/ DKA, AKI, hyperkalemia, confusion, and

		had an **acute inferior MI** per report of observation on cardiac monitor. Patient expired 2 days after admission. Adjudicated cause of death was DKA.
(b) (6)	Placebo	68 yo F w/ shortness of breath, found to have **urosepsis** and DKA. Admitted to the ICU and after 12 hours had respiratory distress requiring intubation, followed by PEA arrest. Patient was resuscitated once but died later that day. Adjudicated cause of death was infection (sepsis).
(b) (6)	Placebo	81 yo F who had a cardiac arrest at home, was resuscitated and admitted bradycardic, hypotensive, w/ **inferior wall STEMI** complicated by cardiogenic shock and profound bradycardia, also in DKA. Pt required CPR, intubation, and external pacing as well as intra-aortic ballon pump placement. Cardiac cath revealed 100% RCA occlusion which was stented. Patient ultimately expired. Adjudicated cause of death was CV death due to acute MI.

Changes in Bicarbonate

Bicarbonate was collected at the randomization, end-of-treatment, and closing visits. The Applicant reported the number of patients with any post-baseline bicarbonate value ≤13 mmol/L. In the OT-SAS population, there was only 1 patient in the dapagliflozin arm with a post-baseline bicarbonate ≤13 mmol/L, and 7 patients in the placebo arm with a post-baseline bicarbonate ≤13 mmol/L. The Applicant did not present any additional analyses of bicarbonate levels.

Reviewer Comment*: There were more deaths associated with DKA events in the dapagliflozin arm compared with the placebo arm (6 vs. 3). Review of the narratives reveals that the causes of death were multifactorial and the DKA events had a clear precipitating factor in most cases (i.e., infection, acute MI, and malignancy). Adjudicators identified one patient in each arm for whom DKA was determined to be the cause of death. All patients who died in association with a DKA event had T2DM.*

Ketoacidosis is a labeled Warning and Precaution for all SGLT2 inhibitors based on post-marketing reports. The Applicant's proposed labeling for this sNDA adds a description of the imbalance in DKA events observed in the DELCARE trial to the Adverse Reactions section of the label. I concur with the addition of this information, which will be important for prescribers.

8.5.9. Amputations

Amputations were an AESI in DECLARE due to the safety concern identified in the canagliflozin CVOT. An imbalance in amputations was observed in the CANVAS program, with an approximately 2-fold increased incidence of amputations affecting the foot and leg (primarily the toes) in patients randomized to the canagliflozin arms in the CANVAS and CANVAS-R trials. There were no imbalances in amputations observed in the EMPA-REG OUTCOME trial or the dapagliflozin development program. Due to the CANVAS results, the Agency released a Drug Safety Communication on May 18, 2016 and the DECLARE investigators were advised to designate amputations an AESI to be collected prospectively, and to examine the safety database for amputation events. The eCRF was updated to capture details of amputation events. Evaluation of amputations was also a PAM in the EU.

Amputation events were balanced between treatment arms. Per the Applicant's report, there were 123 subjects (1.4%) with amputations in the dapagliflozin arm and 113 subjects (1.3%) in the placebo arm. Most amputations were reported as SAEs (110 out of 123 amputations in the dapagliflozin arm, and 100 out of 113 amputations in the placebo arm). Table 53 summarizes amputation events, most of which involved the lower limbs.

Table 53. Summary of Amputation Events in DECLARE (SAS Population)

Category	Number (%) of patients	
	Dapa 10 mg	Placebo
	SAS (N=8574)	SAS (N=8569)
Patients with amputation	123 (1.4)	113 (1.3)
1 amputation	78 (0.9)	83 (1.0)
2 amputations	31 (0.4)	21 (0.2)
3 amputations	10 (0.1)	6 (<0.1)
>3 amputations	4 (<0.1)	3 (<0.1)
Type of event		
Trauma by accident	3 (<0.1)	0
Surgical amputation	115 (1.3)	113 (1.3)
Spontaneous/non-surgical amputation	6 (<0.1)	1 (<0.1)
Anatomic localisation for surgical or spontaneous/non-surgical amputation		
Lower limb amputation	117 (1.4)	110 (1.3)
Event rate per 1000 subject years	3.4	3.2
Big toe	32 (0.4)	38 (0.4)
Index toe	33 (0.4)	27 (0.3)
Middle toe	23 (0.3)	25 (0.3)
Fourth toe	16 (0.2)	16 (0.2)
Little toe	23 (0.3)	21 (0.2)
Trans metatarsal	16 (0.2)	13 (0.2)
Foot	4 (<0.1)	1 (<0.1)
Below knee	26 (0.3)	17 (0.2)
Above knee	20 (0.2)	13 (0.2)
Other	5 (<0.1)	2 (<0.1)
Upper limb amputation	3 (<0.1)	3 (<0.1)
Event rate per 1000 subject years	0.1	0.1
Thumb	0	1 (<0.1)
Index finger	0	1 (<0.1)
Middle finger	1 (<0.1)	1 (<0.1)
Ring finger	3 (<0.1)	0
Little finger	0	0
Hand	0	0
Below elbow	0	0
Above elbow	0	0

Derived from: Table 11.3.2.3.1.4
SAS includes amputations that occurred after the first dose of study drug up to the Closing Visit.
Location not recorded for trauma by accident. Amputations at the same hospitalisation will be counted as 2 amputations in case of different anatomical laterality.
Dapa Dapagliflozin; N Number of patients per treatment group; SAS Safety analysis set

Source: DECLARE CSR, Table 31, p. 112-113

Review of amputation events was challenging because this category of events was added as an AESI late in the trial, and events were not adjudicated. I was unable to reproduce the Applicant's analysis in JMP or JReview using the ADAE dataset, likely due to MedDRA coding concerns rather than an issue with the dataset. However, both the Safety Statistical reviewer and I were able to confirm the Applicant's analysis using the ADSFTTE (time-to-first event for safety outcomes) dataset. This dataset is derived from MedDRA PTs that captured events leading to amputation; I reviewed the list of PTs used by the Applicant to capture amputations, most related to limb ischemic events, and found them to be acceptable. I used JReview to recapitulate the Applicant's analysis and Dr. Xia used SAS to derive the same results. Dr. Xia's findings are presented below in Table 54.

Table 54. FDA Analysis of Amputation Events (SAS and OT-SAS Populations)

On-Study Population

Subjects with at least 1 spontaneous/nonsurgical amputation	Placebo	Dapagliflozin
N*	8569	8574
Events (IR** per 100 PY)	113 (0.34)	120 (0.36)
Hazard Ratio*** [95% CI]	-	1.062 [0.821, 1.373]

On-Treatment Population

Subjects with at least 1 spontaneous/nonsurgical amputation	Placebo	Dapagliflozin
N*	8569	8574
Events (IR** per 100 PY)	93 (0.32)	102 (0.34)
Hazard Ratio*** [95% CI]	-	1.072 [0.809, 1.419]

Source: Analysis generated from ADSFTTE dataset using SAS by Dr. Sherman Xia

> ***Reviewer Comment:*** *The Applicant's analysis of amputation events differed slightly from the FDA analysis, but the conclusions do not change. There is no evidence from review of these data that dapagliflozin is associated with an increased risk of amputation events when added to standard of care in the studied population.*

8.5.10. Urinary Tract Infections (UTIs)

In the original dapagliflozin development program more patients experienced UTIs in the dapagliflozin treatment groups compared with placebo. However, this safety signal could not be fully characterized due to the small number of events overall and the small number of SAEs. Evaluating complicated UTIs, pyelonephritis, and urosepsis in DECLARE was a U.S. PMR. Only SAEs and DAEs were collected for this category of events. The Applicant's analysis of UTI SAEs/DAEs is presented below. While fewer patients in the dapagliflozin arm had SAEs in this category, more patients had DAEs in the dapagliflozin arm compared with placebo. The number of patients experiencing more than one UTI SAE/DAE was balanced between treatment arms.

Table 55. Summary of SAEs/DAEs of Urinary Tract Infection (OT-SAS Population)

UTI Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least one UTI SAE/DAE	**127 (1.5)**	**133 (1.6)**
Event rate per 1000 subject-years	**4.1**	**4.5**
UTI SAE	**79 (0.9)**	**109 (1.3)**
UTI DAE	**61 (0.7)**	**35 (0.4)**
Urinary tract infection	74 (0.9)	71 (0.8)
Urosepsis	20 (0.2)	22 (0.3)
Pyelonephritis	5 (0.06)	13 (0.2)
Cystitis	11 (0.1)	6 (0.07)
Pyelonephritis acute	8 (0.09)	13 (0.2)
Prostatitis	4 (0.05)	8 (0.09)
Urethritis	4 (0.05)	0
Escherichia urinary tract infection	1 (0.01)	2 (0.02)
Urinary tract infection bacterial	2 (0.02)	0
Urinary tract infection fungal	2 (0.02)	0
Bacterial prostatitis	1 (0.01)	0
Perinephric abscess	1 (0.01)	0
Pyelitis	1 (0.01)	0
Urinary tract infection enterococcal	0	2 (0.02)
Cystitis glandularis	0	1 (0.01)
Cystitis ulcerative	0	1 (0.01)
Prostatic abscess	0	0
Pyelonephritis chronic	0	0
Renal abscess	0	1 (0.01)

Source: Adapted from Table 11.3.2.2.6.1 in the DECLARE CSR Appendix 11 and DECLARE Summary of Clinical Safety, p. 23

I used the Applicant's UTI CMQ flag in the ADAE dataset in JReview to confirm the Applicant's analysis. I also performed a broad CMQ using MAED for all UTIs (serious and non-serious) and events were balanced between treatment arms, with 792 patients (9.2%) in the dapagliflozin arm and 769 patients (9.0%) experiencing any UTI (see Appendix 13.3 for list of PTs used in the broad CMQ).

To further explore the concern for complicated UTIs, I used JReview to search a broad CMQ to capture PTs suggestive of Complicated UTIs (see Appendix 13.3 for list of PTs in this CMQ). This search strategy identified 64 patients (0.8%) in the dapagliflozin arm and 74 patients (0.9%) in the placebo arm with complicated UTIs. Most of these patients were designated as having SAEs (59 patients in the dapagliflozin arm and 68 patients in the placebo arm). Again, there was no imbalance between treatment arms.

Reviewer Comment: *In the studied population, the addition of dapagliflozin to standard of care did not increase the incidence of UTIs or complicated UTIs. There were more UTI DAEs in the dapagliflozin arm compared with placebo.* (b) (4)

8.5.11. Genital Infections

In the original dapagliflozin development program the frequency of genital infections was higher in dapagliflozin-treated subjects versus comparators. However, this safety signal could not be fully characterized due to the small number of events overall and the small number of SAEs. Only SAEs and DAEs were collected for this category of events. The Applicant's findings for genital infections, collected using a prespecified list of PTs in their CMQ, are presented below in Table 56. There was a clear imbalance in events unfavorable to dapagliflozin, although the number of patients experiencing SAEs in this category was balanced. Most genital infection events were DAEs.

Table 56. Summary of SAEs/DAEs of Genital Infection (OT-SAS Population)

Genital Infection Event Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least one genital infection SAE/DAE	**76 (0.9)**	**9 (0.1)**
Event rate per 1000 subject-years	**2.5**	**0.3**
Genital Infection SAE	**2**	**2**
Genital Infection DAE	**74**	**7**
Balanoposthitis	28 (0.3)	3 (0.04)
Vulvovaginal candidiasis	8 (0.09)	2 (0.02)
Vulvovaginal mycotic infection	8 (0.09)	0
Vulvovaginitis	7 (0.08)	1 (0.01)
Genital infection fungal	5 (0.06)	1 (0.01)
Balanitis candida	4 (0.05)	0
Genital candidiasis	4 (0.05)	0
Vaginal infection	3 (0.03)	1 (0.01)
Genital infection	3 (0.03)	0
Vulvitis	3 (0.03)	0
Cellulitis of male external genital organ	1 (0.01)	1 (0.01)
Balanoposthitis infective	1 (0.01)	0
Penile infection	1 (0.01)	0

Source: Adapted from Tables 11.3.2.2.7.1 and 11.3.2.2.7.2 in the DECLARE CSR Appendix 11

I confirmed the Applicant's analysis using the ADAETTE dataset in JReview. To further explore the concern for complicated genital infections, I used JReview to search a broad CMQ to capture PTs suggestive of Complicated Genital Infections (see Appendix 13.3 for list of PTs in this CMQ). This search strategy identified 29 patients (0.3%) in the dapagliflozin arm and 15 patients (0.2%) in the placebo arm with treatment-emergent complicated genital infections. I also used MAED to search broad CMQs for Genital Infections and Genital Mycotic Infections see Appendix 13.3 for list of PTs). These analyses confirmed the same pattern of findings; thus, details of these analyses will not be described further. When analyzed by age group (<65 years and ≥65 years) and gender these findings were consistent as well.

Reviewer Comment: *Genital Mycotic Infections are a labeled Warning and Precaution for this product. Labeling negotiations are ongoing regarding the presentation of the genital mycotic infection findings from DECLARE in Section 6.*

8.5.12. Fournier's Gangrene (FG)

Based on postmarketing reports of cases of necrotizing fasciitis of the perineum 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 SGLT2i use in the FAERS 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 USPI and patient **Medication Guide** for all products in the SLGT2i class. Based on this safety concern and communications with the FDA, the Applicant conducted a search of the DECLARE safety database prior to database lock and unblinding, using their an SMQ with the following preferred terms: "Necrotising fasciitis", "Necrotising fasciitis fungal", "Necrotising fasciitis streptococcal", "Necrotising fasciitis staphylococcal", "Scrotal gangrene", "Perineal abscess", "Perineal cellulitis", "Perineal infection", "Necrotising soft tissue infection", "Penile abscess", "Penile infection", "Scrotal abscess", "Scrotal infection", "Clitoris abscess", "Vulval abscess", "Rectal abscess", "Fascial infection", "Perineal necrosis", "Myofascitis". The Applicant and the TIMI group then medically assessed the identified cases and determined that there were 8 cases overall in the SAS population, and 6 cases in the OT-SAS population, that qualified as FG. Cases were then unblinded as to treatment arm, yielding 1 case in the dapagliflozin arm and 5 cases in the placebo arm in the OT-SAS population. I reviewed the case narratives and a synopsis of each case is presented in Table 57 below.

Of note, the case definition used by DPV-I to confirm potential FG events in their Pharmacovigilance review (dated June 1, 2018) required that patients have a necrotizing infection of the perineum (including vulva/vagina OR scrotum OR buttocks) AND surgical debridement was done because of the necrotizing infection. Reports were excluded if they did not specifically state that the perineal infection was necrotizing OR if there was no surgical intervention. Reports were also excluded if an alternate etiology was identified or if there was insufficient information about the case to determine causality.

Table 57. Summary of Fournier's Gangrene Cases (Safety Population)

Subject ID	Treatment Arm	Synopsis of Narrative
(b) (6)	Dapagliflozin	66 yo obese M with scrotal abscess, underwent incision and drainage and hospitalized for IV antibiotics, discharged home after 2 days; no microorganism identified. Patient continued IP throughout and fully recovered.
(b) (6)	Placebo	65 yo obese M admitted with groin pain and assessed by Urology consultant to have Fournier's gangrene; received IV antibiotics and extensive surgical debridement of the buttocks, scrotum and bilateral thighs followed by ICU admission. Continued IP throughout and fully recovered.

(b) (6)	Placebo	65 yo morbidly obese M who had a fall on his left hip, and was hospitalized 5 days later with AKI in the setting of sepsis, noted to have redness of the groin and thigh. CT scan revealed gas in the soft tissue of the left perineum and thigh. He received antibiotics and surgical debridement. IP was interrupted. Patient fully recovered from the event.
(b) (6)	Placebo	51 yo obese M hospitalized with rectal pain and swelling, diagnosed with Fournier's gangrene of the left scrotal/perirectal area. Treated with three rounds of incision and debridement, IV antibiotics, and wound vac. Treatment with IP was interrupted. Patient recovered but required ongoing wound care to the area.
(b) (6)	Placebo	67 yo overweight M who presented to the hospital with general malaise and was noted to have soft tissue swelling of the perineum, extending over the testicles to the penile corona. Cultures grew group A Streptococcus. Patient received IV antibiotics and extensive surgical debridement, followed by a second round of debridement and skin grafting. Patient discontinued IP permanently and ultimately recovered.
(b) (6)	Placebo	66 yo overweight M hospitalized with perineal swelling and fever, diagnosed with Fournier's gangrene and treated with surgical debridement and IV antibiotics. Patient had a prolonged hospitalization complicated by Pseudomonas UTI. Treatment with IP was discontinued; patient ultimately recovered with sequelae.

I also searched the safety database using a broad CMQ for Fournier's gangrene (see Appendix 13 for complete list of PTs). Using this search strategy I did not identify any additional cases that were suspicious for FG.

Reviewer Comment: *Two cases reported by the Applicant may not be true cases of FG: one dapagliflozin case and one placebo case. The case in question in the dapagliflozin-treated patient was a scrotal abscess that responded to incision and drainage and a short course of inpatient antibiotics; there is no mention of surgical debridement. One placebo patient reported a fall five days before the diagnosis of necrotizing fasciitis of the perineum and thigh, so precipitating trauma in this morbidly obese patient was another possible etiology of the infection. Without more details about the cases, it is difficult to make a conclusive determination. However, from review of this data I conclude that in the studied population, the addition of dapagliflozin to standard of care did not increase the incidence of Fournier's gangrene.* (b) (6)

8.5.13. Pancreatitis

An imbalance in pancreatitis was not observed in the original dapagliflozin development program, nor has an imbalance been observed in the EMPA-REG OUTCOME trial. However, there have been post-marketing reports of acute pancreatitis in the SGLT2i class (the majority associated with canagliflozin use), and in the canagliflozin development program there was a case of fatal hemorrhagic pancreatitis in a canagliflozin-treated subject as well as an imbalance in serious and overall pancreatitis events not favoring canagliflozin. In the CANVAS program the number of pancreatitis events was small, but there was a numerical imbalance not favoring canagliflozin. At the time of canagliflozin's approval there was a PMR for enhanced pharmacovigilance for necrotizing, hemorrhagic, and fatal pancreatitis cases for a period of five years. Therefore, pancreatitis was added as an AESI for DECLARE and evaluation of pancreatitis was an EU PAM.

The Applicant reported SAEs/DAEs for pancreatitis using a narrow SMQ search strategy. The results of this analysis are presented below, and events were balanced between treatment arms.

Table 58. Applicant's Analysis of Pancreatitis SAEs/DAEs by Preferred Term

	Number (%) of subjects			
	Dapa 10 mg		Placebo	
Preferred term[a]	SAS (N=8574)	OT-SAS (N=8574)	SAS (N=8569)	OT-SAS (N=8569)
Subjects with at least 1 Pancreatitis event	30 (0.3)	24 (0.3)	29 (0.3)	25 (0.3)
Event rate per 1000 subject years	0.9	0.8	0.8	0.8
Pancreatitis acute	13 (0.2)	12 (0.1)	15 (0.2)	12 (0.1)
Pancreatitis	12 (0.1)	10 (0.1)	12 (0.1)	10 (0.1)
Pancreatic pseudocyst	2 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Pancreatitis chronic	2 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Pancreatitis necrotising	2 (<0.1)	1 (<0.1)	0	0
Pancreatic necrosis	1 (<0.1)	1 (<0.1)	0	0
Pancreatitis relapsing	1 (<0.1)	0	2 (<0.1)	1 (<0.1)
Pancreatic abscess	0	0	1 (<0.1)	1 (<0.1)

Source: Excerpted from DECLARE Summary of Clinical Safety, p. 76

The Acute Pancreatitis SMQ (Narrow search) in MAED yielded 33 patients (0.4%) with acute pancreatitis events in the dapagliflozin arm and 31 patients (0.4%) in the placebo arm. I also performed a broad CMQ in MAED and the results of this analysis did not identify an imbalance

in events (see Appendix 13.3 for list of PTs used in the broad CMQ).

I reviewed the case narratives for the 3 patients in the dapagliflozin arm who were reported with the PTs "Pancreatitis necrotizing" and "Pancreatic necrosis". One case occurred during the study follow-up period, more than 30 days after dapagliflozin treatment had been stopped. Details of this case will not be discussed further. The other two cases are summarized below.

Table 59. Summary of Necrotizing Pancreatitis Cases in DECLARE (OT-SAS Population)

Subject ID	Treatment Arm	Synopsis of Narrative
(b) (6)	Dapagliflozin	72 yo F w/ gallstone pancreatitis complicated by pancreatic pseudocyst formation. Patient was treated with ERCP, pseudocyst drainage, and antibiotics. She recovered after a prolonged hospitalization. The event was coded as "pancreatitis necrotizing".
(b) (6)	Dapagliflozin	63 yo M w/ gallstone pancreatitis complicated by pancreatic pseudocyst formation. He was admitted for elective cholecystectomy and was discharged home in good condition. "Pancreatic necrosis" was coded as a PT.

Reviewer Comment: *There was no imbalance in pancreatitis observed in the DECLARE trial. From the limited details provided in the case narratives, it is difficult to determine whether the cases coded as necrotizing pancreatitis or pancreatic necrosis were coded appropriately. These cases may have been more mild than these PTs would suggest, especially considering that both patients fully recovered. Notably, both patients had a plausible alternative etiology for development of pancreatitis (i.e., gallstones).*

8.5.14. Clinical Consequences of Increased Hematocrit

Increases in mean hemoglobin/hematocrit concentrations were observed during the original dapagliflozin clinical development program, and this observation has been consistent across the SGLT2 inhibitor class. Both the EMPA-REG OUTCOME CVOT and the CANVAS Program reported similar mean increases in hemoglobin/hematocrit as were observed in DECLARE. Whether these increases translate into clinically meaningful events is less clear, however. In the EMPA-REG OUTCOME trial there was an imbalance in non-fatal stroke unfavorable to empagliflozin (3.0% of patients in the empagliflozin treatment groups vs. 2.4% of patients in the placebo group experienced this endpoint), but thromboembolic events excluding stroke were balanced between treatment groups. In the CANVAS program there was also no imbalance in venous thromboembolic events between treatment arms; most VTEs were pulmonary emboli or deep venous thromboses and the number of events was small overall. Because these drugs are

known to be associated with increases in hemoglobin/hematocrit and volume depletion, it is clinically plausible that thromboembolic events could occur. Evaluating clinical consequences of increased hematocrit for dapagliflozin was an EU PAM.

As discussed in Section 8.4 (Laboratory Findings), more patients in the dapagliflozin arm had increases in hematocrit >55% or hemoglobin >18 g/dL compared with placebo. Overall 202 patients (2.4%) in the dapagliflozin arm and 64 patients (0.7%) had such abnormalities during the trial, representing a clear imbalance. The Applicant identified arterial and venous embolic and thrombotic events using an SMQ for this category of events (the Applicant's list of PTs is provided in Sequence 0459 of the submission in the Analysis Dataset Definition file). The Applicant's analysis of patients with events captured in this SMQ, along with patients with abnormalities in hemoglobin or hematocrit who also had an event in this SMQ, are presented in below. Slightly more patients in the dapagliflozin arm had AEs in the embolic or thrombotic event SMQ, and more patients had such events in association with elevated hematocrit/hemoglobin, although the number of such cases was small overall.

Table 60. Summary of Embolic and Thrombotic Events and Hematology Parameter Abnormalities in DECLARE (OT-SAS Population)

	Dapagliflozin 10 mg (N=8574)	Placebo (N=8569)
Number of patients (%)		
Embolic or thrombotic event OR marked abnormality in haematocrit or haemoglobin (%)	859 (10.0)	676 (7.9)
Embolic or thrombotic event (%)[a]	681 (7.9)	618 (7.2)
Marked abnormality in haematocrit or haemoglobin (%)[b]	202 (2.4)	64 (0.7)
Embolic or thrombotic event AND marked abnormality in haematocrit or haemoglobin (%)[c]	24 (0.3)	6 (<0.1)

Derived from: Table 8.9

[a] AE indicating any patient with an AE coded to a PT included in the SMQ Embolic and thrombotic events
[b] Lab indicating any patient with a marked abnormality in elevated haematocrit (>55%) or haemoglobin (>18 g/dL)
[c] Combination of [a] and [b]

Source: Excerpted from DECLARE Summary of Clinical Safety, Table 7, p. 33

I reviewed the list of PTs included in the Applicant's SMQ for this category of events and concluded that the list used to generate Table 60 was too broad to inform the safety review in a way that would allow for meaningful clinical conclusions. For example, the Applicant's PT list included acute myocardial infarctions and strokes, which were adjudicated events analyzed as part of the primary efficacy variable and were balanced between treatment arms (see Section 6 for discussion). It is possible that "lumping" these events into a broad SMQ could obscure a safety finding. Therefore, to explore this potential safety signal, I used JMP to search the ADAE

dataset for treatment-emergent AEs using a CMQ for venous embolic and thrombotic events (see Appendix 13.3 for complete list of PTs in this CMQ; only PTs that were actually observed in the trial are shown in Table 61 below). This search strategy identified 61 patients (0.7%) with events in the dapagliflozin arm and 52 patients (0.6%) with events in the placebo arm.

Table 61. Results of Broad CMQ, Treatment-Emergent Venous Embolic and Thrombotic Events

Venous Embolic and Thrombotic Events Parameter	Dapagliflozin 10mg (N=8574) n (%)	Placebo (N=8569) n (%)
Subjects with at least one venous embolic and thrombotic event	**61 (0.7)**	**52 (0.6)**
Total number of venous embolic and thrombotic events	**68**	**58**
Pulmonary embolism	25 (0.3)	22 (0.3)
Deep vein thrombosis	24 (0.3)	18 (0.2)
Venous thrombosis	5 (0.1)	0
Thrombosis	3 (0.03)	2 (0.02)
Thrombophlebitis	3 (0.03)	6 (0.1)
Thrombophlebitis superficial	2 (0.02)	1 (0.01)
Pulmonary infarction	1 (0.01)	1 (0.01)
Venous thrombosis limb	1 (0.01)	0
Jugular vein thrombosis	1 (0.01)	0
Post thrombotic syndrome	1 (0.01)	0
Iliac vein occlusion	0	1 (0.01)
Portal vein thrombosis	0	1 (0.01)
Postoperative thrombosis	0	1 (0.01)
Pulmonary thrombosis	0	1 (0.01)
Splenic vein thrombosis	0	1 (0.01)
Vena cava thrombosis	0	1 (0.01)

Source: Derived from ADAE dataset using JMP

In the dapagliflozin arm there were 4 patients listed in the ADAE dataset with treatment-emergent pulmonary embolism who died, compared with 6 patients in the placebo arm. I reviewed the narratives for these cases and found that in the dapagliflozin arm 1 patient had a PE after hip replacement surgery, 1 patient had a PE in association with soft tissue sarcoma, and investigators were unable to confirm the PE diagnosis in 2 patients (the deaths were reported by relatives via telephone and medical records could not be obtained).

I also reviewed case narratives for all treatment-emergent venous embolic and thrombotic events in each treatment arm that were categorized as SAEs: **42 patients** in the dapagliflozin arm vs. **34 patients** in the placebo arm). I eliminated cases in which there was a clear

precipitating cause of the venous embolic or thrombotic event (e.g., malignancy, history of DVT/PE, genetic condition, surgery including orthopedic procedures, recent prolonged immobilization) and a few cases in which there were no corroborating medical records available to confirm a family member's report of the event. This yielded **21 patients** in the dapagliflozin arm vs. **14 patients** in the placebo arm with events that had no obvious precipitating cause in the narratives.

Reviewer Comments: *The number of patients with PE was similar in the DECLARE program to the CANVAS program (21/5790 patients in the canagliflozin-treated groups vs. 12/4344 patients in the placebo groups). Venous embolic and thrombotic events do not appear to be a safety issue for dapagliflozin based on the results of DECLARE alone, but a meta-analysis of events across the CVOTs in the class might better inform this potential safety signal, which has a mechanistically plausible basis.*

8.6. Safety Analyses by Demographic Subgroups

For subgroup analyses related to the MACE endpoint (the primary safety endpoint that was also a primary efficacy endpoint), see Section 7.

Age

In the SAS population, there were 1092 patients ≥75 years of age. The median duration of exposure in this subgroup was 47 months in each treatment group, similar to the median duration of exposure of 48 months for the overall trial population.

Analyzing deaths by age group using JMP showed that the number of deaths among patients ≥75 years old was balanced between treatment arms: approximately 13% of patients in this age group died in each treatment arm during the trial (71 patients in the dapagliflozin arm and 74 patients in the placebo arm).

Table 62. Summary of Adverse Events in Patients ≥75 Years of Age (Safety Population)

Adverse event[a]	Number (%) of patients			
	Dapa 10 mg		Placebo	
	SAS (N=537)	OT-SAS (N=537)	SAS (N=555)	OT-SAS (N=555)
Number of patients with:				
AE leading to death	71 (13.2)	46 (8.6)	73 (13.2)	44 (7.9)
At least 1 SAE	287 (53.4)	260 (48.4)	304 (54.8)	264 (47.6)
At least 1 study drug-related SAE[b]	18 (3.4)	18 (3.4)	15 (2.7)	15 (2.7)
Any AE leading to premature permanent discontinuation of study drug	83 (15.5)	83 (15.5)	76 (13.7)	76 (13.7)
Any SAE leading to premature permanent discontinuation of study drug	40 (7.4)	40 (7.4)	40 (7.2)	40 (7.2)
At least 1 adjudicated malignancy[c]	54 (10.1)	49 (9.1)	60 (10.8)	50 (9.0)
At least 1 hepatic event with causality to IP adjudicated as definite or highly likely[d]	0	0	0	0
At least 1 event of fracture[c]	40 (7.4)	32 (6.0)	32 (5.8)	24 (4.3)
At least 1 event of symptoms suggestive of volume depletion[c]	24 (4.5)	21 (3.9)	35 (6.3)	31 (5.6)
At least 1 SAE/DAE of hypersensitivity reaction[c]	5 (0.9)	4 (0.7)	5 (0.9)	4 (0.7)
At least 1 SAE/DAE of urinary tract infection[c]	18 (3.4)	16 (3.0)	13 (2.3)	10 (1.8)
At least 1 SAE/DAE of genital infection[c]	4 (0.7)	4 (0.7)	2 (0.4)	2 (0.4)
At least 1 renal event[c]	56 (10.4)	48 (8.9)	73 (13.2)	62 (11.2)
At least 1 major hypoglycaemic event	9 (1.7)	9 (1.7)	16 (2.9)	14 (2.5)
At least 1 event of surgical or spontaneous/non-surgical amputation	7 (1.3)	5 (0.9)	8 (1.4)	5 (0.9)
At least 1 event of definite diabetic ketoacidosis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)

Source: DECLARE Summary of Clinical Safety, Table 11, p. 41

Subgroup analyses by age ≥65 years and ≤65 years were already discussed for the primary safety and efficacy variables and AESIs were already discussed in the relevant subsections.

Reviewer Comment: *While subgroup analyses should be interpreted with caution, the overall pattern of adverse events observed in the age group ≥75 years is consistent with observations in the general DECLARE population. The proportion of patients ≥75 years of age who died or had AEs in several categories that were AESIs (e.g., fracture events, symptoms suggestive of volume depletion) was larger than the proportion in the general trial population, merely reflecting that*

older patients are more likely to experience these events. However, there were no imbalances between treatment arms that would suggest new or different safety signals in the subpopulation ≥75 years of age compared with the general trial population.

Sex

Deaths were balanced between treatment groups when analyzed by gender, although numerically fewer women died in the dapagliflozin arm compared with the placebo arm.

Table 63. Deaths in the DECLARE trial by Sex (SAS Population)

	Dapagliflozin 10mg (N=8574) n/N (%)	Placebo (N=8569) n/N (%)
Total Deaths	**529 (6.2)**	**569 (6.6)**
Sex		
Male	369/5405 (6.8)	378/5323 (7.1)
Female	160/3169 (5.0)	191/3246 (5.9)

Source: Derived from ADYB and ADSL datasets using JMP

Subgroup analyses by sex for the primary safety and efficacy variables, and for AESIs, were already discussed in the relevant subsections.

Reviewer Comment: *Subgroup analyses by sex do not change the overall efficacy and safety conclusions derived from this trial.*

Race

Table 64. Deaths in the DECLARE trial by Race (SAS Population)

	Dapagliflozin 10mg (N=8574) n/N (%)	Placebo (N=8569) n/N (%)
Total Deaths	**529 (6.2)**	**569 (6.6)**
Race		
White	446/6837 (6.5)	472/6802 (6.9)
Black or African American	18/293 (6.1)	28/308 (9.1)
Asian	45/1148 (3.9)	46/1154 (4.0)
American Indian or Alaska Native	3/52 (5.8)	5/52 (9.6)
Native Hawaiian or Other Pacific Islander	1/9 (11.1)	0/13
Other	16/235 (6.8)	18/240 (7.5)

Source: Derived from ADYB and ADSL datasets using JMP

Subgroup analyses by race for the primary safety and efficacy variables, and for AESIs, were already discussed in the relevant subsections.

Reviewer Comment: *Subgroup analyses by race do not change the overall efficacy and safety conclusions derived from this trial.*

8.7. Specific Safety Studies/Clinical Trials

Not applicable for this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Please see Section 8.5.1 for discussion of malignancies observed in this trial.

8.8.2. Human Reproduction and Pregnancy

No randomized data on use in pregnant or nursing women were collected because these women were excluded from participation in the trial. Dapagliflozin is not recommended in the second and third trimesters of pregnancy based on animal data showing adverse renal effects in fetal rats. Dapagliflozin is also not recommended during breastfeeding due to the presence of dapagliflozin in the breastmilk of lactating rats, and the absence of human data regarding the presence of the drug in breastmilk.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in this trial.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The concern for overdose, drug abuse, withdrawal, or rebound is low with use of dapagliflozin. Overdose was defined as the accidental or intentional ingestion of any dose of study drug that was considered excessive and medically important. There were no cases of overdose reported during the trial. Issues of withdrawal, rebound, and drug abuse potential have not been evaluated, and only the 10 mg dose of dapagliflozin was studied in this trial.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Both dapagliflozin and dapagliflozin-metformin are approved products. The most recent PBRER covering the period from October 5, 2017 to October 4, 2018, was submitted on December 13,

2018. (b) (4) uring the period covered by this PBRER, there were in total 580 events (563 case reports) of ketoacidosis (of which 514 were serious) from all dapagliflozin postmarketing sources (538 from spontaneous reports, including spontaneous reports from Regulatory Authorities and the literature, [of which 490 were serious] and 42 from non-interventional/post-marketing studies [of which 24 were serious]). All case reports were included regardless of indication reported (e.g., off-label use in T1D). The Applicant considers all events of diabetic ketoacidosis, ketoacidosis and metabolic acidosis as serious. The most frequently reported events by PT were 'Diabetic ketoacidosis', 'Ketoacidosis', and 'Euglycaemic diabetic ketoacidosis'. Six events reported in the period had fatal outcomes. As already discussed in this review, the Applicant has added information regarding DKA events observed in DECLARE to Section 6 of the product labeling.

8.9.2. Expectations on Safety in the Postmarket Setting

Both dapagliflozin and dapagliflozin-metformin ER are approved products for the treatment of T2DM. While only the 10mg dose was studied in the DECLARE trial, and the population was limited to those with preserved renal function at baseline, the trial nonetheless provides a large body of additional information to better-characterize the safety profile of dapagliflozin. The updates to the safety information presented in the labeling implemented with this efficacy supplement, along with continued routine pharmacovigilance, are appropriate.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified by the other review disciplines that would affect regulatory decision-making, product labeling, or post-marketing requirements.

8.10. Integrated Assessment of Safety

The DECLARE trial provides a large body of information to supplement our understanding of the safety of dapagliflozin. The trial excluded an increased risk of MACE associated with addition of dapagliflozin to standard of care in a relevant study population at risk of CV events, thus fulfilling the CV safety assessment required under PMR 2121-5 and meeting the standard of non-inferiority set forth in FDA Guidance. The trial also assessed key adverse events of special interest for dapagliflozin and the SGLT2 inhibitor class. Overall, safety findings in the trial were consistent with the approved labeling, or reassuring regarding safety concerns identified during the initial NDA review cycles (e.g., bladder cancer, hepatic events). An imbalance in diabetic

ketoacidosis was observed, reflected in the updated product labeling. However, imbalances favorable to dapagliflozin were observed for other AESIs (e.g., AKI, major hypoglycemia). Overall the conclusion of this safety review is that there were no findings that would outweigh the substantial benefit of reducing the risk of hospitalization for heart failure in the studied population.

9. Advisory Committee Meeting and Other External Consultations

This sNDA was not discussed at an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The product labeling is not yet finalized at the time of this review. The Applicant submitted the following proposed key changes to the prescribing information for dapagliflozin and dapagliflozin-metformin ER:

- **Section 1 Indications and Usage**—To add the following (b) (4) new indication statements:
  - (b) (4)
  - (b) (4)

  Reviewer Comment: *I agree with addition of a modified indication statement reflecting reduction in the risk of hospitalization for heart failure in adults with T2DM and established CV disease or multiple CV risk factors.* (b) (4)

- **Section 2 Dosage and Administration**—To add a statement that the recommended dosage to reduce the risk of hospitalization for heart failure is 10 mg daily.

  Reviewer Comment*: I agree with this labeling revision.*

- **Section 5 Warnings and Precautions**—To remove the Warnings and Precautions statements for bladder cancer and macrovascular outcomes. (b) (4)

  Reviewer Comment: *I agree with removing the W&Ps for bladder cancer and macrovascular outcomes. I also favor removal of the W&P for Increased LDL-C, as the DECLARE findings excluded an increased risk of MACE and demonstrated a slight decrease in LDL-C in the dapagliflozin arm.*

  (b) (4)

  Other labeling revisions to this section are still undergoing negotiation.

- **Section 6 Adverse Reactions**—To update several subheadings with DECLARE data and to add a section describing the DECLARE diabetic ketoacidosis findings.

Reviewer Comment: *I agree with the addition of the DKA findings from DECLARE to this Section. Labeling negotiations surrounding the Applicant's other proposed revisions, including Acute Kidney Injury and Renal Impairment, are ongoing.*

- (b) (4)

Reviewer Comment: *I do not agree with addition of* (b) (4) *because we are removing the W&P for Bladder Cancer based on clinical trial data.* (b) (4)

- **Section 14 Clinical Trials**—To present the primary and secondary efficacy findings supportive of the Applicant's proposed new indications.

Reviewer Comment*: I agree with presentation of the efficacy data describing the results for MACE and its components, and hospitalization for heart failure/CV death and its components. Labeling negotiations surrounding description of the renal endpoint in this trial are ongoing.*

10.2. Nonprescription Drug Labeling

Not applicable for this submission.

11.Risk Evaluation and Mitigation Strategies (REMS)

Not applicable for this submission.

12.Postmarketing Requirements and Commitments

This efficacy supplement triggers the Pediatric Research Equity Act (PREA) because of new proposed indications. We agree with the Applicant's request for a full waiver for the proposed indications because pediatric studies are impossible or highly impractical: the conditions heart failure (b) (4) in patients with type 2 diabetes and established CV disease or multiple risk factors primarily occur in the adult population and are rare in pediatric patients. At the Pediatric Review Committee (PeRC) meeting on August 28, 2019, the committee members

agreed with our recommendation for a full waiver for pediatric studies.

13.Appendices

13.1. References

References are provided as footnotes throughout this review.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): D1693C00001 (DECLARE)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4794		
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): 7		
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: _____ Significant payments of other sorts (SPOOS): 6 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study Sponsor stock, stock options, or other financial interest that exceeds $50,000: 1 Sponsor of covered study: _____		
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) 12		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3 Adverse Events of Special Interest Custom MedDRA Queries (CMQs) List of Preferred Terms

Acute Kidney Injury:
Acute kidney injury; Acute phosphate nephropathy; Albumin urine present; Albuminuria; Anuria; Artificial kidney device user; Autoimmune nephritis; Azotaemia; Blood bicarbonate abnormal; Blood bicarbonate decreased; Blood creatinine abnormal; Blood creatinine increased; Blood phosphorus abnormal; Blood phosphorus increased; Blood potassium abnormal; Blood potassium increased; Blood sodium abnormal; Blood sodium decreased; Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratio increased; Bloody peritoneal effluent; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Dialysis; Dialysis device insertion; Dialysis disequilibrium syndrome; Dialysis membrane reaction; Dialysis related complication; Eosinophils urine present; Foetal renal impairment; Fractional excretion of sodium; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Haemodialysis; Haemodialysis complication; Haemodialysis-induced symptom; Haemofiltration; Hypercreatininaemia; Hyperkalaemia; Hyperphosphataemia; Hypervolaemia; Hypoalbuminaemia; Hyponatraemia; Hyponatriuria; Inadequate haemodialysis; Intradialytic parenteral nutrition; Inulin renal clearance abnormal; Inulin renal clearance decreased; Kidney injury molecule-1; Leukocyturia; Metabolic acidosis; Microalbuminuria; Neonatal anuria; Nephritic syndrome; Nephritis; Nephropathy; Nephropathy toxic; Nephrotic syndrome; Obstructive nephropathy; Oedema due to renal disease; Oliguria; Peritoneal cloudy effluent; Peritoneal dialysis; Peritoneal dialysis complication; Peritoneal effluent abnormal; Peritoneal effluent erythrocyte count increased; Peritoneal effluent leukocyte count increased; Peritoneal equilibration test abnormal; Peritoneal fluid analysis abnormal; Peritoneal fluid protein abnormal; Peritoneal fluid protein increased; Peritoneal permeability increased; Postoperative renal failure; Postrenal failure; Potassium wasting nephropathy; Prerenal failure; Protein urine present; Proteinuria; Red blood cells urine positive; Reflux nephropathy; Renal failure; Renal failure neonatal; Renal function test abnormal; Renal impairment; Renal impairment neonatal; Renal injury; Renal papillary necrosis; Renal replacement therapy; Renal transplant; Renal tubular disorder; Renal tubular dysfunction; Renal tubular injury; Renal tubular necrosis; Secondary hypertension; Tubulointerstitial nephritis; Ultrafiltration failure; Ultrasound kidney abnormal; Uraemia odour; Uraemic acidosis; Uraemic encephalopathy; Urea renal clearance decreased; Uridrosis; Urinary casts present; Urine albumin/creatinine ratio abnormal; Urine albumin/creatinine ratio increased; Urine

output decreased; Urine protein/creatinine ratio abnormal; Urine protein/creatinine ratio increased; Venogram renal abnormal; White blood cells urine positive

Acute Kidney Injury and Chronic Renal Failure:
Acquired cystic kidney disease; Acute kidney injury; Acute phosphate nephropathy; Albumin urine present; Albuminuria; Aluminium overload; Anuria; Artificial kidney device user; Autoimmune nephritis; Azotaemia; Biopsy kidney abnormal; Blood 1,25-dihydroxycholecalciferol decreased; Blood bicarbonate abnormal; Blood bicarbonate decreased; Blood calcium abnormal; Blood calcium decreased; Blood creatinine abnormal; Blood creatinine increased; Blood erythropoietin abnormal; Blood erythropoietin decreased; Blood parathyroid hormone abnormal; Blood parathyroid hormone increased; Blood phosphorus abnormal; Blood phosphorus increased; Blood potassium abnormal; Blood potassium increased; Blood sodium abnormal; Blood sodium decreased; Blood urea abnormal; Blood urea increased; Blood urea nitrogen/creatinine ratio increased; Bloody peritoneal effluent; Bone cyst; C3 glomerulopathy; Calcification of muscle; Calciphylaxis; Chronic allograft nephropathy; Chronic kidney disease; Chronic kidney disease-mineral and bone disorder; Coma uraemic; Continuous haemodiafiltration; Creatinine renal clearance abnormal; Creatinine renal clearance decreased; Creatinine urine abnormal; Creatinine urine decreased; Crystal nephropathy; Destructive spondyloarthropathy; Diabetic end stage renal disease; Diabetic nephropathy; Dialysis; Dialysis amyloidosis; Dialysis device insertion; Dialysis disequilibrium syndrome; Dialysis membrane reaction; Dialysis related complication; Diffuse mesangial sclerosis; Effective peritoneal surface area increased; Encephalopathy; End stage renal disease; Eosinophils urine present; Extensive interdialytic weight gain; Fibrillary glomerulonephritis; Focal segmental glomerulosclerosis; Foetal renal impairment; Fractional excretion of sodium; Glomerular filtration rate abnormal; Glomerular filtration rate decreased; Glomerulonephritis; Glomerulonephritis chronic; Glomerulonephritis membranoproliferative; Glomerulonephritis membranous; Glomerulonephritis minimal lesion; Glomerulonephritis proliferative; Glomerulonephritis rapidly progressive; Glomerulonephropathy; Glomerulosclerosis; Goodpasture's syndrome; Haemodialysis; Haemodialysis complication; Haemodialysis-induced symptom; Haemofiltration; Haemolytic uraemic syndrome; Haemorrhagic diathesis; Haemorrhagic fever with renal syndrome; Hepatitis virus-associated nephropathy; Hepatorenal failure; Hepatorenal syndrome; High turnover osteopathy; HIV associated nephropathy; Hypercalcaemic nephropathy; Hypercreatininaemia; Hyperkalaemia; Hyperparathyroidism; Hyperparathyroidism secondary; Hyperphosphataemia; Hypertensive nephropathy; Hypervolaemia; Hypoalbuminaemia; Hypocalcaemia; Hyponatraemia; Hyponatriuria; IgA nephropathy; IgM nephropathy; Immunotactoid glomerulonephritis; Inadequate haemodialysis; Intercapillary glomerulosclerosis; Intradialytic parenteral nutrition; Inulin renal clearance abnormal; Inulin renal clearance decreased; Ischaemic nephropathy; Kidney fibrosis; Kidney injury molecule-1; Kidney small; Leukocyturia; Low turnover osteopathy; Lupus nephritis; Mesangioproliferative glomerulonephritis; Metabolic acidosis; Microalbuminuria; Neonatal anuria; Nephritic syndrome; Nephritis; Nephrogenic anaemia; Nephrogenic systemic fibrosis; Nephropathy; Nephropathy toxic; Nephrosclerosis; Nephrotic syndrome; Normochromic

normocytic anaemia; Obstructive nephropathy; Oedema due to renal disease; Oliguria; Osteodystrophy; Osteomalacia; Pancreatorenal syndrome; Paraneoplastic glomerulonephritis; Paraneoplastic nephrotic syndrome; Parathyroid gland enlargement; Pericarditis; Pericarditis uraemic; Peritoneal cloudy effluent; Peritoneal dialysis; Peritoneal dialysis complication; Peritoneal effluent abnormal; Peritoneal effluent erythrocyte count increased; Peritoneal effluent leukocyte count increased; Peritoneal equilibration test abnormal; Peritoneal fluid analysis abnormal; Peritoneal fluid protein abnormal; Peritoneal fluid protein increased; Peritoneal permeability increased; Pigment nephropathy; Polyomavirus-associated nephropathy; Postoperative renal failure; Postrenal failure; Potassium wasting nephropathy; Prerenal failure; Protein urine present; Proteinuria; Red blood cells urine positive; Reflux nephropathy; Renal amyloidosis; Renal and liver transplant; Renal and pancreas transplant; Renal atrophy; Renal failure; Renal failure neonatal; Renal function test abnormal; Renal impairment; Renal impairment neonatal; Renal injury; Renal papillary necrosis; Renal replacement therapy; Renal rickets; Renal transplant; Renal tubular atrophy; Renal tubular disorder; Renal tubular dysfunction; Renal tubular injury; Renal tubular necrosis; Secondary hypertension; Tubulointerstitial nephritis; Ultrafiltration failure; Ultrasound kidney abnormal; Uraemia odour; Uraemic acidosis; Uraemic encephalopathy; Uraemic gastropathy; Uraemic myopathy; Uraemic neuropathy; Uraemic pruritus; Urate nephropathy; Urea renal clearance decreased; Uridrosis; Urinary casts present; Urine albumin/creatinine ratio abnormal; Urine albumin/creatinine ratio increased; Urine output decreased; Urine protein/creatinine ratio abnormal; Urine protein/creatinine ratio increased; Vascular calcification; Venogram renal abnormal; White blood cells urine positive

Volume Depletion:
Acute kidney injury; Anuria; Blood osmolarity increased; Blood pressure ambulatory decreased; Blood pressure decreased; Blood pressure diastolic decreased; Blood pressure immeasurable; Blood pressure orthostatic abnormal; Blood pressure orthostatic decreased; Blood pressure systolic decreased; Blood pressure systolic inspiratory decreased; Blood urea nitrogen/creatinine ratio increased; Capillary nail refill test abnormal; Central venous pressure decreased; Circulatory collapse; Decreased ventricular preload; Dehydration; Diastolic hypotension; Dizziness postural; Femoral pulse decreased; Hypoperfusion; Hypotension; Hypovolaemia; Hypovolaemic shock; Left ventricular end-diastolic pressure decreased; Mean arterial pressure decreased; Neonatal anuria; Orthostatic heart rate response increased; Orthostatic hypotension; Orthostatic intolerance; Peripheral circulatory failure; Postural orthostatic tachycardia syndrome; Prerenal failure; Presyncope; Pulmonary arterial pressure decreased; Pulmonary arterial wedge pressure decreased; Pulse volume decreased; Radial pulse decreased; Renal ischaemia; Shock; Syncope; Urine flow decreased; Urine output decreased; Venous pressure decreased; Venous pressure jugular decreased; Volume blood decreased

Urinary Tract Infections:

Acute focal bacterial nephritis; Adenoviral haemorrhagic cystitis; Asymptomatic bacteriuria; Bacterial prostatitis; Bacterial pyelonephritis; Bacteriuria; Bacteriuria in pregnancy; Bladder candidiasis; Bladder diverticulitis; Candiduria; Costovertebral angle tenderness; Culture urine positive; Cystitis; Cystitis bacterial; Cystitis erosive; Cystitis escherichia; Cystitis glandularis; Cystitis gonococcal; Cystitis haemorrhagic; Cystitis helminthic; Cystitis interstitial; Cystitis klebsiella; Cystitis pseudomonal; Cystitis ulcerative; Cystitis viral; Cystitis-like symptom; Cytomegalovirus urinary tract infection; Dysuria; Emphysematous cystitis; Emphysematous pyelonephritis; Escherichia pyelonephritis; Escherichia urinary tract infection; Fungal cystitis; Genitourinary chlamydia infection; Genitourinary tract gonococcal infection; Genitourinary tract infection; HIV associated nephropathy; Kidney infection; Leukocyturia; Malacoplakia vesicae; Mycoplasma genitalium infection; Nephritis; Nitrite urine present; Nitrituria; Perinephric abscess; Perinephritis; Polyomavirus-associated nephropathy; Prostatic abscess; Prostatitis; Prostatovesiculitis; Pyelocystitis; Pyelonephritis; Pyelonephritis acute; Pyelonephritis chronic; Pyelonephritis fungal; Pyelonephritis mycoplasmal; Pyelonephritis viral; Pyonephrosis; Pyuria; Renal abscess; Renal cyst infection; Renal syphilis; Renal tuberculosis; Streptococcal urinary tract infection; Trigonitis; Tuberculosis bladder; Tuberculosis of genitourinary system; Tuberculosis ureter; Urachal abscess; Ureter abscess; Ureteritis; Urethral abscess; Urethral carbuncle; Urethral papilloma; Urethral stricture post infection; Urethritis; Urethritis chlamydial; Urethritis gonococcal; Urethritis mycoplasmal; Urethritis trichomonal; Urethritis ureaplasmal; Urinary bladder abscess; Urinary tract abscess; Urinary tract infection; Urinary tract infection bacterial; Urinary tract infection enterococcal; Urinary tract infection fungal; Urinary tract infection neonatal; Urinary tract infection pseudomonal; Urinary tract infection staphylococcal; Urinary tract infection viral; Urinary tract inflammation; Urine leukocyte esterase positive; Urogenital infection bacterial; Urogenital infection fungal; Urogenital trichomoniasis; Urosepsis; Viral haemorrhagic cystitis; White blood cells urine positive

Complicated Urinary Tract Infection:
Bacterial pyelonephritis; Cystitis erosive; Cystitis ulcerative; Emphysematous cystitis; Emphysematous pyelonephritis; Escherichia pyelonephritis; Kidney infection; Perinephric abscess; Prostatic abscess; Pyelocystitis; Pyelonephritis; Pyelonephritis acute; Pyelonephritis chronic; Pyelonephritis fungal; Pyelonephritis mycoplasmal; Pyelonephritis viral; Pyonephrosis; Renal abscess; Renal cyst infection; Urachal abscess; Ureter abscess; Urethral abscess; Urethral stricture post infection; Urinary bladder abscess; Urinary tract abscess; Urosepsis

Complicated Genital Infections:
Acquired phimosis; Cellulitis of male external genital organ; Circumcision; Clitoris abscess; Erosive balanitis; Gangrenous balanitis; Genital abscess; Penile abscess; Phimosis; Vaginal abscess; Vaginal cellulitis; Vaginal erosion; Vaginal exfoliation; Vaginal haemorrhage; Vaginal lesion; Vulval abscess; Vulval cellulitis; Vulvovaginal ulceration

Genital Infections:

Acquired phimosis; Bacterial prostatitis; Bacterial vaginosis; Bacterial vulvovaginitis; Balanitis candida; Balanoposthitis; Balanoposthitis infective; Bartholinitis; Bartholin's abscess; Candida cervicitis; Cellulitis of male external genital organ; Cervicitis; Cervicitis cystic; Cervicitis mycoplasmal; Cervicitis streptococcal; Circumcision; Clitoris abscess; Endometriosis; Endometritis bacterial; Epididymitis; Erosive balanitis; Escherichia vaginitis; Fallopian tube abscess; Gangrenous balanitis; Genital abscess; Genital burning sensation; Genital candidiasis; Genital discharge; Genital herpes zoster; Genital infection; Genital infection bacterial; Genital infection female; Genital infection fungal; Genital infection male; Genital infection viral; Genital rash; Genitourinary tract infection; Hydrocele male infected; Intrauterine infection; Mycoplasma genitalium infection; Myometritis; Oophoritis; Orchitis; Ovarian abscess; Ovarian bacterial infection; Parametric abscess; Parametritis; Pelvic abscess; Pelvic infection; Pelvic inflammatory disease; Pelvic inflammatory disease mycoplasmal; Pelvic sepsis; Penile abscess; Penile infection; Perineal abscess; Perineal infection; Phimosis; Prostate infection; Prostatic abscess; Prostatitis; Prostatitis Escherichia coli; Prostatovesiculitis; Pruritus genital; Pyometra; Pyospermia; Rectovaginal septum abscess; Salpingitis; Salpingo-oophoritis; Scrotal abscess; Scrotal gangrene; Scrotal infection; Scrotal inflammation; Seminal vesicular infection; Seminal vesiculitis; Spermatic cord funiculitis; Testicular abscess; Toxic shock syndrome streptococcal; Tubo-ovarian abscess; Urogenital infection bacterial; Urogenital infection fungal; Uterine abscess; Uterine infection; Vaginal abscess; Vaginal cellulitis; Vaginal discharge; Vaginal erosion; Vaginal exfoliation; Vaginal haemorrhage; Vaginal infection; Vaginal lesion; Vaginal odour; Vaginal ulceration; Vaginitis gardnerella; Vaginitis viral; Vulval abscess; Vulval cellulitis; Vulval disorder; Vulval oedema; Vulvitis; Vulvovaginal burning sensation; Vulvovaginal candidiasis; Vulvovaginal discomfort; Vulvovaginal disorder; Vulvovaginal dryness; Vulvovaginal erythema; Vulvovaginal human papilloma virus infection; Vulvovaginal inflammation; Vulvovaginal mycotic infection; Vulvovaginal pain; Vulvovaginal pruritus; Vulvovaginal swelling; Vulvovaginal ulceration; Vulvovaginitis; Vulvovaginitis streptococcal

Genital Mycotic Infections:
Acquired phimosis; Balanitis candida; Balanoposthitis; Balanoposthitis infective; Bartholinitis; Bartholin's abscess; Candida cervicitis; Cellulitis of male external genital organ; Cervicitis cystic; Circumcision; Clitoris abscess; Endometriosis; Epididymitis; Erosive balanitis; Fallopian tube abscess; Gangrenous balanitis; Genital abscess; Genital burning sensation; Genital candidiasis; Genital discharge; Genital infection; Genital infection female; Genital infection fungal; Genital infection male; Genital rash; Genitourinary tract infection; Hydrocele male infected; Intrauterine infection; Myometritis; Oophoritis; Orchitis; Ovarian abscess; Parametric abscess; Parametritis; Pelvic abscess; Pelvic infection; Pelvic inflammatory disease; Pelvic sepsis; Penile abscess; Penile infection; Perineal abscess; Perineal infection; Phimosis; Prostate infection; Prostatic abscess; Prostatitis; Prostatovesiculitis; Pruritus genital; Pyometra; Pyospermia; Rectovaginal septum abscess; Salpingitis; Salpingo-oophoritis; Scrotal abscess; Scrotal gangrene; Scrotal infection; Seminal vesicular infection; Seminal vesiculitis; Spermatic cord funiculitis; Testicular abscess; Tubo-ovarian abscess; Urogenital infection fungal; Uterine

abscess; Uterine infection; Vaginal abscess; Vaginal cellulitis; Vaginal discharge; Vaginal erosion; Vaginal exfoliation; Vaginal haemorrhage; Vaginal infection; Vaginal lesion; Vaginal odour; Vulval abscess; Vulval cellulitis; Vulval disorder; Vulval oedema; Vulvitis; Vulvovaginal burning sensation; Vulvovaginal candidiasis; Vulvovaginal discomfort; Vulvovaginal disorder; Vulvovaginal dryness; Vulvovaginal erythema; Vulvovaginal inflammation; Vulvovaginal mycotic infection; Vulvovaginal pain; Vulvovaginal pruritus; Vulvovaginal swelling; Vulvovaginal ulceration; Vulvovaginitis

Fournier's Gangrene:
Cellulitis of male external genital organ; Erosive balanitis; Fascial infection; Fasciitis; Gangrenous balanitis; Necrotising fasciitis; Necrotising fasciitis fungal; Necrotising fasciitis staphylococcal; Necrotising fasciitis streptococcal; Necrotising myositis; Necrotising soft tissue infection; Penile abscess; Penile erythema; Penile infection; Penile pain; Penile swelling; Penis disorder; Perineal abscess; Perineal infection; Perineal necrosis; Perineal pain; Scrotal abscess; Scrotal cyst; Scrotal inflammation; Scrotal pain; Scrotal swelling; Testicular cyst; Testicular pain; Vaginal abscess; Vaginal infection; Vulva cyst; Vulval abscess; Vulval cellulitis; Vulvitis; Vulvovaginal inflammation; Vulvovaginal swelling; Vulvovaginitis

Pancreatitis:
Abdominal compartment syndrome; Abdominal distension; Abdominal pain; Abdominal pain upper; Abdominal rebound tenderness; Abdominal rigidity; Abdominal tenderness; Abdominal X-ray; Acute abdomen; Amylase abnormal; Amylase creatinine clearance ratio abnormal; Amylase increased; Ascites; Autoimmune pancreatitis; Bilirubin conjugated abnormal; Blood bilirubin increased; Blood trypsin increased; Computerised tomogram abdomen; Computerised tomogram abdomen abnormal; Cullen's sign; Cytomegalovirus pancreatitis; Endocrine pancreatic disorder; Endoscopic retrograde cholangiopancreatography; Endoscopic retrograde cholangiopancreatography abnormal; Endoscopic ultrasound; Endoscopic ultrasound abnormal; Exocrine pancreatic function test; Exocrine pancreatic function test abnormal; Faecal elastase concentration abnormal; Faecal elastase concentration decreased; Fat necrosis; Gastrointestinal pain; Gastrointestinal sounds abnormal; Grey Turner's sign; Haemorrhagic ascites; Haemorrhagic necrotic pancreatitis; Hereditary pancreatitis; Hyperamylasaemia; Hyperbilirubinaemia; Hyperlipasaemia; Ileus paralytic; Intra-abdominal pressure increased; Ischaemic pancreatitis; Jaundice; Lipase abnormal; Lipase increased; Lipase urine increased; Lung infiltration; Lupus pancreatitis; Magnetic resonance cholangiopancreatography; Nausea; Nuclear magnetic resonance imaging abdominal; Nuclear magnetic resonance imaging abdominal abnormal; Oedematous pancreatitis; Pancreatic abscess; Pancreatic calcification; Pancreatic duct rupture; Pancreatic enzyme abnormality; Pancreatic enzymes abnormal; Pancreatic enzymes increased; Pancreatic failure; Pancreatic fibrosis; Pancreatic haemorrhage; Pancreatic injury; Pancreatic necrosis; Pancreatic phlegmon; Pancreatic pseudocyst; Pancreatic pseudocyst drainage; Pancreatitis; Pancreatitis acute; Pancreatitis bacterial; Pancreatitis chronic; Pancreatitis fungal; Pancreatitis haemorrhagic; Pancreatitis helminthic; Pancreatitis

mumps; Pancreatitis necrotising; Pancreatitis relapsing; Pancreatitis viral; Pancreatorenal syndrome; Peripancreatic fluid collection; Premenstrual cramps; Secretin test; Secretin test increased; Steatorrhoea; Traumatic pancreatitis; Vomiting; Vomiting projectile

Venous Embolic and Thrombotic Events:
Axillary vein thrombosis; Brachiocephalic vein occlusion; Budd-Chiari syndrome; Catheterisation venous; Cavernous sinus thrombosis; Central venous catheterisation; Cerebral venous thrombosis; Compression garment application; Deep vein thrombosis; Deep vein thrombosis postoperative; Embolism venous; Hepatic vein occlusion; Hepatic vein thrombosis; Homans' sign positive; Iliac vein occlusion; Inferior vena cava syndrome; Inferior vena caval occlusion; Intracranial venous sinus thrombosis; Jugular vein occlusion; Jugular vein thrombosis; Mahler sign; May-Thurner syndrome; Mesenteric vein thrombosis; Mesenteric venous occlusion; Obstetrical pulmonary embolism; Obstructive shock; Ophthalmic vein thrombosis; Ovarian vein thrombosis; Paget-Schroetter syndrome; Pelvic venous thrombosis; Penile vein thrombosis; Phlebectomy; Portal vein cavernous transformation; Portal vein occlusion; Portal vein thrombosis; Portosplenomesenteric venous thrombosis; Post procedural pulmonary embolism; Post thrombotic syndrome; Postoperative thrombosis; Postpartum venous thrombosis; Pulmonary embolism; Pulmonary infarction; Pulmonary microemboli; Pulmonary oil microembolism; Pulmonary thrombosis; Pulmonary vein occlusion; Pulmonary veno-occlusive disease; Pulmonary venous thrombosis; Renal vein embolism; Renal vein occlusion; Renal vein thrombosis; Retinal vein occlusion; Retinal vein thrombosis; SI QIII TIII pattern; Splenic vein occlusion; Splenic vein thrombosis; Subclavian vein thrombosis; Superior sagittal sinus thrombosis; Superior vena cava occlusion; Superior vena cava syndrome; Thrombophlebitis; Thrombophlebitis migrans; Thrombophlebitis neonatal; Thrombophlebitis superficial; Thrombosed varicose vein; Thrombosis; Thrombosis corpora cavernosa; Transverse sinus thrombosis; Vascular graft; Vena cava embolism; Vena cava filter insertion; Vena cava filter removal; Vena cava thrombosis; Venogram abnormal; Venoocclusive disease; Venoocclusive liver disease; Venous angioplasty; Venous occlusion; Venous operation; Venous recanalisation; Venous repair; Venous stent insertion; Venous thrombosis; Venous thrombosis in pregnancy; Venous thrombosis limb; Venous thrombosis neonatal; Visceral venous thrombosis

Appendix 13.4 Applicant list of Preferred Terms for Identification of Potential DKA Cases

Ketoacidosis; Diabetic ketoacidosis; Ketosis; Diabetic ketoacidotic hyperglycaemic coma; Diabetic metabolic decompensation; Acidosis; Metabolic acidosis; Uremic acidosis; Blood ketone body; Blood ketone body increased; Blood ketone body present; Acetonaemia; Ketonuria; Urine ketone body; Urine ketone body present; Anion gap; Anion gap abnormal; Anion gap increased; Blood pH abnormal; Blood pH decreased; Organic acid analysis abnormal; Blood bicarbonate decreased; Acid-base balance disorder mixed; Hyperosmolar hyperglycaemic state; Diabetic coma; Diabetic hyperglycaemic coma; Diabetic hyperosmolar coma; Coma acidotic; Lactic acidosis; Diabetic ketosis; Euglycaemic diabetic ketoacidosis

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/s/

MICHELLE CAREY
10/09/2019 03:26:23 PM

PATRICK ARCHDEACON
10/15/2019 01:50:42 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

PHARMACOLOGY REVIEW(S)

Memorandum

PHARMACOLOGY/TOXICOLOGY

MEMO TO FILE

Date:	10/17/2019
NDA:	202293-S18; 205649-S11
Sponsor:	AstraZeneca AB
Drug:	Farxiga®
Reviewer:	Huiqing Hao, Ph.D.

This memorandum is to document that there is no action indicated from a nonclinical perspective for the submission of NDA202293-S18 and NDA 205649-S11, as no new nonclinical studies were submitted to support these sNDAs and there are no changes in the nonclinical section of the label.

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/s/

HUIQING HAO
10/17/2019 03:33:18 PM

FEDERICA BASSO
10/17/2019 03:35:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA202293/S-18 and NDA 205649/ S-011
Supplement #:	18
Drug Name:	Farxiga (dapagliflozin) and Xigdou XR (dapagliflozin and metformin) extended release tables
Indication(s):	(b) (4) [redacted]
Applicant:	AstraZeneca
Date(s):	Stamp Date: December 18, 2018 Primary Review Due Date: September 9, 2019 PDUFA Goal Date: October 18, 2019
Review Priority:	Standard
Biometrics Division:	DBII
Statistical Reviewer:	Yun Wang, PhD
Concurring Reviewers:	Mark Rothmann, PhD, Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Michelle Carey, MD, Clinical Reviewer Patrick Archdeacon, MD, Acting Team Leader
Project Manager:	Richard Whitehead

Keywords: Survival Analysis, Multiple Imputation, Bayesian Shrinkage Estimation

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LIST OF TABLES

(b) (4)

LIST OF FIGURES

1 EXECUTIVE SUMMARY

AstraZeneca submitted an efficacy supplement for Dapagliflozin to fulfill the post-marketing requirements for NDA 202293, which were to conduct the DECLARE cardiovascular outcome trials (CVOT) and assess the risk of bladder cancer associated with dapagliflozin. Based on the DECLARE study results, the applicant is seeking for the following two new indications for the use of dapagliflozin in patients with Type 2 diabetes mellitus (T2DM):

(b) (4)

This review covers the efficacy results of the DECLARE study and evaluates the strength of the clinical evidence for supporting the proposed indications from statistical perspective.

1.1 Brief overview of clinical study

Study DECLARE was a multicenter, randomized, double-blind, placebo-controlled phase IIIb study to evaluate the effect of dapagliflozin on CV and renal outcomes in patients with T2DM with or without established CV disease. There were two primary endpoints: time from randomization to first occurrence of a major adverse cardiovascular event (MACE); time to hospitalization for heart failure or CV death. If the non-inferiority test of time to first MACE was statistically significant, superiority in time to first MACE and superiority in time to hospitalization for heart failure or CV death would be tested simultaneously with alpha equally split between two tests. If none of these two superiority tests achieved statistical significance, the formal statistical test will stop at this point. If only one test achieved statistical significance, then its allocated alpha will be recycled to the other non-significant test. Only if superiority was achieved in both time to first MACE and time to hospitalization for heart failure or CV death, further secondary endpoints would be tested hierarchically.

1.2 Statistical Issues and Findings

Findings and issues from the DECLARE study that will be discussed in this review include:

- Significant difference in the composite endpoint of hospitalization for heart failure or CV death appeared due to the difference in hospitalization for heart failure between treatment arms.

(b) (4)

1.3 Collective Evidence

Superiority test for time to first MACE was not statistically significant with a hazard ratio (HR) of 0.93 and a 95% confidence interval (CI) (0.84, 1.03). The upper bound of the hazard ratio did

not rule out 1 but was less than 1.3, which fulfilled the postmarking safety requirement for ruling out a 30% increase in cardiovascular risk.

Dapagliflozin showed superiority in reducing the risk of hospitalization for heart failure or CV death (HR: 0.83 [95% CI: 0.73 to 0.95]). However, it appeared that the difference was mainly driven by the hospitalization for heart failure (HR: 0.73 [95% CI: 0.61 to 0.88]). The results of CV death showed no difference (HR:0.98, [95% CI: 0.82 to 1.17]).

Superiority of dapagliflozin over placebo was not achieved for MACE. All alpha was used at this point, any further comparative analyses should be considered as exploratory. (b) (4) [redacted]

1.4 Conclusion and Recommendations

My review of the statistical evidence found that dapagliflozin reduces the risk of hospitalization for heart failure compared to the placebo. (b) (4) [redacted]. Overall, I recommend approval of the indication: to reduce the risk of new or worsening heart failure (HF) as measured by occurrence of hospitalization for HF, (b) (4) [redacted].

2 INTRODUCTION

2.1 Class and Indication

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor approved in 2014, indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The approved doses are 5 mg and 10 mg once daily.

On December 18, 2018, the applicant submitted an efficacy supplement and proposed new indications for the use of dapagliflozin based on the clinical data from the DECLARE Cardiovascular Outcomes Trial, "Dapagliflozin effect on cardiovascular events: A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of cardiovascular death, myocardial infarction or ischemic stroke in patients with type 2 diabetes". The applicant is seeking for marketing approval for the use of dapagliflozin in adults with T2DM to reduce the risk of:

(b) (4) [redacted]

2.2 Data Sources

The data and final study reports were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link:
\\CDSESUB1\evsprod\NDA202293\202293.enx

The information needed for this review was obtained from Module 1 FDA regional information, Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Reports.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

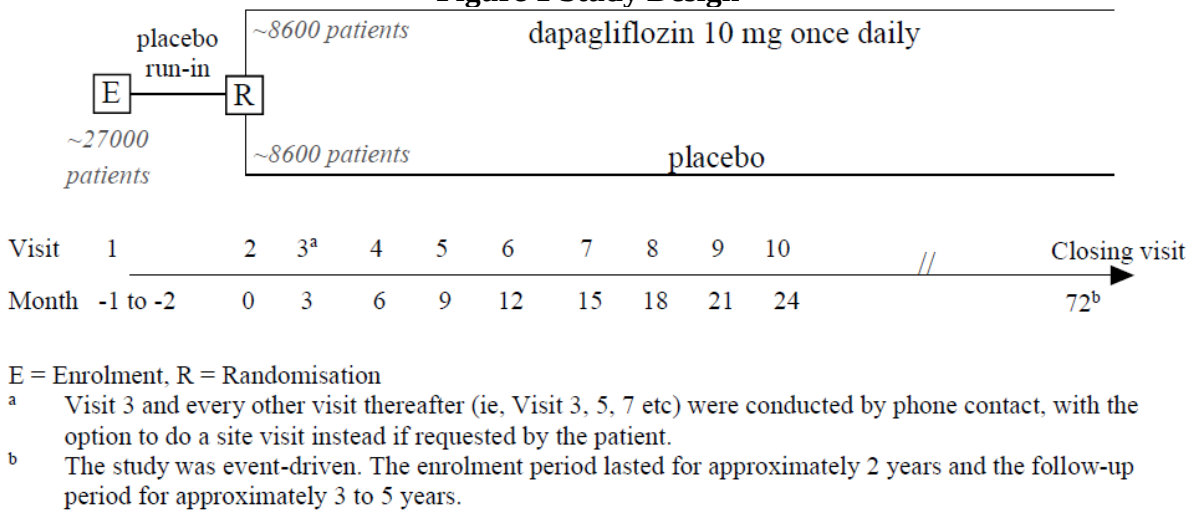
The datasets for the reviewed study were found to be in good organization and were provided as .xpt files. The analysis datasets included both derived and enriched data (such as formatted variables, derived endpoints, etc.). I was able to replicate the results on the efficacy endpoints presented in the Clinical Study Report (CSR) for supporting the proposed indications. My review is based on the analysis methods prespecified in the statistical analysis plan for the efficacy endpoints.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study DECLARE was a multicenter, randomized, double-blind, placebo-controlled phase IIIb study to evaluate the effect of dapagliflozin on CV and renal outcomes in patients with T2DM with or without established CV disease. The study was an event driven trial. A total of 1390 MACE events were required for demonstrating superiority of dapagliflozin over placebo by reducing 15% risk in MACE with 85% power. Patients were randomized with 1:1 ratio to receive either 10 mg dapagliflozin once daily or placebo. There were 27000 patients enrolled and 17160 patients randomized in the study. Figure 1 shows the overview of the study design.

Figure 1 Study Design



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Source: Applicant's Clinical Study Report (CSR)

Dual Primary Endpoints: Time to first occurrence of MACE, which consists of CV death, myocardial infarction (MI), and ischemic stroke; Time to first occurrence of hospitalization for HF and CV death.

Key Secondary Endpoints:

- Renal composite endpoint: confirmed sustained ≥40% decrease in eGFR to eGFR <60mL/min/1.73m^2 using CKD-EPI equation and/or ESRD

- All-cause mortality (time-to-event)

3.2.2 Statistical Methodologies

Sample size determination: Collection of 1390 MACE events was required to provide 85% power to demonstrate superiority of dapagliflozin over placebo with HR of 0.85 at one-sided alpha of 0.025. The assumed annual event rate was 2.1% for placebo and the assumed annual study rate was 1% over a 3-year accrual period and 3-year minimum follow-up. Therefore, a total of 17150 patients were required to be randomized in the study. With these assumptions and 1390 MACE events collected, the study was estimated to have >99% power to the test rule out a 30% increase in CV risk.

Applicant's analysis method: Cox proportional hazards model was used to analyze the time-to-event variables. The model was stratified by baseline hematuria and baseline CV risk, with treatment as a model term.

Analysis population: The intent-to-treat (ITT) population included all randomized patients irrespective of protocol adherence and continued participation in the study. This defined analysis population (ITT) was considered the primary analysis set for the primary and secondary endpoints and for exploratory efficacy endpoints. Patients who withdraw consent to participate in the study (or are lost to follow-up) will be included up to the date of their study termination except for vital status known through public records.

Control of type I error: The closed testing procedure was utilized to control the familywise type I error at one-sided 0.025. If the non-inferiority of MACE is achieved at one-sided alpha 0.0231, then the alpha will split in half (alpha=0.001155), and test for superiority for MACE and superiority for hospitalization for HF and CV death respectively. If none of these two superiority tests achieved statistical significance, the formal statistical test will stop at this point. If only one test achieved statistical significance, then its allocated alpha will be recycled to the other non-significant test. Only if superiority was achieved in both time to first MACE and time to hospitalization for heart failure or CV death, further secondary endpoints would be tested hierarchically. Table 1 summarizes the testing procedure for the primary and secondary endpoints.

Table 1 Confirmatory Testing Procedures Using One-sided Alphas

H01: Non-inferiority for MACE (alpha = 0.0231)[a]	
Now the alpha will split into independent testing of the co-primary composites in parallel:	
H02: Superiority for MACE (alpha = 50% of primary alpha)[c]	**H03: Superiority for hospitalization for heart failure/CV death (alpha = 50% of primary alpha)[c]**
• H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73m^2 and/or ESRD (dialysis for at least 90 days or kidney transplant, confirmed sustained eGFR <15 mL/min/1.73m^2) and/or renal or CV death [b]	
• H05: Superiority for all-cause mortality[d]	

[a] The alpha of 0.0231 represents the final one-sided significance level to be used when the study has been completed in entirety. At an interim analysis, testing for superiority will occur, and the alpha for superiority will be replaced by 0.000095 at the first and 0.00614 at the second interims. Non-inferiority will be tested only at the completion of the study.

[b] With the exception of all-cause mortality, secondary endpoints will only be tested once, at the completion of the trial or if the decision is made to terminate the trial early. The alpha will be controlled for the overall Type I error across the primary and secondary endpoints and across the interims and final analysis.

[c] If this analysis occurs at completion of the trial, the alpha will be 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalization for heart failure/CV death.

[d] All-cause mortality is assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it will be tested second following MACE. If the study terminates at an interim analysis, all-cause mortality will remain as the 2nd endpoint following the test for superiority of MACE. If the final analysis occurs at the completion of the trial, all-cause mortality will be tested as presented in this table,.

Source: Applicant's CSR

Data monitoring committee and interim analyses: An independent data monitoring committee was responsible for safeguarding the interests of the patients by assessing the safety data during the trial conduct and evaluating the efficacy data for the prespecified interim analysis. The interim efficacy analyses were specified to occur when 1/3 and 2/3 of the target number of MACE events has occurred. The first interim efficacy analysis was conducted in February 2016 and the second in June 2017.

Reviewer's comment: The applicant revised the testing procedure during the trial conduct by adding the composite endpoint of hospitalization for heart failure or CV death and renal composite endpoint. The applicant stated that the revision was based on the external information of EMPA-REG trial that showed the benefit of reducing the risk of heart failure and renal outcomes. An IR has been sent to the sponsor to clarify whether the revised testing procedure was finalized before the conduct of the first unblinded efficacy analysis. The applicant confirmed the changes to the endpoint hierarchy was before the first interim efficacy analysis in February 2016.

Applicant's sensitivity analysis:
In the primary analysis, patients with incomplete follow-up of the endpoint events were censored at the date of last clinical assessment. A multiple imputation approach was used to impute the endpoint events between the censoring data and 21 MAY 2018, the date when the Executive Committee instructed the sites to commence closing visit, as the censoring date for all patients. The details of the approach are presented as follows:

- For patients with incomplete follow-up, the event time was imputed based on the treatment hazards rates from the patients who discontinued but continued to be followed up. The estimated hazard rates and the simulation models were adjusted for CV disease history with respect to MACE and for CV disease history and HF history with respect to the composite of hospitalization for heart failure or CV death. Imputations were conducted separately within each treatment group.
- The imputation models were based on an exponential distribution if the assumption of the constant hazard rates over time was appropriate, or a piecewise exponential will be used if is not appropriate. The variability in the hazard rate was incorporated by taking a random draw of the log hazard rate from a normal distribution.

Reviewer's Comments: The applicant used a Cox proportional hazard model to estimate the effect of dapagliflozin on time-to-event endpoints compared with placebo. Dropouts were censored at the time of dropout—this relies on an assumption that dropouts have the same event hazard as those patients who remained in follow-up ("non-informative censoring") on the same treatment arm. This could potentially introduce bias if the non-administrative dropouts (withdrawal of consent or lost-to-follow-up) were related to the event of interest. Therefore, we requested the applicant conduct the above sensitivity analyses to assess the assumption of non-informative censoring.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The first patient was enrolled on 25 April 2013. The last patient was randomized on 30 June 2015, and the last patient completed the last visit on 11 September 2018. The median follow-up time was 4.2 years. Table 2 summarizes the patients disposition for the randomized population. A total of 17160 patients were randomized in 882 sites across 33 countries. There were 17 randomized patients (8 in Dapagliflozin group and 9 in placebo group) who did not receive any dose of study drug. About 76.8% patients completed the study treatment, where more patients in the placebo group (25.1%) discontinued the study drug compared to the patients in the dapagliflozin group (21.1%).

Table 2 Patient Disposition

	Dapagliflozin 10mg	**Placebo**
Randomized	**N=8582 n (%)**	**N=8578 n (%)**
Complete the study*	8473 (98.7%)	8433 (98.3%)
Death	522 (6.08%)	559 (6.52%)
Did not complete the study	109 (1.27%)	145 (1.69%)
Withdrawal Consent	97 (1.13%)	127 (1.48%)
Lost to follow-up	12 (0.14%)	18 (0.21%)
Randomized	**N=8582 n (%)**	**N=8578 n (%)**
Completed the study drug	6763 (78.8%)	6418 (74.8%)
Did not complete the study drug	1815 (21.1%)	2153 (25.1%)
Unknown study drug status	4 (0.05%)	7 (0.08%)

Source: Reviewer, generated based on applicant's analysis data flags
**defined as complete follow-up of the first occurrence of the primary efficacy endpoints*

Table 3 and Table 4 summarizes the demographics and patient baseline characteristics. No imbalances were found between the treatment groups.

Table 3 Demographic Data – ITT population

	Dapagliflozin 10mg (N=8582)	**Placebo (N=8578)**
Age		
Mean (SD)	64 (6.8)	64 (6.8)
Categorical Age, n (%)		
<65 years	4631 (54.0%)	4622 (53.9%)
>=65 years	3951 (46.0%)	3956 (46.1%)
Sex, n (%)		
Male	5411 (63.1%)	5327 (62.1%)
Female	3171 (36.9%)	3251 (37.9%)
Region, n(%)		
Europe	3806 (44.3%)	3823 (44.6%)
North America	2737 (31.9%)	2731 (31.8%)
Asia/Pacific	1093 (12.7%)	1093 (12.7%)
Latin America	946 (11.0%)	931 (10.9%)
Race, n (%)		
White	6843 (79.7%)	6810 (79.4%)
Asian	1148 (13.4%)	1155 (13.5%)
Black	295 (3.44%)	308 (3.59%)
American Indian or Alaska Native	52 (0.61%)	52 (0.61%)
Native Hawaiian or Other Pacific	9 (0.10%)	13 (0.15%)
Other	235 (2.74%)	240 (2.80%)
Ethnicity, n (%)		
Not Hispanic or Latino	7284 (84.9%)	7308 (85.2%)
Hispanic or Latino	1298 (15.1%)	1270 (14.8%)

Source: Reviewer reproduced

Table 4 Baseline Characteristics Data – ITT population

	Dapagliflozin 10 mg (N=8582)	Placebo (N=8578)
Duration of Diabetes (Years)		
Mean (SD)	12 (7.7)	12 (7.9)
Baseline BMI , n (%)		
>=30 kg/m^2	5145 (60.0%)	5042 (58.8%)
<30 kg/m^2	3432 (40.0%)	3532 (41.2%)
Baseline Systolic Blood Pressure, n (%)		
>=130 mmHg	5494 (64.0%)	5423 (63.2%)
<130 mmHg	3088 (36.0%)	3155 (36.8%)
Baseline Diastolic Blood Pressure, n (%)		
<80 mmHg	4549 (53.0%)	4618 (53.8%)
>=80 mmHg	4033 (47.0%)	3960 (46.2%)
Baseline Hematuria (IRVS), n (%)		
Negative	7516 (87.6%)	7511 (87.6%)
Positive	1066 (12.4%)	1067 (12.4%)
eGFR, n (%)		
>=90 mL/min/1.73m²	4137 (48.2%)	4025 (46.9%)
>=60 - <90 mL/min/1.	3838 (44.7%)	3894 (45.4%)
<60 mL/min/1.73m²	606 (7.06%)	659 (7.68%)
Baseline HbA1c, n (%)		
>=9 %	2297 (26.8%)	2164 (25.2%)
>=8 - <9 %	2193 (25.6%)	2327 (27.1%)
>=7 - <8 %	3317 (38.7%)	3309 (38.6%)
<7 %	773 (9.01%)	774 (9.03%)
Baseline CV Risk (IRVS), n (%)		
Multiple Risk Factor	5093 (59.3%)	5091 (59.3%)
Established CV Disease	3489 (40.7%)	3487 (40.7%)

Source: Reviewer reproduced

3.2.4 Results and Conclusions

3.2.4.1 MACE results

The increased cardiovascular risk of dapagliflozin compared to placebo was ruled out. However, the superiority of dapagliflozin over placebo in MACE was not achieved based on the pre-specified closed testing procedure (see Table 5). The results of each component of the MACE and other related exploratory endpoints supported the findings with the MACE endpoint.

Reviewer's comment: There were 156 undetermined deaths (73 in dapagliflozin group and 83 in placebo group). These were not considered as CV deaths in the applicant's defined MACE endpoint. I additionally performed an analysis for MACE, where undetermined deaths were handled as CV deaths. The applicant's MACE results were similar to the results when included those events as CV deaths.

Table 5 Time to first adjudicated MACE - ITT population

	Dapagliflozin N = 8582 Events (%)	Placebo N = 8578 Events (%)	Dapagliflozin vs Placebo Hazard Ratio (95% CI)	P value
MACE	756(8.8)	803 (9.4)	0.93 (0.84, 1.03)	0.1723
CV-death	166 (1.9)	167 (1.9)		
Non-fatal MI	377 (4.4)	428 (5.0)		
Non-fatal Stroke	213 (2.5)	208 (2.4)		
MACE*	824 (9.6)	878 (10.2)	0.93 (0.85,1.02)	0.1353
All MI	393 (4.6)	441 (5.1)	0.89 (0.77, 1.01)	0.0801
All Stroke	235 (2.7)	231 (2.7)	1.01 (0.84, 1.21)	0.9156
Non-CV death	211 (2.5)	238 (2.8)	0.88 (0.74, 1.06)	0.1926
MACE-free survival§	1015 (11.8)	1090 (12.7)	0.92 (0.85,1.01)	0.0676

MACE: major adverse cardiovascular event; CV: cardiovascular; MI: Myocardial infarctions
* Undetermined deaths were included as CV deaths
§ MACE-free survival: Time to first event among adjudicated all-cause mortality, non-fatal MI, or non-fatal stroke.
°P value (two-sided) is based on the Wald statistic for superiority of Hazard Ratio. P-value for testing non-inferiority of dapagliflozin vs. placebo on MACE is 0.0003, where the non-inferiority margin is 1.3.
Source: Reviewer

3.2.4.2 Hospitalization for Heart Failure/CV Death

Table 6 summarizes the percentages of subjects experiencing the composite endpoint events within treatment arms and the analysis results from the Cox models and the log-rank tests. The superiority of dapagliflozin over placebo was confirmed for the composite endpoint of heart failure hospitalization or CV death. The estimated hazard ratio of dapagliflozin over placebo was 0.83 [95% CI: (0.73, 0.95)] and the stratified log-rank test yielded a p-value of 0.0052. The composite endpoint of heart failure hospitalization or CV death occurred in 417(1.7%) in Dapagliflozin patients and 496 (5.8%) in placebo patients. However, it appeared that this significant reduction in risk of this composite endpoint were mainly driven by the single component – hospitalization for heart failure (212 [2.5%] patients in dapagliflozin group, 286 [3.3%] patients in placebo group).

Table 6 Time to First Occurrence of Hospitalization for Heart Failure or CV Death, All-cause Mortality (ITT)

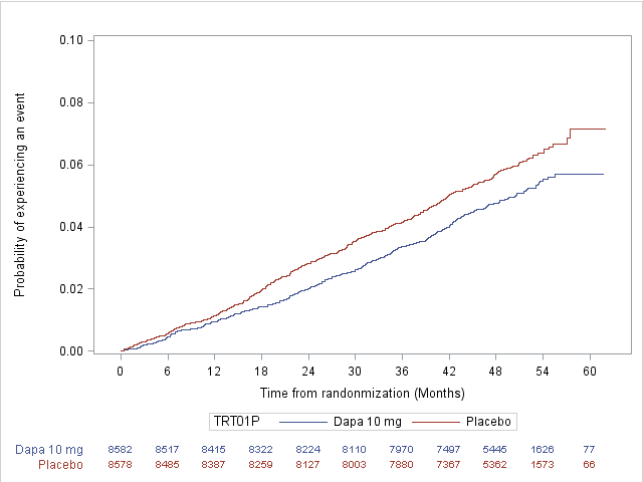
Efficacy Endpoints	Dapagliflozin 10mg N=8582 Events (%)	Placebo N=8578 Events (%)	Hazard Ratio	p-value*
Composite endpoint				
Hospitalization for Heart Failure or CV death	417 (4.7%)	496 (5.8%)	0.83 (0.73, 0.95)	0.0052
Components				
Hospitalization for Heart Failure	212 (2.5%)	286 (3.3%)	0.73 (0.61, 0.88)	0.0006
CV Death	245 (2.9%)	249 (2.9%)	0.98 (0.82, 1.17)	0.8306
Other endpoints				
All-cause mortality	529 (6.2%)	570 (6.6%)	0.93 (0.82, 1.04)	0.198
Hospitalization for Heart Failure or death from congestive heart failure (1)	229 (2.7%)	304 (3.5%)	0.75 (0.63, 0.88)	0.007

Hazard ratios and CIs are calculated from Cox proportional hazards model (Wald test) stratified by baseline CV risk group and haematuria with treatment as a model term.
*Nominal P-value is calculated based on a stratified log-rank test.
(1) derived by the reviewer
Source: Reviewer

As presented in Figure 2, the hospitalization for heart failure showed a similar pattern of the Kaplan Meier curves as the composite endpoint, where the divergence of the two groups appeared after approximately 1 year of the treatment. No separation of survival curves was observed for CV death among the two groups, and the percentages of subjects experiencing CV death were the same. No differences were detected in either time to CV death or time to all-cause mortality between the dapagliflozin and placebo groups.

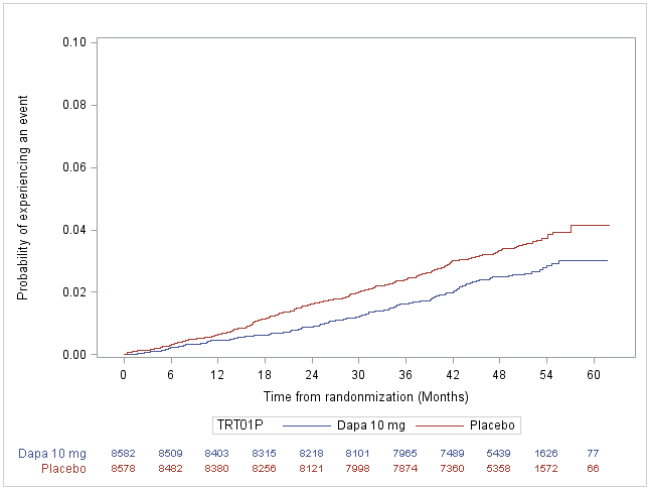
Figure 2 Kaplan-Meier plots of time to first occurrence of Hospitalization for Heart Failure or CV Death, All-cause Mortality (ITT)

A. The composite of hospitalization for heart failure and cardiovascular death



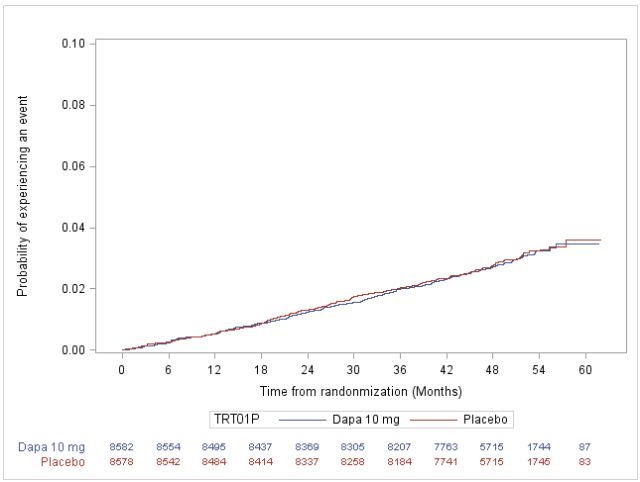
Source: Reviewer

B. Hospitalization for heart failure



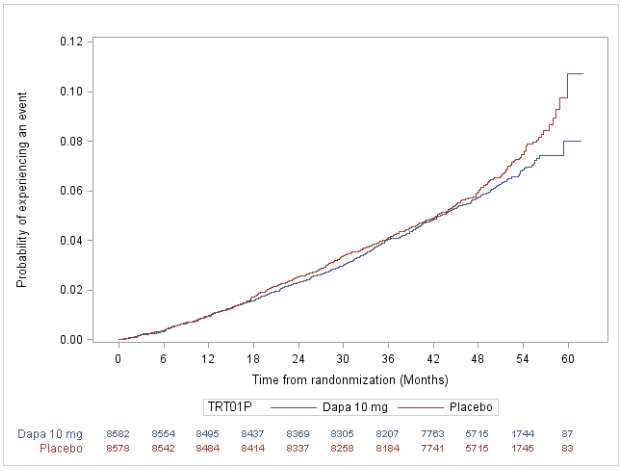
Source: Reviewer

C. CV death



Source: Reviewer

D. All-cause mortality



Source: Reviewer

The cutoff date of the study was May 21, 2018. Incomplete follow-ups were defined as censored subjects without event of the hospitalization for heart failure or CV death before the cutoff date. The proportions of subjects with incomplete follow-up on the composite endpoint were 6.6% (563/8582) in the placebo group and 5.8% (496/8582) in the dapagliflozin group. Results from the sensitivity analysis with multiple imputation, using the off-treatment data from patients who discontinued but continued to be followed up, showed an estimated HR of 0.84[95% CI: 0.74, 0.96,], which were similar to the primary results [HR 0.83, 95% CI (0.73, 0.95)].

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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Race, Age, and Geographic Region

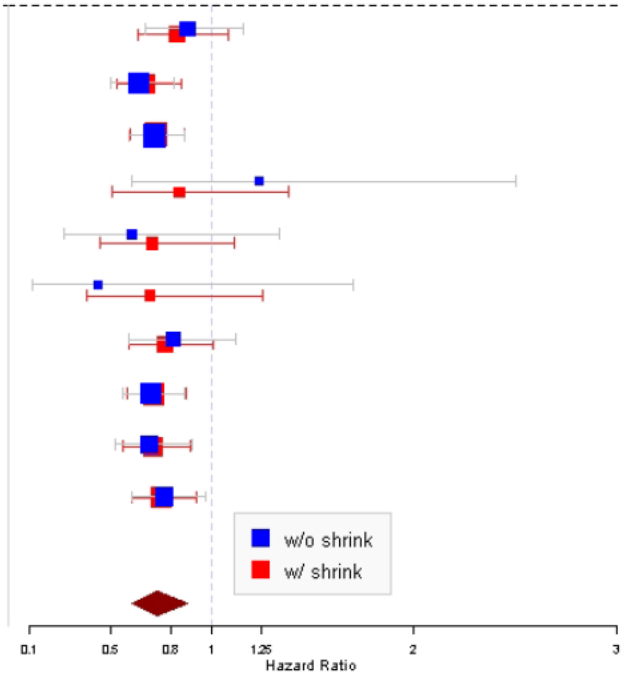
Subgroup analyses were conducted for sex, race, age, geographic region on time to hospitalization for heart failure. The total variability in the sample treatment effects, estimated from the model stratified by subgroup, consists of within subgroup variability of the sample estimator and across subgroup variability in underlying/true effects. Assuming the main effects across the subgroups are exchangeable, shrinkage estimation could be used to address the concerns of random highs and/or random lows due to a small sample and provide better precision. Therefore, I conducted shrinkage estimation to describe and evaluate the treatment effects across the subgroups. The following assumptions are made on the Bayesian hierarchical modelling:

- $Y_i \sim N(\mu_i, \sigma_i^2)$, where Y_i represents the observed subgroup log HR for the i^{th} subgroup level
- σ_i^2 is the estimated sample variance for the i^{th} subgroup level
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 16)$, $1/\tau^2 \sim$Gamma (0.001, 0.001)

Figure 4 presents the subgroup analysis results using shrinkage estimation compared to the sample estimation. Compared with sample estimates, the shrinkage estimates regressed towards to the overall estimates with narrower confidence interval. More specifically, the shrinkage estimation borrowed information from other levels of a subgroup when estimating the treatment effect for a specific group. For subgroup with small number of events (e.g. race=Asian, Black, or Other), the shrinkage estimates were closer to the overall treatment effect. The findings were consistent across the levels of subgroups.

Figure 4 Subgroup Analysis Results for Time to Hospitalization for Heart Failure

Subgroup		HR w/o Shrink	HR w/ Shrink
Age	<65 years	0.88	0.83
	>=65 years	0.64	0.67
Race	White	0.72	0.72
	Asian	1.24	0.84
	Black	0.61	0.71
	Other	0.44	0.69
Sex	Female	0.81	0.77
	Male	0.7	0.72
Region	North America	0.69	0.71
	Other	0.77	0.75
Overall		**0.73**	



Source: Reviewer

5 SUMMARY AND CONCLUSIONS

The DECLARE study was designed to address the postmarketing requirement that dapagliflozin does not increase cardiovascular risk in patients with type 2 diabetes mellitus. The study fulfilled the postmarketing safety requirement, demonstrated the non-inferiority of dapagliflozin compared to placebo in MACE events, but failed to demonstrate the superiority in MACE. Based on the results of the composite endpoint of hospitalization for heart failure or CV death, dapagliflozin demonstrated a treatment effect on reducing the risk of hospitalization for heart failure and no effect on cardiovascular death.

5.1 Statistical Issues

Statistical issues discussed in this review include:

- Statistical difference in the composite endpoint of hospitalization for heart failure or CV death was primarily driven by the difference between treatments in rate of hospitalization for heart failure
- (b) (4)

5.2 Labeling Recommendations

The applicant proposed to add the new indications in labelling stating that dapagliflozin reduces the risk of hospitalization for heart failure [redacted] (b) (4)

I recommend [redacted] (b) (4) grant the indication for reducing risk of new or worsening heart failure as measured by hospitalization for heart failure in section 1. In section 14, my recommendation is to report HRs with 95% CI without including nominal p-values for the single components of the composite of hospitalization for heart failure or CV death, as the 95% CI would still provide useful information on the uncertainty of the estimated treatment effects of dapagliflozin compare to placebo. [redacted] (b) (4)

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/

YUN WANG
10/01/2019 03:12:16 PM

MARK D ROTHMANN
10/01/2019 03:15:14 PM
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # (Supplement #):	202293 (S-018), 205649 (S-011)
Drug Name:	Farxiga (dapagliflozin), Xigduo XR (dapagliflozin and metformin)
Indication(s):	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)
Applicant(s):	AstraZeneca
Date(s):	Stamp date: 12/18/2018 PDUFA date: 10/18/2019
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Changming (Sherman) Xia, Ph.D.
Concurring Reviewers:	Bo Li, Ph.D. Mat Soukup, Ph.D., Deputy Division Director
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Michelle Carey, M.D., Medical Officer Patrick Archdeacon, M.D., Medical Team Leader
Project Manager:	Richard Whitehead
Keywords:	MACE, non-inferiority, cardiovascular, SGLT2 inhibitor, safety, post-marketing requirement, bladder cancer, amputation

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1 EXECUTIVE SUMMARY

1.1 Background

This is a statistical review of the "Dapagliflozin Effect on CardiovascuLAR Events" trial (DECLARE; D1693C00001), a cardiovascular outcomes trial (CVOT) designed to compare dapagliflozin to placebo on cardiovascular (CV) risk in patients with type 2 diabetes mellitus (T2DM). This review evaluates the Major Adverse Cardiovascular Event (MACE) composite endpoint consisting of CV death, myocardial infarction (MI) or ischemic stroke, as well as bladder cancer and amputation associated with dapagliflozin in DECLARE.

Dapagliflozin was approved in the United States (US) on January 08, 2014 (FARXIGA®, New Drug Application [NDA] 202293) as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. MACE and bladder cancer were listed in the original approval letter as potential safety signals requiring further evaluation. The following post-marketing requirements (PMRs) were included in the US Food and Drug Administration (FDA) approval letter[1]:

> *2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of **MACE** (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than **1.3**. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and **bladder cancer**, complicated genital infections, complicated urinary tract infections/pyelonoephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.*
>
> *2121-6 To assess the risk of **bladder cancer** associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of **2.0** for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.*

The study report and data of DECLARE were submitted by AstraZeneca under NDA 202293 Supplement 18 to fulfill these PMRs and to support new efficacy claim(s). The statistical goal of this review is to assess: 1) whether the hazard ratio (HR) of MACE associated with dapagliflozin relative to placebo met the risk margin of 1.3; 2) the safety endpoint of bladder cancer; 3) the safety endpoint of amputation, based on the results of DECLARE. For a statistical review of the efficacy aspects of DECLARE, the reader is referred to the review by Dr. Susie Sinks from the Division of Biometrics II.

1.2 Findings

Based on input provided by the Division of Metabolism and Endocrinology Products (DMEP), the safety endpoints evaluated in this review are:

- MACE;
- Bladder cancer;
- Amputation.

There were no statistical concerns on the design, conduct, and pre-specified analyses of the primary and other safety endpoints evaluated in this review.

Table 1 and Table 2 show a summary of the analysis results of these safety endpoints observed in DECLARE. MACE was the pre-specified primary safety endpoint in DECLARE. After accounting for the interim analyses, a one-sided alpha of 0.0231 was left for the final hypothesis testing of non-excessive CV risk, or equivalently, testing whether the upper 95.38% confidence interval (CI) was below the pre-set risk margin of 1.3 for MACE. As shown in Table 1, the estimated HR for MACE is 0.933 with a 95.38% CI of [0.843, 1.032]. Since the upper bound of the CI was below 1.3, DECLARE successfully ruled out the risk margin of 1.3 for MACE, from a statistical perspective. Consistent results were observed in sensitivity and subgroup analyses. Therefore, PMR 2121-5 was considered as fulfilled.

Table 1 Analysis of MACE in DECLARE (Full Analysis Set *)

	Dapagliflozin N = 8582	**Placebo** N = 8578	**HR (Dapa to Pbo)^** [95.38% CI‡]
MACE	756	803	
(IR / 100 PY) †	(2.30)	(2.46)	
			0.933 [0.843, 1.032]

* Full Analysis Set included all randomized subjects. Subjects were analyzed according to their randomized treatment.
^ HR: Hazard Ratio of dapagliflozin to placebo.
† IR: Incidence Rate. PY: Person Years.
‡ CI: Confidence Interval.
Source: FDA statistical reviewer

DECLARE was designed to collect sufficient number of subjects (at least 66) with any bladder cancer event to exclude a 2-fold increase in risk of bladder cancer at the nominal (unadjusted) 2-sided alpha level of 5%. As shown in Table 2, the observed HR and nominal 95% CI was 0.572 [0.353, 0.927] for bladder cancer. Given the criteria set forth in PMR 2121-6 and the adequacy of the design of DECLARE, from a statistical perspective the evidence from DECLARE is sufficient to support that dapagliflozin is not associated with a 2-fold or higher increase in risk of bladder cancer, thereby satisfying PMR 2121-6.

No formal hypothesis testing was planned or performed for amputation. The observed HR and nominal 95% CI was 1.062 [0.821, 1.373] (Table 2) for amputation. The numbers of amputation events were generally balanced between the two arms. The DECLARE trial did not observe an elevated risk associated with dapagliflozin for amputation.

Table 2 Analysis of Bladder Cancer and Amputation in DECLARE (Safety Analysis Set *)

	Dapagliflozin N = 8574	Placebo N = 8569	HR (Dapa to Pbo)^ [95% CI‡]
Bladder cancer (IR / 100 PY) †	26 (0.08)	45 (0.13)	0.572 [0.353, 0.927]
Amputation (IR / 100 PY) †	120 (0.36)	113 (0.34)	1.062 [0.821, 1.373]

* Safety Analysis Set included subjects who were randomized and treated. Subjects were analyzed according to the actual treatment they received.
^ HR: Hazard Ratio of dapagliflozin to placebo.
† IR: Incidence Rate; PY: Person Year.
‡ CI: Confidence Interval (nominal).
Source: FDA statistical reviewer

2 INTRODUCTION

2.1 Overview and Regulatory Background

Dapagliflozin (trade name: FARXIGA®) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. Dapagliflozin was first approved in the US in January 2014 (NDA 202293) for use in the treatment of T2DM in adults as an adjunct to diet and exercise.

The FDA approval letter of the original application stated the following post-marketing requirements:

> *There have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus and available data have not definitively excluded the potential for this serious risk with Farxiga (dapagliflozin). As such, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Farxiga (dapagliflozin).*
>
> *Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:*
>
> *2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the*

2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than 1.3. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and bladder cancer, complicated genital infections, complicated urinary tract infections/pyelonoephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.

The timetable you submitted on December 20, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: submitted May 9, 2013
Trial Completion: June 2019
Final Report Submission: June 2020

2121-6 To assess the risk of bladder cancer associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of 2.0 for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.

The timetable you submitted on December 20, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: January 2015
Trial Completion: June 2024
Final Report Submission: December 2024

PMR 2121-5 required the applicant to conduct a separate post-marketing trial to demonstrate non-excessive risk of dapagliflozin versus placebo for MACE with a pre-specified risk margin of 1.3 and DECLARE was designed to fulfill this requirement. In the original dapagliflozin clinical development program there was an imbalance in bladder cancer events between dapagliflozin and comparator. PMRs 2121-5 and 2121-6 also required the applicant to further evaluate the safety signal of bladder cancer.

In 2015-2016, amputation was identified as a potential safety concern for SGLT2 inhibitors, following reports of a higher risk for amputation from another drug in the same class. Subsequently, electronic case report form (eCRF) pages were implemented to capture additional details regarding all potential amputation events occurring during the study. Retrospective reviews of potential amputation events were conducted by the applicant to ensure events were captured throughout the trial.

This review of DECLARE involved several submissions by AstraZeneca for FARXIGA® (dapagliflozin) under NDA 202293 Supplement 18 on December 18, 2018. It is also cross-referenced to NDA 205649, XIGDUO® XR (dapagliflozin and metformin) Extended Release.

2.2 Data Sources

The applicant submitted the clinical study report (CSR) and analysis datasets for NDA 202293 Supplement 18 on December 18, 2018. The format, content and documentation of the datasets were adequate for the statistical reviewer to conduct a statistical evaluation of the safety endpoints in this review. The application package was submitted under five separate electronic Common Technical Document (eCTD) sequence numbers and the Electronic Document Room (EDR) links to this submission are listed below:

EDR Locations:

\\CDSESUB1\evsprod\NDA202293\0457 (Adjudication packages, submitted on 11/16/2018)
\\CDSESUB1\evsprod\NDA202293\0458 (Case Report Forms, submitted on 11/27/2018)
\\CDSESUB1\evsprod\NDA202293\0459 (Analysis and tabulation data, submitted on 12/1/2018)
\\CDSESUB1\evsprod\NDA202293\0460 (Office of Scientific Investigation listings, submitted on 12/12/2018)
\\CDSESUB1\evsprod\NDA202293\0461 (CSR, submitted on 12/18/2018)

The following datasets and define files were used to conduct the analyses in this review:

(Subject level data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adsl.xpt

(Time to adjudicated safety event data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adsftte.xpt

(Time to adjudicated efficacy event data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adeftte.xpt

(Time to adverse event data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adaette.xpt

(Time to status event data, including discontinuation and disposition events)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adsttte.xpt

(Lab data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adlb.xpt

(Lab data, in conventional units)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adlb2.xpt

(Adverse event data)
\\CDSESUB1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\adae.xpt

(Adjudicated event data)
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(Define file)
\\cdsesub1\evsprod\NDA202293\0459\m5\datasets\d1693c00001-declare\analysis\adam\datasets\define.xml

3 STATISTICAL EVALUATION

This statistical review evaluates the safety endpoints of MACE, bladder cancer and amputation of trial DECLARE submitted under NDA 202293 Supplement 18 by AstraZeneca.

3.1 Data and Analysis Quality

Data and reports for this trial were submitted electronically. The reviewer was able to perform the analyses in the review and reproduce the safety findings included in the study report using the submitted electronic data files. No major data quality issue was identified during the review.

3.2 Evaluation of Efficacy

For a statistical evaluation of efficacy in DECLARE (NDA 202293 S18), the reader is referred to the review authored by Dr. Susie Sinks of Division of Biometrics II.

3.3 Evaluation of Safety

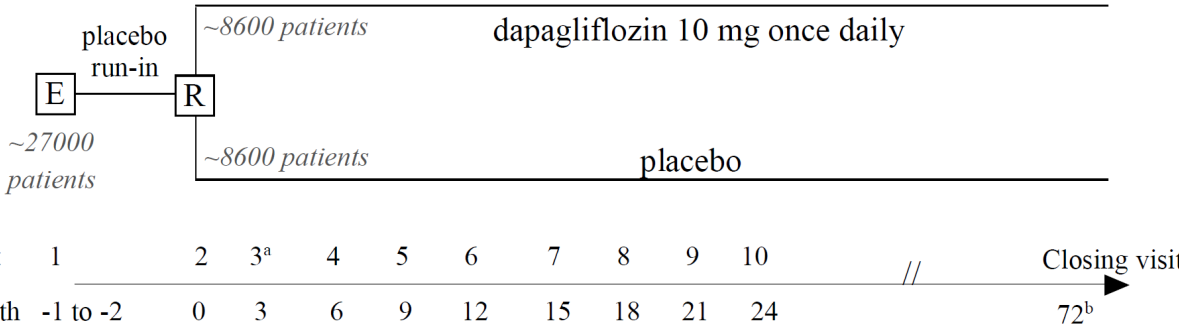
3.3.1 Study Design and Endpoints

3.3.1.1 Study Design

DECLARE is a multicenter, randomized, double-blind, placebo-controlled, Phase 3b/4, event-driven cardiovascular outcomes trial to evaluate the effect of dapagliflozin relative to placebo on

CV risk when added to current background therapy in subjects with T2DM and with either known CV disease or at least two risk factors for CV disease in addition to T2DM. The trial was to accrue at least 1390 subjects with adjudicated MACE events. The trial schematic is shown in Figure 1.

Figure 1 Trial Schematic, DECLARE



E = Enrolment, R = Randomisation

[a] Visit 3 and every other visit thereafter (ie, Visit 3, 5, 7 etc) were conducted by phone contact, with the option to do a site visit instead if requested by the patient.

[b] The study was event-driven. The enrolment period lasted for approximately 2 years and the follow-up period for approximately 3 to 5 years.

Source: CSR by the applicant, Page 20

Randomization was stratified by CV risk category (2 levels: established CV disease; multiple risk factors without established CV disease) and hematuria status (2 levels: positive and negative). Subjects were randomized using fixed block size into one of 4 randomization groups corresponding to these stratification factors.

Reviewer's Comment: *1550 subjects (780 in the dapagliflozin arm and 770 in the placebo arm) were assigned randomization codes according to incorrect entry of baseline stratification factors. The applicant did not explain the reason for the incorrect entry of baseline stratification factors. Sensitivity analyses using derived baseline stratification variables did not show an impact on the primary analysis results.*

Subjects were to return to the site every 6 months for clinical assessment. Assessment of treatment compliance was also performed at these 6-month visits. In addition, phone contacts were performed at a 3-month interval in between regular visits. All randomized subjects, whether taking randomized study drug or not, were followed up to the end of the study for vital status, CV events and occurrence of cancer.

The statistical design was based on demonstrating non-excessive risk (i.e. non-inferiority) of MACE in dapagliflozin compared to placebo. It was estimated that approximately 1390 subjects with adjudicated MACE events from a total of 17150 randomized subjects would be needed to rule out a hazard ratio larger than 1.3 associated with dapagliflozin with a one-sided alpha of 0.0231 and >99% statistical power, under the assumptions of a true hazard ratio of 1.0 and an annual event rate of 2.1% on placebo and an annual study withdrawal rate of 1.0% over 3-year accrual period

and 3-year minimum follow-up. If non-excessive risk was concluded, this sample size was also to be designed to provide 85% statistical power to demonstrate superiority (HR < 1.0) for MACE with a one-sided alpha of 0.0231, assuming a true HR of 0.85.

Reviewer's Comment: *The one-sided alpha of 0.0231 in the final analysis accounted for two planned interim analyses to preserve the overall one-sided alpha level at 0.025, using the O'Brien-Fleming alpha spending rule. See the Interim Analyses section for more details.*

3.3.1.2 Study Endpoints

Based on the input provided by DMEP, the safety endpoints evaluated in this review are:

- MACE
- Bladder cancer
- Amputation

MACE

MACE was the primary safety endpoint of DECLARE, which was a composite endpoint of CV death, MI, or ischemic stroke.

Bladder Cancer

Bladder cancer was prospectively collected in DECLARE. All possible malignancies (excluding non-melanoma skin cancer) were reported by the site into a malignancy specific form in the eCRF in addition to the serious adverse events (SAE) form. All confirmed events of bladder cancer should lead to the discontinuation of investigational product.

Amputation

Events related to amputation were reported as adverse events (AE) or SAE, and details regarding the amputation procedure were captured in a specific eCRF. The amputation events analyzed in this review included those with reported terms of "Surgical amputation" or "Spontaneous/non-surgical amputation", excluding "Trauma by accident". The eCRF page for amputation is available in Appendix 5.4.

Amputation events were initially collected prospectively for planned exploratory efficacy analyses. While the trial was ongoing, following the report of a higher risk for amputation from another drug in the same class, eCRF pages were implemented to capture additional details regarding all potential amputation events, and retrospective reviews of potential amputation events were conducted to ensure events throughout the trial were captured.

3.3.1.3 Adjudication of Study Endpoints

An independent, blinded Clinical Event Adjudication Committee (CEC) was appointed by the Thrombolysis in Myocardial Infarction (TIMI) Study Group and approved by the applicant. All components of MACE and bladder cancer were adjudicated by the CEC. The amputation endpoint was not adjudicated by the CEC.

3.3.2 Statistical Methods

The primary safety objective of trial DECLARE was to compare dapagliflozin versus placebo on the incidence of composite endpoint MACE, consisting of CV death, MI and ischemic stroke. As shown in Figure 2, the first step of the confirmatory testing procedure was to test non-excessive risk (i.e., non-inferiority) for MACE (H1), which is the focus of this review. Hypotheses that follow H1 in the hierarchy (H02, H03, H04, H05) are related to efficacy/superiority claims and are not within the scope of this review.

Reviewer's Comment: *Note that bladder cancer and amputation were not listed as part of the confirmatory testing procedure and no alpha was allocated for formal hypothesis testing of these two endpoints.*

Figure 2 Confirmatory Testing Procedure of DECLARE

<table>
<tr><td colspan="2">H1: Non-inferiority for MACE (α=0.0231)[a]</td></tr>
<tr><td colspan="2">The α splits into independent testing of the primary composites in parallel:</td></tr>
<tr><td>H02: Superiority for MACE (α=50% of primary α)[b]</td><td>H03: Superiority for hospitalisation for heart failure or CV death (α=50% of primary α)[b]</td></tr>
<tr><td colspan="2">H04: Superiority for renal composite endpoint: Confirmed sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESRD (dialysis ≥90 days or kidney transplantation, confirmed sustained eGFR <15 mL/min/1.73 m^2) and/or renal or CV death[c]</td></tr>
<tr><td colspan="2">H05: Superiority for all-cause mortality[d]</td></tr>
</table>

[a] At the interim analyses, the α for superiority was replaced by 0.000095 (first interim) and 0.00614 (second interim), and no testing for non-inferiority was performed.

[b] The α was 0.01155 (50% of 0.0231) for superiority for MACE and 0.01155 (50% of 0.0231) for superiority for hospitalisation for heart failure or CV death.

[c] With the exception of all-cause mortality, secondary endpoints were only tested once. The α was controlled for the overall Type I error across the primary and secondary variables and across the interims and final analysis.

[d] All-cause mortality was assessed at interim analyses as part of the stopping guidelines. At the interim analyses, it was tested second following MACE. If the study had been stopped following an interim analysis, all-cause mortality would have remained as the 2nd endpoint following the test for superiority of MACE. Because the study ran to completion, all-cause mortality was tested as presented in this table.

CV Cardiovascular; eGFR Estimated glomerular filtration rate; ESRD End-stage renal disease; H Hypothesis; MACE Major adverse cardiovascular events

Source: Applicant's CSR, Page 40

3.3.2.1 Statistical Hypothesis

For the primary safety endpoint MACE, the following hypothesis of non-excessive risk for dapagliflozin versus placebo was to be tested against the pre-specified risk margin of 1.3:

$$H1_{null}: HR \geqslant 1.3 \text{ vs. } H1_{alternative}: HR < 1.3.$$

Non-excessive CV risk is demonstrated when the null hypothesis $H1_{null}$ can be rejected at an overall one-sided alpha level of 0.025. After adjusting for two planned interim analyses, an alpha of 0.0231 was left for the final testing of non-excessive risk. If the upper 95.38% confidence interval of the estimated HR is less than 1.3, then $H1_{null}$ is rejected and non-excessive risk is demonstrated.

For the safety endpoint bladder cancer, the following hypothesis of non-excessive risk for dapagliflozin versus placebo was to be tested against the pre-specified risk margin of 2.0:

$$H2_{null}: HR \geqslant 2.0 \text{ vs. } H2_{alternative}: HR < 2.0.$$

Non-excessive risk in bladder cancer is demonstrated when the upper bound of the 95% CI is less than 2.0. No multiplicity adjustment was planned or performed for the testing of bladder cancer.

3.3.2.2 Interim Analyses

Two formal interim analyses of MACE were planned and performed by an independent Data Monitoring Committee (DMC), which was appointed jointly by the TIMI Study Group, Hadassah Medical Center and the applicant. These two interim analyses took place when 1/3 and 2/3 of the planned total of 1390 subjects with MACE events had been observed in the trial respectively. The first interim analysis used a one-sided α level of 0.00095 and the second interim analysis used a one-sided α level of 0.00614. According to the O'Brien-Fleming alpha-spending rule, a one-sided alpha level of 0.0231 was left for the final analysis. At each interim analysis, superiority of MACE was tested at the specified alpha level, and if statistically significant, superiority of all-cause mortality was to be tested at the same alpha level. If superiority was achieved for both endpoints, the DMC was to evaluate the CV and other safety data, including bladder cancers and liver events, to determine if the benefit of dapagliflozin treatment was unequivocal and overwhelming and thereby justified a recommendation to stop the study early. The DMC recommended for the trial to continue as planned following both interim analyses. No ad-hoc interim analyses for efficacy took place.

Interim monitoring for bladder cancers was conducted regularly to be able to communicate potential signals with regulatory authorities. Interim analyses for bladder cancer took place after 8, 16, 24, and 32 events and additional analyses could occur at the discretion of the DMC. The interim analyses were assessed at an overall alpha level of 0.10 with a Pocock alpha-spending rule.

3.3.2.3 Analysis Populations

The following analysis populations were prospectively defined in the statistical analysis plan (SAP):

Full Analysis Set (FAS): The FAS population included all randomized subjects. Subjects were analyzed according to their randomized assignment. All events observed until the end of the study were included for analysis. FAS is the primary analysis population for MACE.

Safety Analysis Set (SAS): The SAS population included all randomized and treated subjects who had data observed at any time after first randomized dose till the end of the study. Subjects were analyzed according to the actual treatment they received. 17 subjects (dapagliflozin: 8; placebo: 9) who were randomized but did not receive study drug were excluded from SAS but included in FAS. All events observed until the end of the study are included for analysis. SAS is the primary analysis population for bladder cancer and amputation.

***Reviewer's Comment**: The censoring scheme defined above for FAS and SAS is equivalent to an "on-study" censoring scheme for event ascertainment:*

- *Events that occurred by the date of the last visit or study contact (where a clinical event assessment was performed) for each individual subject were included in the analysis, irrespective of treatment exposure;*
- *Subjects who had not experienced the event of interest were censored on the date of the last clinical assessment in the study.*

On-Treatment Safety Analysis Set (OT-SAS): The OT-SAS population consisted of the same subjects as SAS, but only events occurring within 30 days after the end of treatment were included for analysis. OT-SAS is the sensitivity analysis population for MACE, bladder cancer and amputation.

***Reviewer's Comment**: The censoring scheme defined above for OT-SAS is equivalent to an "on-treatment + 30 days" censoring scheme for event ascertainment:*

- *Events that occurred while the subject was on study treatment or within 30 days after the last date of treatment were included in the analysis;*
- *Subjects who had not experienced the event of interest were censored on the last date of treatment + 30 days, or the end of the study, whichever is earlier.*

3.3.2.4 Analysis Methods for MACE

The primary analysis of time to first adjudicated event of the composite endpoint MACE was evaluated through a Cox proportional hazards model with the only covariate for randomized treatment group (dapagliflozin or placebo) stratified by the two randomization stratification factors: CV risk category (established CV disease or multiple risk factors without established CV disease) and baseline hematuria (positive or negative). The primary analysis was conducted on the FAS population. If the upper bound of the 95.38% confidence interval for the estimated hazard ratio of time to first MACE event for subjects in the dapagliflozin group relative to subjects in the placebo group is less than 1.3, then non-excessive CV risk was concluded.

***Reviewer's Comment**: The submitted datasets contained two sets of variables for baseline CV risk category and hematuria status: cvrgr1/bhemgr1 and cvrgr2/bhemgr2. The second set of variables (cvrgr2/bhemgr2) was used in the primary, secondary and subgroup analysis models for baseline hazard stratification, because it was used for randomization. However, the applicant indicated that 1550 subjects (dapagliflozin: 780; placebo: 770) had protocol violations of being assigned randomization code according to incorrect baseline stratification factors, i.e. cvrgr2/bhemgr2. The first set of variables (cvrgr1/bhemgr1) was derived using available medical history (MH) and laboratory (LB) data, according to definitions in Appendix 5.1 and was used for sensitivity analysis to evaluate the impact of the protocol violations during randomization and for subgroup analysis to define the subgroups of baseline CV risk category and hematuria status.*

Using the same statistical model as the primary analysis, exploratory time-to-first-event analyses were performed for individual components of the MACE composite endpoint, including:

- CV death
- MI (fatal and non-fatal)
- Ischemic stroke (fatal and non-fatal)

For the analyses of each component of MACE, subjects were censored on the date when last known to be free of that specific component of interest, regardless of occurrence(s) of other components of MACE.

To evaluate the effects of potential differential treatment discontinuation, on-treatment analyses were performed for the primary endpoint MACE by including only events that occurred within 30 days after the end of treatment using the OT-SAS population. The hazard ratio and associated 95.38% confidence interval were calculated using the same Cox model as the primary analysis.

To evaluate the effects of randomization according to incorrect baseline stratification factors (baseline CV risk category and hematuria), sensitivity analyses of MACE were performed using stratification factors derived from medical history and laboratory data, and without using any stratification variables in the Cox models.

3.3.2.5 Analysis Methods for Bladder Cancer and Amputation

Bladder cancer and amputation were analyzed using Cox proportional hazards models with actual treatment as the only covariate and stratified by baseline CV risk category and hematuria (randomization stratification factors), including all events observed during the study in the SAS population. Estimated HRs, nominal 95% CIs and Kaplan-Meier (K-M) curves were presented.

3.3.3 Results

3.3.3.1 Demographic and Baseline Characteristics

In DECLARE, 25698 subjects were enrolled from 8821 sites in 33 countries and 17160 randomized subjects were included in the primary analysis (FAS), and 16906 (98.5%) subjects completed the study.

Table 3 Disposition and Exposure

	Dapagliflozin	Placebo	Total
Enrolled	-	-	25698
Randomized (FAS)	8582	8578	17160
Treated (SAS)	8574	8569	17143
Completed study*	8473	8433	16906
Discontinued drug prematurely	1807	2144	3951

* Subjects were considered to have completed the study if they did not withdraw consent and were not lost to follow-up. (variable *complfl* in adsl.xpt)
Source: Created by FDA statistical reviewer using adsl.xpt, adds.xpt and adsttte.xpt

As shown in Table 4, the median study follow-up (dapagliflozin: 4.1 years; placebo: 4.1 years) and median treatment exposure (dapagliflozin: 4.0 years; placebo: 3.9 years) were similar between the two arms. There were more subjects in the placebo arm who discontinued treatment early, compared to the dapagliflozin arm (dapagliflozin: 1807; placebo: 2144). The most common reason of premature permanent discontinuation of study drug was "subject decision".

Table 4 Study Follow-Up and Treatment Exposure (FAS)

	Dapagliflozin N = 8582	Placebo N = 8578
Total study follow-up* (years)	34346	34201
Median study follow-up (years)	4.1	4.1
Total treatment exposure† (years)	30108	29319
Median treatment exposure (years)	4.0	3.9
Did not complete study (%)	109 (1.3)	145 (1.7)
Consent withdrawn **(%)**	97 (1.1)	127 (1.5)
Lost to follow-up **(%)**	12 (0.1)	18 (0.2)
Premature discontinuation of study drug (%)	1807 (21.1)	2144 (25.0)
Subject decision **(%)**	825 (9.6)	1086 (12.7)
Adverse events **(%)**	671 (7.8)	548 (6.4)
Development of discontinuation criteria **(%)**	38 (0.4)	60 (0.7)
Other reasons **(%)**	273 (3.2)	450 (5.2)

* Calculated using *lastdt – randdt* + 1 in the adsl dataset
† Calculated using *trtedt – trtsdt* + 1 in the adsl dataset
Source: Created by FDA statistical reviewer using adds.xpt and adsl.xpt.

Table 5 shows the demographic and baseline characteristics of subjects in the FAS population by randomized treatment. Sex, age, race, baseline CV status and baseline hematuria, summarized in

this table, were balanced between the two arms. Approximately 37% of the subjects in the trial were female. The mean age at baseline was 63.8 years, and approximately 78% of the subjects were classified as White.

Reviewer's Comment: *The applicant-derived variable cvrgr1 (from ecvdfl) labeled subjects without a history of established CV disease in the medical history dataset (MH) as "MULTIPLE RISK FACTORS". According to Table 8 in the applicant's CSR, there were 27 subjects who did not have established CV disease and had less than 2 risk factors. Therefore, the value of cvrgr1 may not accurately reflect the baseline CV status for FAS subjects.*

Table 5 Demographics and Baseline Characteristics (FAS)

	Dapagliflozin	Placebo
	N = 8582	N = 8578
Female (%)	3171 (36.9)	3251 (37.9)
Age (years)		
Mean	63.8	63.9
< 65 (%)	4631 (54.0)	4622 (53.9)
Race		
White (%)	6843 (79.7)	6810 (79.4)
Asian (%)	1148 (13.4)	1155 (13.5)
Others (%)	591 (6.9)	613 (7.1)
Established CV disease at baseline*		
Yes (%)	3474 (40.5)	3500 (40.8)
No (%)	5108 (59.5)	5078 (59.2)
Hematuria at baseline†		
Positive (%)	1230 (14.3)	1222 (14.2)
Negative (%)	7160 (83.4)	7167 (83.6)
Missing (%)	192 (2.2)	189 (2.2)

* Using the variable *ecvdfl* derived from medical history (MH) data. "No" means no medical history record of established CV disease, including those who might potentially have missing records.
† Using the variable *bhemgr1* derived from laboratory (LB) data.
Source: Created by FDA statistical reviewer using dataset adtte.xpt and adsl.xpt.

3.3.3.2 Analysis Results of the Primary Endpoint MACE

3.3.3.2.1 Primary Analysis of MACE

Table 6 shows the results of the pre-specified primary analysis of the composite endpoint of MACE. The incidence rate of subjects who experienced any event in the MACE composite endpoint during the study period was 2.30 per 100 patient years (PY) in the dapagliflozin arm and

2.46 per 100 PY in the placebo arm. The estimated hazard ratio associated with dapagliflozin was 0.933. The upper bound of the 95.38% CI of the HR was 1.032, which was less than the pre-specified risk margin of 1.3. Therefore, the primary analysis results have ruled out a risk of MACE associated with dapagliflozin being larger than 1.3 relative to placebo.

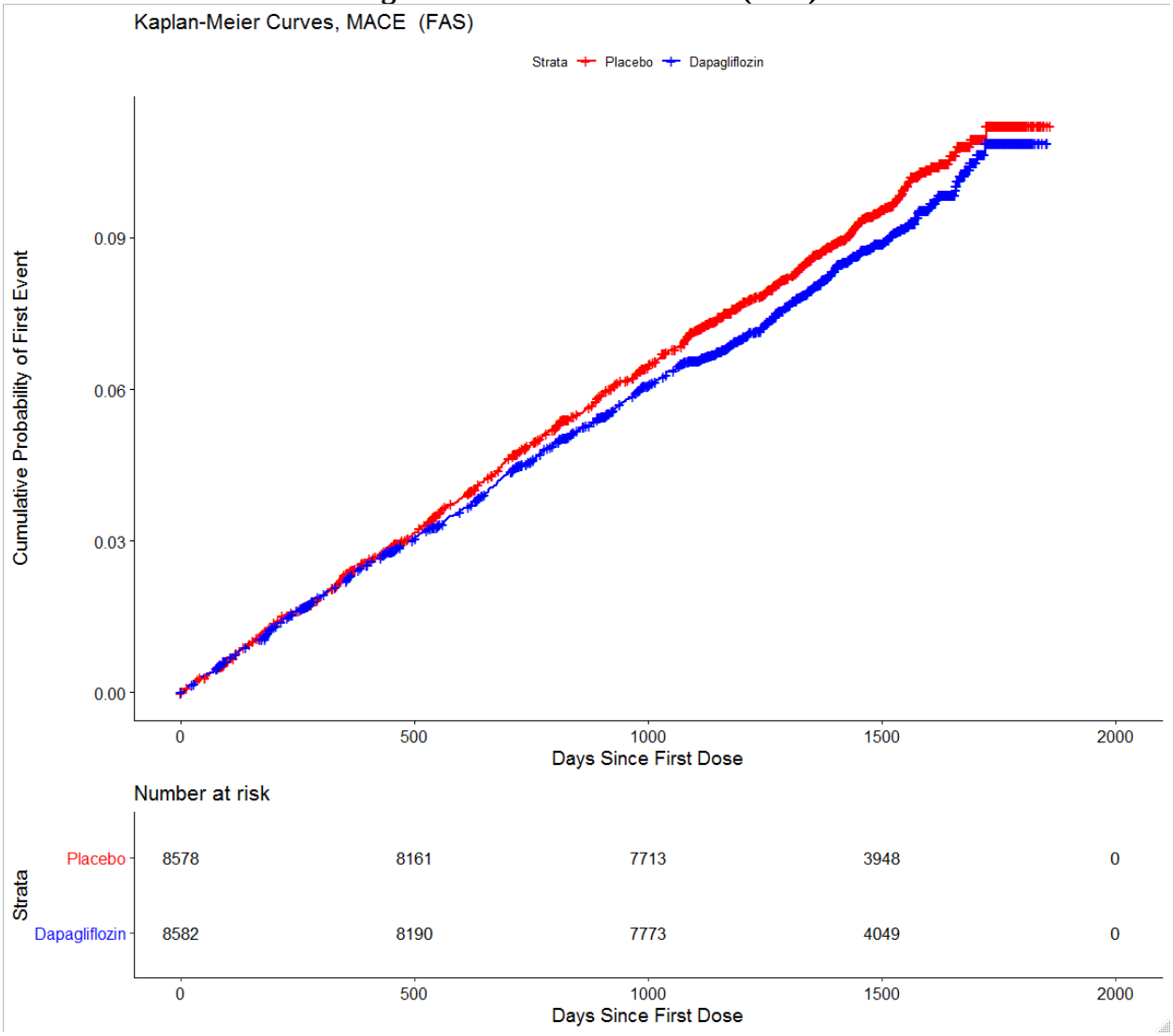
Table 6 Primary Analysis for MACE (FAS)

	Dapagliflozin N=8582	**Placebo** N=8578
# of Subjects (IR *per 100PY*) *	756 (2.30)	803 (2.46)
HR† [95.38% CI]	0.933 [0.843, 1.032]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first MACE event using a Cox proportional hazards model with randomized treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the FAS population.
Source: FDA statistical reviewer using adeftte.xpt

The Kaplan-Meier (K-M) curves by randomized treatment arm are shown in Figure 3. The K-M curve for dapagliflozin started to separate from the K-M curve for placebo around Day 500, but the observed difference was small between the two arms. The confidence bands of the K-M curves for the two arms overlapped throughout the duration of the trial (a K-M plot for MACE with confidence bands is available in Appendix 5.2).

Figure 3 K-M Plot for MACE (FAS)



Source: FDA statistical reviewer using dataset adeftte.xpt

3.3.3.2.2 Individual Components of MACE

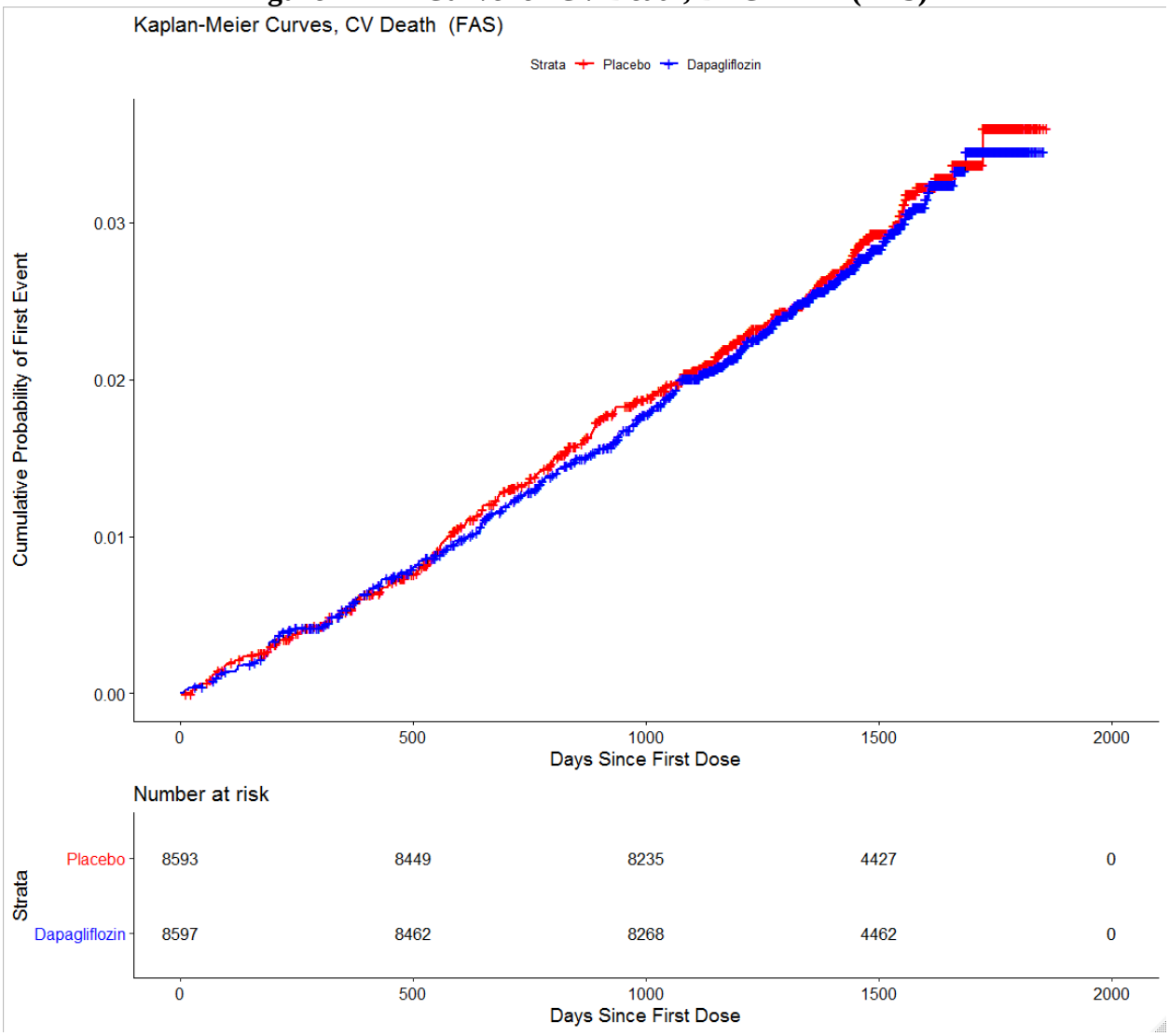
Time-to-first-event analyses were performed for individual components of MACE, including CV death, MI (fatal and non-fatal) and ischemic stroke (fatal and non-fatal). The results were generally consistent with the primary analysis, with all the upper 95% CIs of the estimated HRs being less than 1.3. The estimated HRs were close to 1 for CV death (0.981 [0.822, 1.170]) (Table 7) and ischemic stroke (1.010 [0.842, 1.211]) (Table 9). The estimated HR was numerically lower than 1 for MI (0.886 [0.773, 1.015]) (Table 8), although the nominal 95% CI did not exclude 1. The K-M curves of the two arms for MI started to separate from around Day 500, as shown in Figure 5.

Table 7 Time-to-Event Analysis, CV Death (FAS)

	Dapagliflozin N=8582	**Placebo** N=8578
# of Subjects (IR *per 100PY*) *	245 (0.71)	249 (0.72)
HR† [95% CI]	0.981 [0.822, 1.170]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with randomized treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the FAS population.
Source: FDA statistical reviewer using adeftte.xpt

Figure 4 K-M Curve for CV Death, DECLARE (FAS)



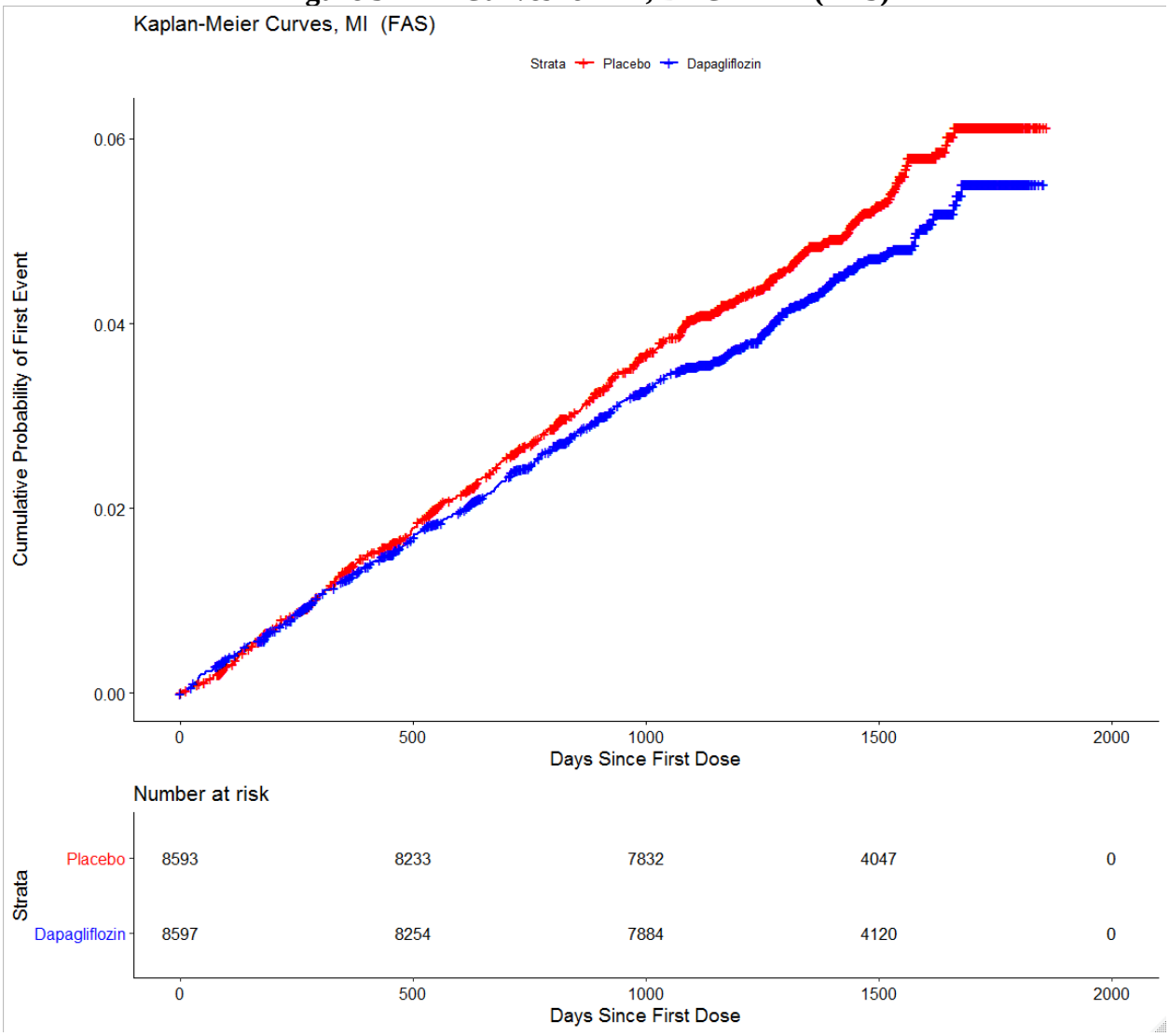
Source: FDA statistical reviewer using adeftte.xpt

Table 8 Time-to-Event Analysis, MI (FAS)

	Dapagliflozin N=8582	**Placebo** N=8578
# of Subjects (IR *per 100PY*) *	394 (1.18)	442 (1.34)
HR† [95% CI]	0.886 [0.773, 1.015]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with randomized treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the FAS population.
Source: FDA statistical reviewer using adeftte.xpt

Figure 5 K-M Curves for MI, DECLARE (FAS)



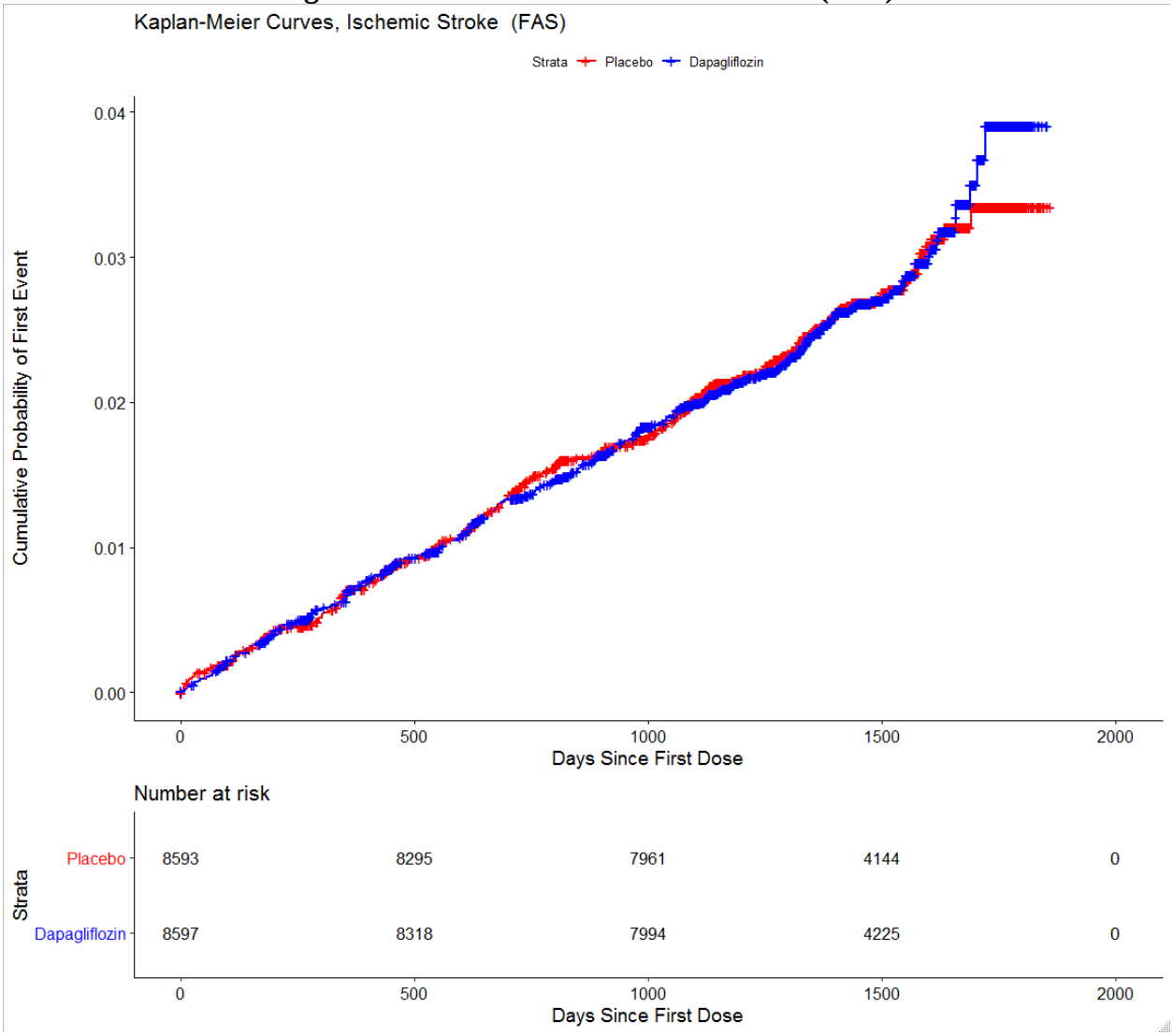
Source: FDA statistical reviewer using adeftte.xpt

Table 9 Time-to-Event Analysis, Ischemic Stroke (FAS)

	Dapagliflozin N=8582	**Placebo** N=8578
# of Subjects (IR *per 100PY*) *	235 (0.70)	231 (0.69)
HR† [95% CI]	1.010 [0.842, 1.211]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with randomized treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the FAS population.
Source: FDA statistical reviewer using adeftte.xpt

Figure 6 K-M Curves for Ischemic Stroke (FAS)



Source: FDA statistical reviewer using adeftte.xpt

3.3.3.2.3 Sensitivity Analysis of MACE: On-Treatment Analysis

An on-treatment sensitivity analysis was performed for MACE by including only events occurred within 30 days after the end of treatment for subjects who received treatment (OT-SAS). 17 subjects who were randomized but did not receive study drug were excluded from this analysis. The estimated HR was 0.928 with a 95.38% CI of [0.832, 1.035] using OT-SAS. The results were consistent with the primary analysis, as shown in Table 10.

Table 10 On-Treatment Sensitivity Analysis for MACE (OT-SAS)

	Dapagliflozin N = 8574	**Placebo** N = 8569
# of Subjects (IR *per 100PY*) *	653 (2.21)	682 (2.38)
HR† [95.38% CI]	0.928 [0.832, 1.035]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first MACE event using a Cox proportional hazards model with actual treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the SAS population.
Source: FDA statistical reviewer using adeftte.xpt

3.3.3.2.4 Sensitivity Analysis of MACE: Analyses using Different Stratification Factors

As discussed in the Analysis Methods for MACE section, there were two sets of variables corresponding to baseline CV risk category and hematuria status, which were part of the primary analysis model. These analyses were intended to evaluate the potential impact of the stratification factors on the primary analysis. As shown in Table 11, the results were consistent with the primary analysis using different stratification factors in the model.

Table 11 Sensitivity Analyses for MACE using Different Stratification Factors (FAS)

	HR [95.38% CI]
Model with randomization stratification factors* (primary analysis)	0.928 [0.832, 1.035]
Model with no stratification	0.934 [0.844, 1.034]
Model with derived stratification factors†	0.937 [0.848, 1.034]

* *cvrgr2*/*bhemgr2*, stratification factors used for randomization.
† *cvrgr1*/*bhemgr1*, derived from medical history (MH) and laboratory (LB) datasets. See Appendix 5.1 for derivation method.
Source: FDA statistical reviewer using adeftte.xpt, lb.xpt, mh.xpt, adsl.xpt

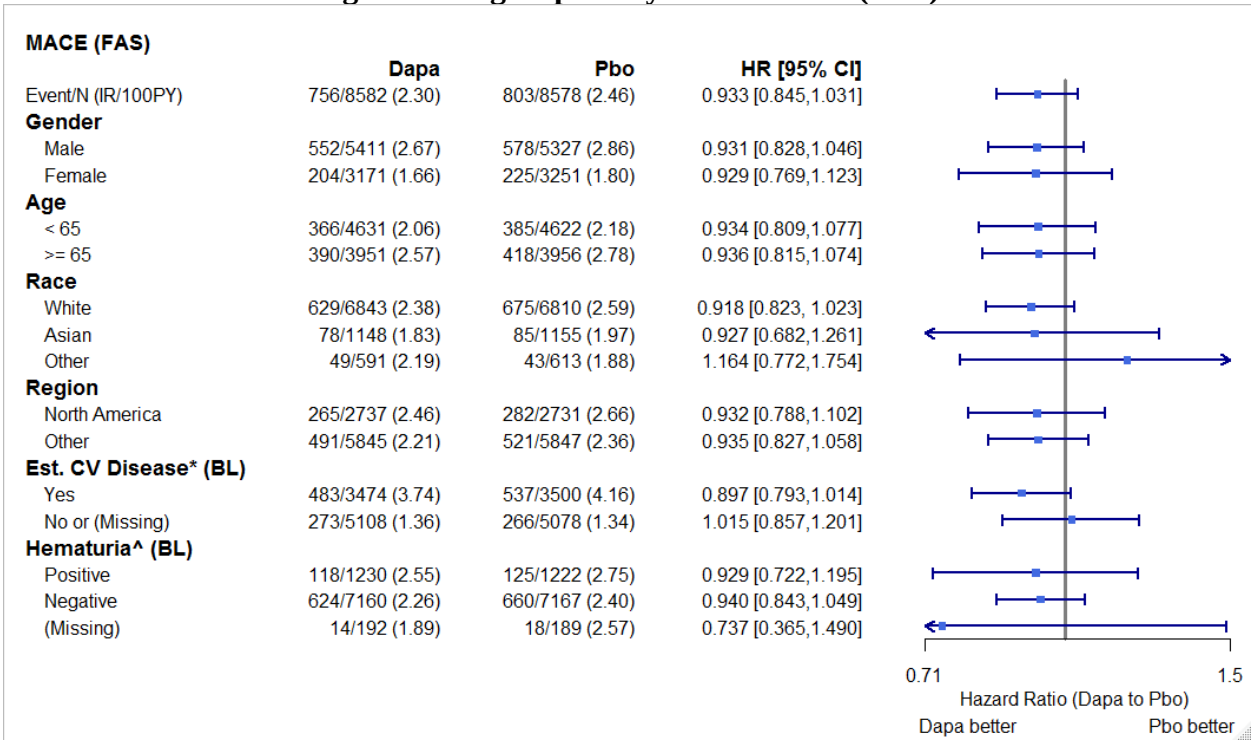
Reviewer's comment: *The applicant also performed a sensitivity analysis using multiple imputation to evaluate the impact of missing follow-up on the analysis results of MACE (see "Response to Food and Drug Administration Information Request Dated 14 August 2019"). The*

estimated HR and 95% CI (0.94 [0.85, 1.03]), with imputed time to event information for subjects without complete follow-up, were consistent with the primary analysis results.

3.3.3.2.5 Subgroup Analyses of MACE

This section discusses subgroup analyses for the primary endpoint of MACE. The Cox proportional hazards models used in subgroup analyses were the same as the primary analysis model. These subgroup analyses were conducted post-hoc and considered exploratory. The forest plot in Figure 7 shows analyses of MACE by subgroups defined by gender, age, race, region, established CV disease at baseline (Y/N) and hematuria status at baseline (positive/negative). No statistically significant interaction was observed between any of these subgroups and dapagliflozin on the risk of MACE. None of the confidence intervals excluded 1 and most of the point estimates were close to or below 1. The highest point estimate was from the race of "other", where there were relatively few events and the confidence interval was wide. The observations in subgroups for MACE were generally consistent with the primary analysis.

Figure 7 Subgroup Analysis for MACE (FAS)



* The variable *ecvdfl* derived from medical history (MH) dataset was used to define the subgroups of Established CV Disease (Baseline).

^ The variable *bhemgr1* derived from laboratory (LB) dataset was used to define the Hematuria Status (Baseline) subgroups.

Source: FDA statistical reviewer using adeftte.xpt and adsl.xpt

3.3.3.3 Analysis Results of Bladder Cancer

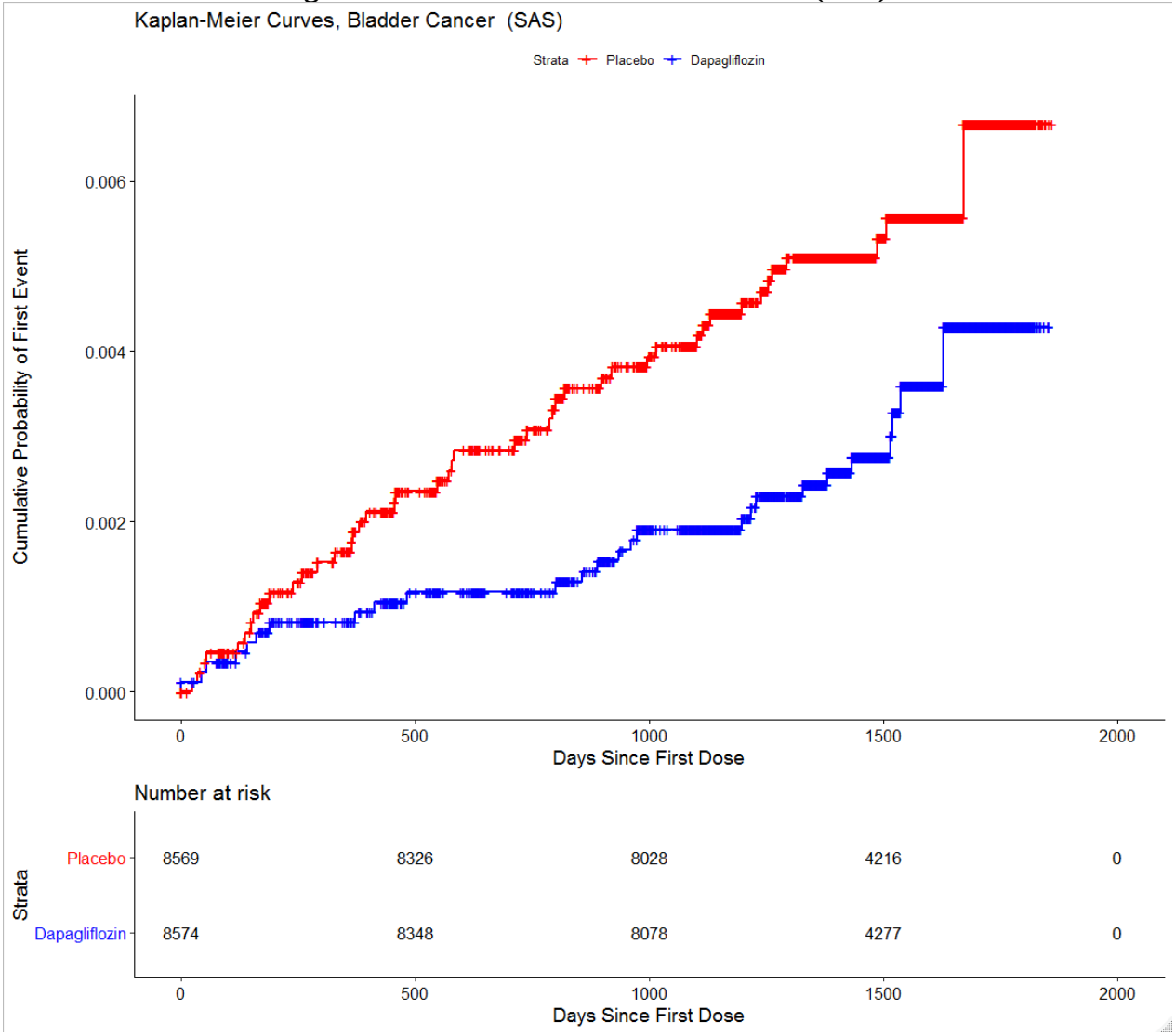
The analysis of bladder cancer in DECLARE did not show an increase of bladder cancer risk associated with dapagliflozin. The estimated HR was 0.574 with a nominal 95% CI of [0.354, 0.931] which was below the pre-specified risk margin of 2.0 for bladder cancer (Table 12). The observed incidence rate of bladder cancer was numerically lower in the dapagliflozin arm (0.08 per 100 PY) than in placebo (0.13 per 100 PY).

Table 12 Time-to-Event Analysis, Bladder Cancer (SAS)

	Dapagliflozin N = 8574	**Placebo** N = 8569
# of Subjects (IR *per 100PY*) *	26 (0.08)	45 (0.13)
HR† [95% CI]	0.574 [0.354, 0.931]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with actual treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the SAS population.
Source: FDA statistical reviewer using adsftte.xpt

Figure 7 K-M Curves for Bladder Cancer (SAS)



Source: FDA statistical reviewer using adsftte.xpt

3.3.3.4 Analysis Results of Amputation

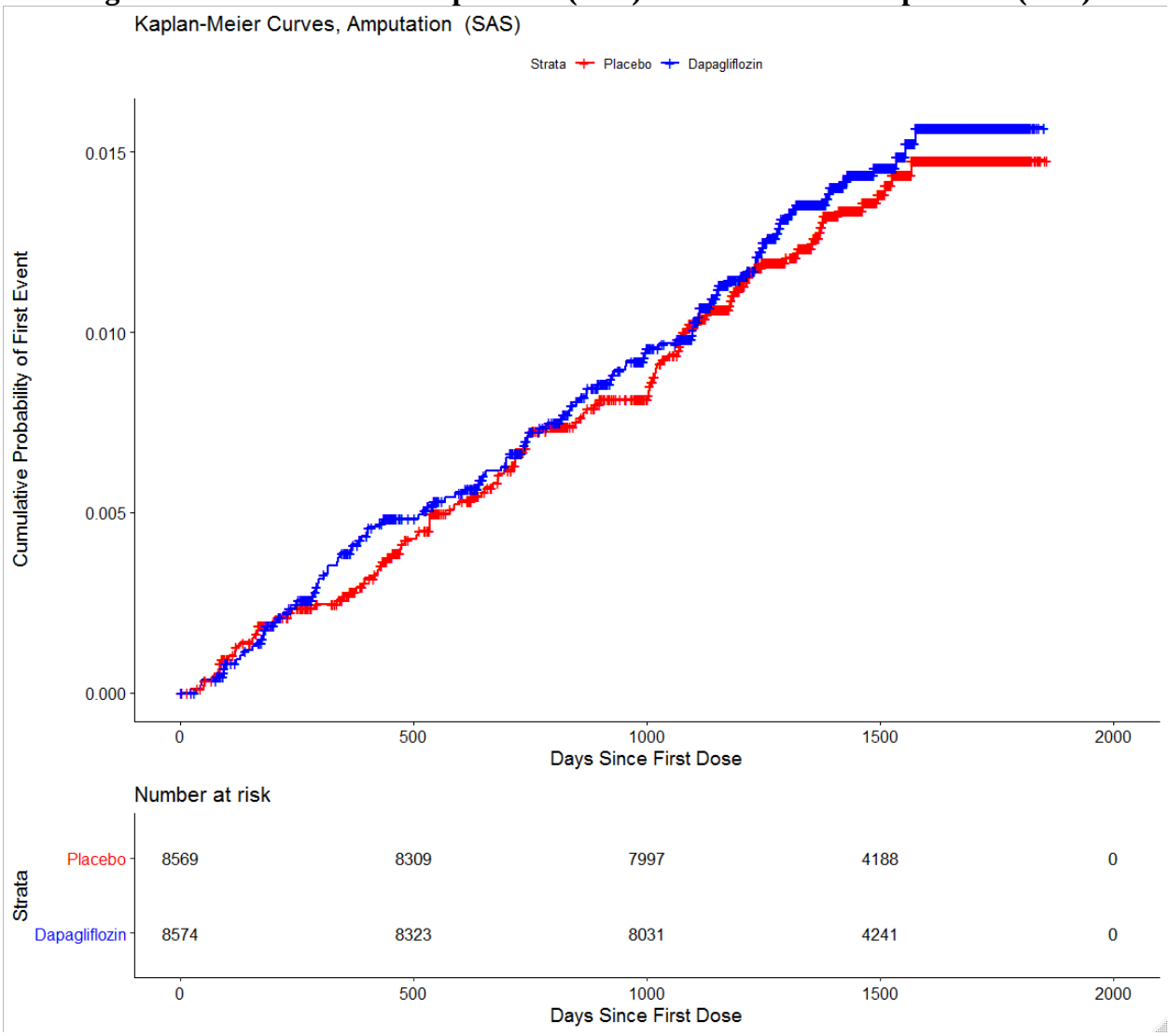
The analysis of amputation in DECLARE did not show evidence of increased risk of amputation associated with dapagliflozin. The IRs of amputation were similar between the two arms (dapagliflozin: 0.36/100PY; placebo: 0.34/100PY). The estimated HR was 1.059 with a nominal 95% CI of [0.819, 1.369].

Table 13 Time-to-Event Analysis for Amputation (SAS)

	Dapagliflozin N = 8574	Placebo N = 8569
# of Subjects (IR *per 100PY*) *	120 (0.36)	113 (0.34)
HR† [95% CI]	1.059 [0.819, 1.369]	-

* IR: Incidence Rate, with the denominator calculated as the period from randomization date until the date of the event or the date of subject being censored. PY: Person Year.
† HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with actual treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the SAS population.
Source: FDA statistical reviewer using adsftte.xpt

Figure 8 K-M Curves for Amputation (SAS)K-M Curves for Amputation (SAS)



Source: FDA reviewer using adsftte.xpt

4 SUMMARY AND CONCLUSIONS

4.1 Statistical Issues

DECLARE was a CVOT designed and powered to rule out a relative excessive risk of MACE events (CV death, MI, ischemic stroke) associated with dapagliflozin compared to placebo, with a target to accrue 1390 subjects with any MACE outcomes. This trial was designed to have >99% power to rule out a pre-specified risk margin of 1.3 with a one-sided 2.5% significance level. Two interim analyses were performed and a one-sided alpha of 0.0231 was left for the final hypothesis testing of non-excessive risk for MACE

The safety endpoints of bladder cancer and amputation were also analyzed using the data from this trial. The SAP for DECLARE did not pre-specify a statistical hypothesis and an associated alpha level for testing the bladder cancer endpoint. However, PMR 2121-6 clearly stated that the objective of DECLARE should be to exclude a two-fold increase in bladder cancer risk. Determination of the appropriate alpha level to be used in such a situation is difficult given the post-hoc nature. In this review the nominal two-sided alpha level of 0.05 was used. No formal hypothesis testing was planned for amputation in the trial's protocol and statistical analysis plan. For bladder cancer and amputation, confidence intervals were presented at a nominal 95% significance level with no adjustment for multiplicity.

There were no statistical concerns on the design, conduct, and pre-specified analyses of the primary and other safety endpoints evaluated in this review. The baseline characteristics and demographics were similar between the two arms. There were more subjects who prematurely discontinued treatment in placebo (2144) than in dapagliflozin (1807), but the total/median treatment exposure and study follow-up duration were similar. The on-treatment analysis results were consistent with the primary analysis.

4.2 Collective Evidence

As summarized in Table 14, DECLARE demonstrated non-excessive risk of dapagliflozin for MACE with the upper bound of 95.38% CI (1.032) lower than the pre-specified risk margin of 1.3. The trial has ruled out an excessive risk in MACE for dapagliflozin based on the pre-specified risk margin. Sensitivity and subgroup analysis results were consistent with this conclusion.

Table 14 Analysis of MACE in DECLARE (Full Analysis Set)

	Dapagliflozin N = 8582	Placebo N = 8578	HR* [95.38% CI‡]
MACE	756	803	
(IR / 100 PY) †	(2.30)	(2.46)	
			0.933 [0.843, 1.032]

* HR: Hazard Ratio of dapagliflozin to placebo, based on an analysis of time to first event using a Cox proportional hazards model with randomized treatment as the only covariate, stratified by the randomization stratification factors of baseline CV risk (*cvrgr2*) and hematuria status (*bhemgr2*), using the FAS population.
† IR: Incidence Rate, calculated as the number of events divided by the sum of duration when subjects were observed for events (from randomization date to event or censoring date). PY: Person Year.
‡ CI: Confidence Interval. After accounting for the interim analyses, a one-sided alpha of 0.0231 was left for the final hypothesis testing, equivalent to testing whether the upper 95.38% CI was lower than the pre-specified non-inferiority margin.
Source: FDA statistical reviewer

DECLARE did not show evidence of increased risk in bladder cancer or amputation associated with dapagliflozin, as shown in Table 15. The incidence rate of bladder cancer was numerically lower in dapagliflozin arm than in placebo arm. The incidence rates were balanced between the two treatment arms for amputation.

Table 15 Analysis of Bladder Cancer and Amputation in DECLARE (Safety Analysis Set)

	Dapagliflozin N = 8574	Placebo N = 8569	HR* [95% CI‡]
Bladder cancer	26	45	
(IR / 100 PY) †	(0.08)	(0.13)	
			0.572 [0.353, 0.927]
Amputation	120	113	
(IR / 100 PY) †	(0.36)	(0.34)	
			1.062 [0.821, 1.373]

* HR: Hazard Ratio of dapagliflozin to placebo, calculated using a Cox proportional hazards model with baseline hazards stratified by baseline CV risk category (*cvrgr2*) and baseline hematuria (*bhemgr2*) used for randomization, analyzed as treated, including subjects who were randomized and treated, using the SAS population.
† IR: Incidence Rate, calculated as # of events divided by the sum of duration when subjects were observed for events (from treatment start date to event or censoring date). PY: Person Year.
‡ CI: Confidence Interval (nominal).
Source: FDA statistical reviewer

4.3 Conclusions and Recommendations

This is a statistical review of trial DECLARE, submitted by AstraZeneca, under NDA 202293 S18, to satisfy PMRs 2121-5 and 2121-6 and to assess the safety endpoints of MACE, bladder cancer and amputation associated with dapagliflozin compared to placebo.

The estimated HR for MACE was 0.933 with a 95.38% CI of [0.843, 1.032]. The upper bound of the CI was below the pre-specified risk margin of 1.3 and demonstrated dapagliflozin's non-excessive risk in MACE compared to placebo.

DECLARE was adequately designed to evaluate the risk of bladder cancer as specified in PMR 2121-6. Specifically, DECLARE prospectively collected and adjudicated bladder cancer and 71 adjudicated bladder cancers were observed. The estimated HR and nominal 95% CI associated with dapagliflozin was 0.572 [0.353, 0.927]. These data showed no evidence of increased risk of bladder cancer associated with dapagliflozin.

Given the criteria set forth in PMRs 2121-5 and 2121-6 and the adequacy of the design of DECLARE, from a statistical perspective the evidence from the DECLARE trial is sufficient to support that dapagliflozin is not associated with a (i) 30% or higher increase in MACE risk (1.3 risk margin) or (ii) 100% or higher increase in risk of bladder cancer (2.0 risk margin), thereby satisfying PMRs 2121-5 and 2121-6.

The analyses of amputation did not show evidence of an elevated risk associated with dapagliflozin, with an observed HR of 1.062 and a nominal 95% CI of [0.821, 1.373].

In conclusion, based on our review of trial DECLARE, it is our opinion that PMRs 2121-5 (MACE) and 2121-6 (bladder cancer) are successfully fulfilled from a statistical perspective. There was no evidence from DECLARE suggesting that dapagliflozin increased the risk of amputation.

5 Appendix

5.1 Derivation of Baseline CV Risk Category and Hematuria Status

ECVDFL: Established CV Disease Flag
= ‘Y’ If MH.MHTERM in ('ESTABLISHED VASCULAR DISEASE') and MH.MHOCCUR ='Y' then ECVDFL ='Y'. Otherwise ECVDFL ='N'.

CVRGR1: CV Risk Category

If ADSL.ECVDFL ='Y' then *CVRGR1* ='ESTABLISHED CV DISEASE', if ADSL.ECVDFL ne 'Y' and (ADSL.MRFFL ='Y' or (ADSL.MRFFL ='N' and RANDFL ='Y')) then CVRGR1 ='MULTIPLE RISK FACTORS', otherwise CVRGR1 =missing.

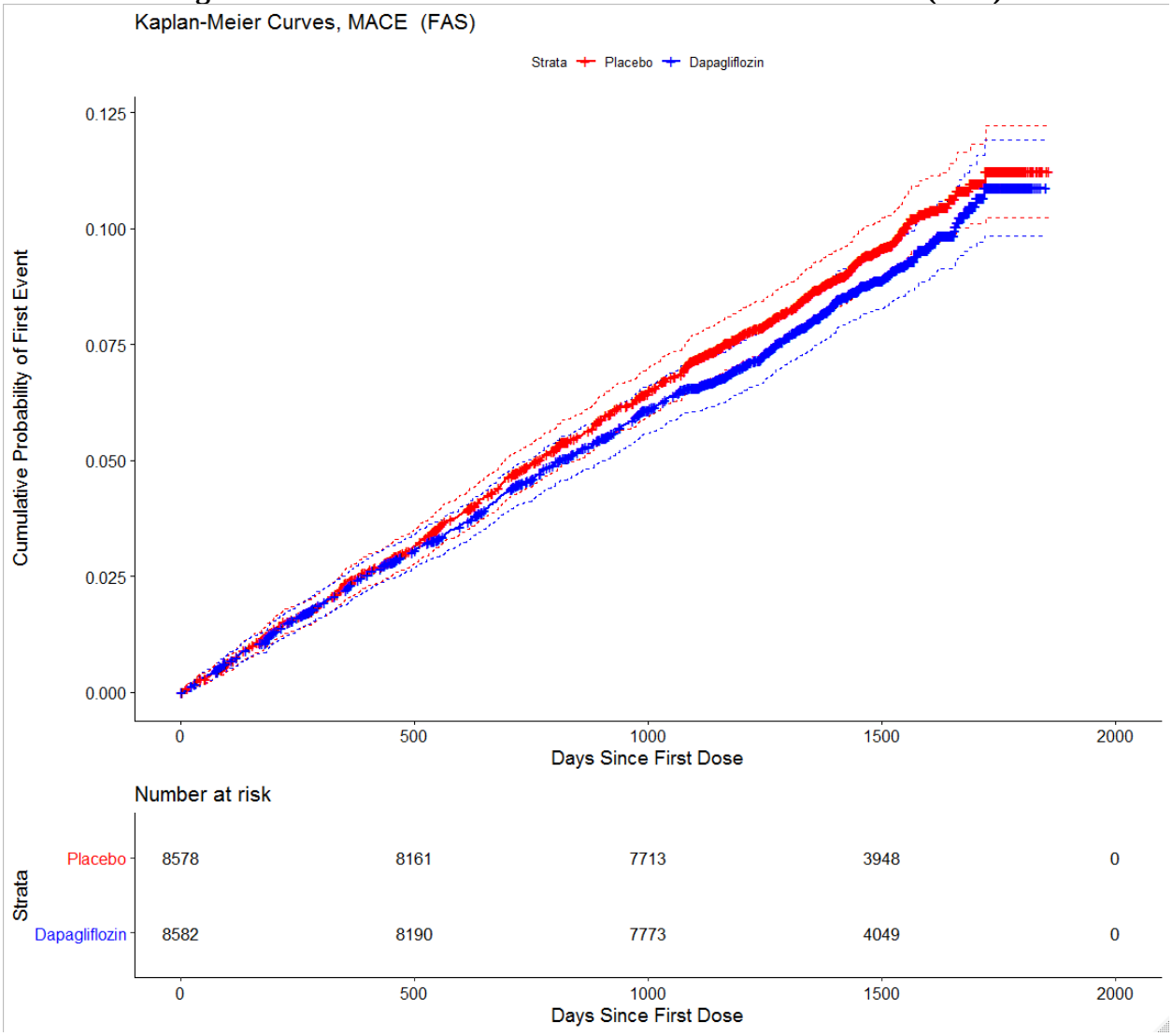
BHEMGR1: Baseline Hematuria Status

1) If LB.LBTESTCD ='RBC' and LB.LBCAT ='URINALYSIS' and LB.LBMETHOD ='DIPSTICK' and **LB.VISITNUM =2** and LB.LBSTRESC in ('POSITIVE' 'BORDERLINE') or If LB.LBTESTCD ='RBC' and LB.LBCAT ='URINALYSIS' and not LB.LBMETHOD ='DIPSTICK' and LB.VISITNUM =1 and LB.LBSTRESC ge 3 RBCs (e.g. including '3-8') then BHEMGR1 ='Positive'. 2) If LB.LBTESTCD ='RBC' and LB.LBCAT ='URINALYSIS' and LB.LBMETHOD ='DIPSTICK' and LB.VISITNUM =2 and LB.LBSTRESC ='NEGATIVE' and If LB.LBTESTCD ='RBC' and LB.LBCAT ='URINALYSIS' and not LB.LBMETHOD ='DIPSTICK' and LB.VISITNUM =1 and LB.LBSTRESC < 3 RBCs (e.g. including '0-3') then BHEMGR1 ='Negative'.

Source: Applicant’s analysis data define file

5.2 K-M Plot for MACE with 95% Confidence Bands

Figure 9 K-M Plot for MACE with 95% Confidence Bands (FAS)

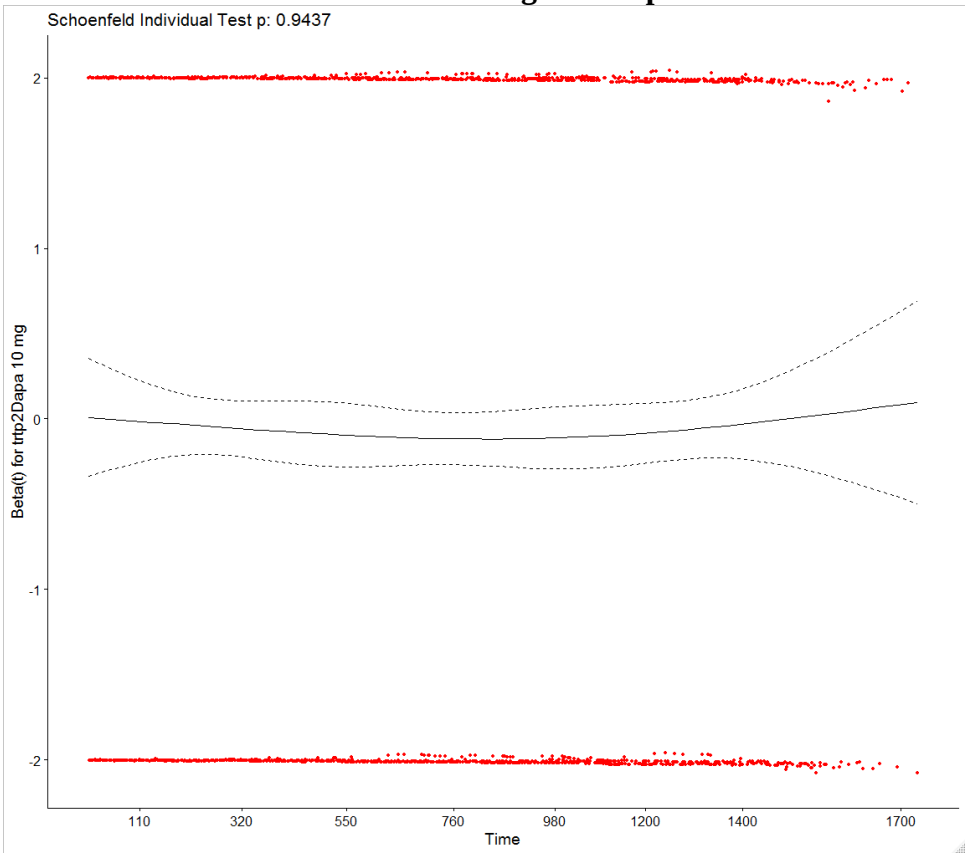


Source: FDA statistical reviewer

5.3 Proportional Hazards Assumption for the Primary Analysis

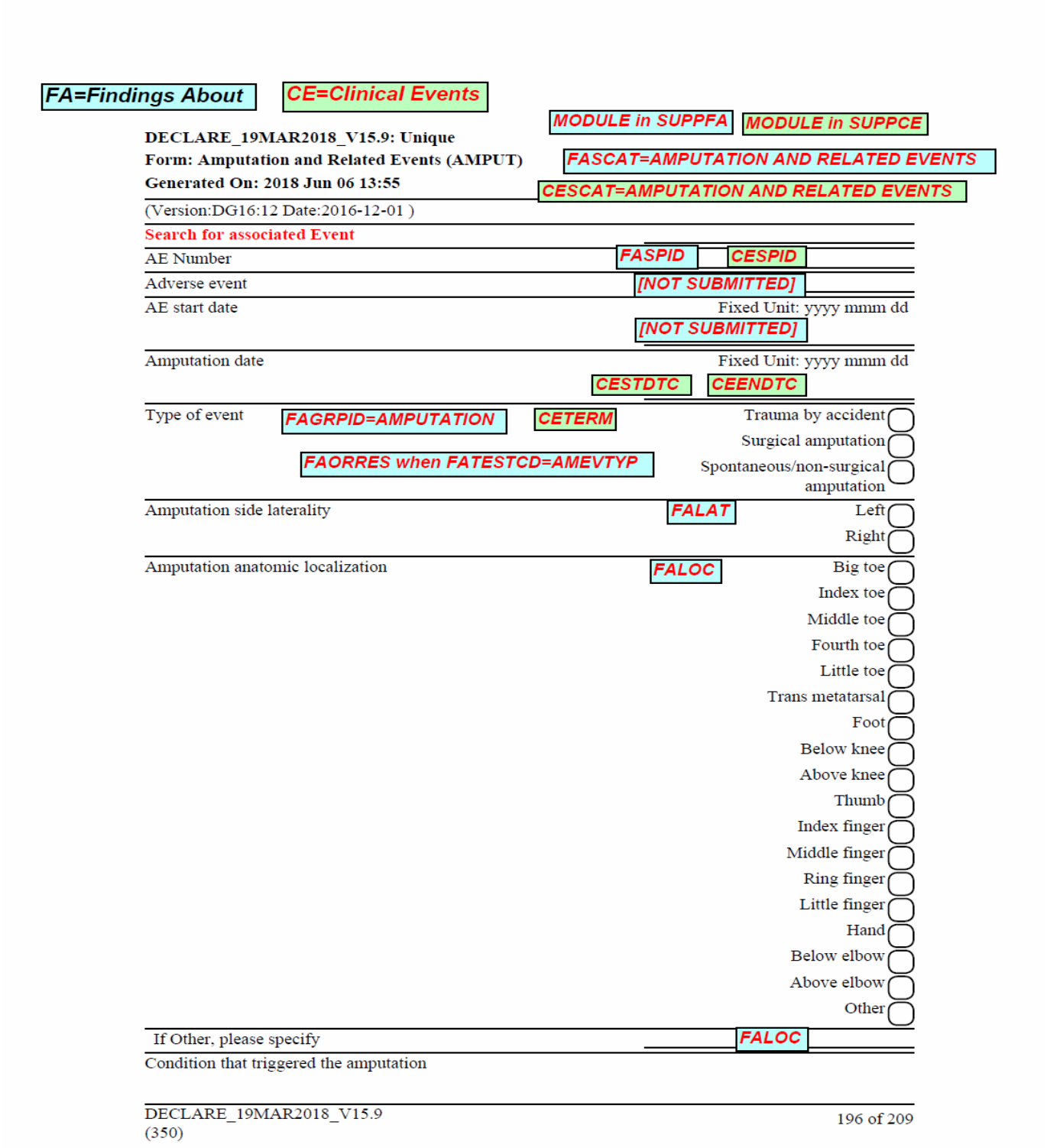
Schoenfeld residuals are plotted for the Cox models used in the primary analysis of MACE. The scaled Schoenfeld residual plot in Figure 10 does not suggest a violation of the proportional hazards assumption with the confidence band containing the horizontal zero line and the p-value = 0.9437.

Figure 10 Schoenfeld Residual Plot for Testing the Proportional Hazards Assumption



Source: FDA statistical reviewer

5.4 Electronic CRF for Amputation in DECLARE



Source: Applicant's tabulation dataset define file

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY MEMORANDUM

NDA	NDA 202293 S-018 & NDA 205649 S-011
Submission Dates	12/18/2018
Drug Name	Farxiga (dapagliflozin), Xigduo XR (dapagliflozin and metformin)
Reviewer	Jing Niu, M.D.
Team Leader	Manoj Khurana, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	AstraZeneca
Formulation; Strength	Farxiga: Tablets, 100 mg, 300 mg Xigduo XR (dapagliflozin/metformin HCl extended-release): Tablets, 2.5 mg/1000 mg, 5 mg/500 mg, 5 mg/1000 mg, 10 mg/500 mg, 10 mg/1000 mg
Indication	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

Dapagliflozin was approved in the United States (US) on January 08, 2014 (FARXIGA, NDA 202293) as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 Diabetes Mellitus (T2DM). Cardiovascular (CV) risk and bladder cancer were listed in the original approval letter as potential safety signals requiring further evaluation. The following post-marketing requirements (PMRs) were included in the US Food and Drug Administration (FDA) approval letter:

- *2121-5 A randomized, double-blind, placebo-controlled trial (the DECLARE trial) evaluating the effect of dapagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of **MACE** (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with dapagliflozin to that observed in the placebo group is less than **1.3**. The long-term effects of dapagliflozin on the incidence of liver toxicity, bone fractures, nephrotoxicity/acute kidney injury, breast and **bladder cancer**, complicated genital infections, complicated urinary tract infections/pyelonoephritis/urosepsis, serious events related to hypovolemia and serious hypersensitivity reactions should also be assessed. The estimated glomerular filtration rate (eGFR) should also be monitored over time to assess for worsening of renal function.*
- *2121-6 To assess the risk of **bladder cancer** associated with dapagliflozin, conduct adequate follow-up beyond completion of the cardiovascular outcomes trial (DECLARE) to observe a total of 66 events of bladder cancer, with 80% power to exclude a relative risk of **2.0** for dapagliflozin versus placebo, assuming a 2-sided alpha of 5%.*

The “Dapagliflozin Effect on CardiovascuLAR Events” trial (DECLARE; D1693C00001), a cardiovascular outcomes trial (CVOT) designed to compare dapagliflozin to placebo on CV risk in patients with T2DM, was conducted to fulfill the PMRs. (b) (4)

(b) (4)

There is no new information relevant to Clinical Pharmacology of dapagliflozin in this supplement: pharmacokinetic evaluations were not conducted in the DECLARE study, and no Clinical Pharmacology related labeling claim has been proposed. We defer the assessment of the claims related to this sNDA to Clinical and Stats disciplines.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	October 4, 2019
To:	Lisa Yanoff, M.D. Acting Director **Division of Metabolism and Endocrinology Products (DMEP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Samantha Bryant, PharmD, BCPS Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route, Application Type/Number, Supplement Number:	FARXIGA (dapagliflozin) tablets, for oral use, NDA 202293/ (b) (4) XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use, NDA 205649/S-011
Applicant:	AstraZeneca

1 INTRODUCTION

On December 18, 2018, AstraZeneca submitted for the Agency's review an Efficacy Supplemental New Drug Application (sNDA) 202293/(b) (4) Required Postmarketing Final Report Under 505(o): DECLARE (Study D1693C00001) for FARXIGA (dapagliflozin) tablets, for oral use and Efficacy sNDA 205649/S-011 DECLARE (Study D1693C00001) Cross Reference to FARXIGA sNDA 202293/(b) (4) (b) (4) for XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use.

The purpose of these submissions is to fulfill two Post-Marketing Requirements (PMRs) under NDA 202293 to conduct the DECLARE Cardiovascular Outcomes Trial and assess the risk of bladder cancer associated with dapagliflozin. In accordance with 21 CFR 314.70, the Applicant has submitted sNDA 205649/S-011 for XIGDUO XR based on the outcomes of the DECLARE study for the use of dapagliflozin and metformin in adults with Type 2 Diabetes Mellitus (T2DM) to reduce the risk of:

- (b) (4)
- (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on December 21, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for FARXIGA (dapagliflozin) tablets, for oral use and XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft FARXIGA (dapagliflozin) tablets, for oral use and XIGDUO XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use MGs received on December 18, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 27, 2019.
- Draft FARXIGA (dapagliflozin) tablets, for oral use and XIGDUO XR (dapagliflozin and metformin HCL extended-release) tablets, for oral use Prescribing Information (PI) received on December 18, 2018, revised by the review division throughout the review cycle, and received by DMPP and OPDP on September 27, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG documents using the Arial font, size 10.

In our collaborative review of the MGs we have:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MGs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MGs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MGs is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: October 3, 2019

To: Richard Whitehead, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Team Leader, OPDP

Subject: OPDP Labeling Comments for FARXIGA® (dapagliflozin) tablets, for oral use and XIGDUO® XR (dapagliflozin and metformin HCl extended-release) tablets, for oral use

NDA: 202293/Supplement 018
205649/Supplement 011

In response to DMEP's consult request dated December 21, 2018, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for Farxiga and Xigduo XR. These supplements (S018 and S011) provide for the addition of the DECLARE study and an expanded indication.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DMEP (Richard Whitehead) on September 27, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

91 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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SAMANTHA E BRYANT
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Clinical Inspection Summary

Date	8/30/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P. H., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Michelle Carey, M.D., M.P.H., Medical Officer Patrick Archdeacon, M.D., M.Phil., Clinical Team Leader Richard Whitehead, M.S., Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	202293s018 and NDA 205649s011
Applicant	AstraZeneca AB
Drug	Dapagliflozin (Farxiga®)
NME	No
Therapeutic Classification	Antidiabetic Agents, Non-Insulin (3031400)
Proposed Indication	Post-Marking Requirement Cardiovascular Outcomes Trial
Consultation Request Date	3/6/2019
Summary Goal Date	9/1/2019
Action Goal Date	10/18/2019
PDUFA Date	10/18/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this supplemental new drug application (sNDA) consisted of two domestic and four foreign clinical sites.

In general, based on the inspections of the six clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity.

II. BACKGROUND

AstraZeneca Pharmaceuticals LP (AstraZeneca), as US Agent on behalf of the sponsor, AstraZeneca AB, submitted a supplemental new drug application (sNDA) 202293/s018 for FARXIGA® (dapagliflozin) 5 mg and 10 mg oral tablets and sNDA 205649 /s011 XIGDUO® XR (dapagliflozin/metformin) fixed-dose combination (FDC) tablet to update their labels. There were two Post-Marketing Requirements (PMRs) for NDA 202293 (PMR 121-5 and PMR 2121-6), which were to conduct the DECLARE Cardiovascular Outcomes Trial (Study D1693C00001) and assess the risk of bladder cancer associated with dapagliflozin, respectively. Both sNDA submissions are based on the same clinical information.

FARXIGA® (dapagliflozin) was approved for the treatment of patients with type 2 diabetes mellitus (T2DM) on January 08, 2014.

XIGDUO® XR was first approved in the US on October 29, 2014.

AstraZeneca is seeking marketing approval for the use of XIDGUO® XR FDC (b) (4)

The completed DECLARE study, entitled "***D**apagliflozin **E**ffect on **C**ardiovascu**LAR** **E**vents: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Subjects with Type 2 Diabetes*", was a multi-center, randomized, double-blind, placebo-controlled Phase IIIb study conducted to evaluate the effect of dapagliflozin on cardiovascular (CV) and renal outcomes in subjects with T2DM with or without established CV disease.

The sponsor of the study was initially AstraZeneca and Bristol-Myers Squibb. AstraZeneca later became the sole sponsor of the study, and sponsor committee membership changed accordingly. The transition of responsibilities from Bristol-Myers Squibb to AstraZeneca started during 2014 and was completed by early 2015.

The study was conducted at 882 sites across 33 countries. Patients with T2DM and established CV disease or with high CV risk were selected. In total, 25,698 subjects were enrolled, 17,160 subjects were randomized, and 16,906 subjects completed the study. The first subject was enrolled on April 25, 2013 and the last subject completed the last visit on September 11, 2018. Unblinding of study data was on September 17, 2018.

DECLARE included a primary safety (non-inferiority) endpoint, dual primary efficacy endpoints, and two secondary efficacy endpoints. The composite of CV death, myocardial infarction, and ischemic stroke (major adverse cardiovascular event [MACE]) was the primary safety variable (tested for non-inferiority) and one of the primary efficacy variables (tested for superiority); the composite of hospitalization for heart failure (HF) and CV death was a dual primary efficacy variable. The secondary variables were a renal composite (composite of confirmed sustained $\geq$ 40% decrease in estimated glomerular filtration rate [eGFR] to eGFR

< 60 mL/min/1.73 m^2 [using CKD-EPI equation] and/or end stage renal disease [dialysis ≥ 90 days or kidney transplantation, confirmed sustained eGFR <15ml/min/1.73 m^2] and renal or CV death), and all-cause mortality.

III. RESULTS (by Site):

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1) Azazuddin A. Ahmed, M.D., 611 W. Roosevelt Rd., Chicago, IL 60607 Site 7971

Dates of inspection: April 16 – April 30, 2019

There were 82 subjects screened and 44 subjects enrolled into the study. There were 21 subject records reviewed.

Dr. Ahmed is a Clinic Investigator at APEX Medical Research, Inc. (AMR), a clinical research center located in Chicago, IL. studies. Dr. Ahmed was also an attending physician in internal medicine at John H. Stroger, Jr. Hospital at the time of the study. Study subjects were recruited from the AMR research volunteer database and from patients at Stroger Hospital.

AMR is owned by Dr. Ahmed's wife. Dr. Ahmed's daughter was the Clinical Research Coordinator for the DECLARE study. AMR is now co-located with two other contract research organizations, Chicago Clinical Research Institute and Clinical Research Academy. While these CROs are legally independent, they share research staff and Director of Clinical Research. AMR moved to its current location in April 2018.

(b) (4) was the institutional review board of record. The site enrolled some Spanish-speaking patients using an IRB-approved Spanish version of the informed consent form (ICF). The site had a Spanish-speaking staff person as a translator for informed consent of non-English speakers. There were also several instances where the site used an outdated version of the ICF and later reconsented subjects using the current versions at following visits.

Study source records were present for all subjects and consisted of worksheets, progress notes, laboratory tests requisitions and reports, randomization confirmation emails, notes to file, and communications with the sponsor/monitor. The files also contained medical record request forms and copies of medical records. There were several monitoring letters

confirming that subjects had been randomized before the medical records had been received and reviewed. The electronic data capture (EDC) audit trail indicates that the study monitors created protocol deviations for the site.

Source records were compared to the sponsor's data line listings. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1) An investigation was not conducted in accordance with the investigational plan. Specifically, nine of 16 reviewed subjects were not eligible for the study. In addition, randomization of many subjects occurred prior to receiving and reviewing medical records confirming their eligibility.
    a. Protocol inclusion criterion #4 specifies inclusion of subjects with "High Risk for CV event", defined as having either established CV disease and/or having multiple risk factors. The following subjects did not meet the protocol definition for inclusion criterion #4:
        - (b) (6) The study record has self-reported history of peripheral arterial obstructive disease. Screening medical records show no evidence subject meets inclusion criteria for peripheral artery disease. The subject was too young to qualify for CVD high-risk (age 55 years; needed to be age >55 years for men per Protocol Amendment 1). *This protocol deviation was picked up by the monitor, who contacted the study project manager; the site was given permission to continue the subject in the study. The mistake is listed as a protocol deviation for stratification, not eligibility.*
        - (b) (6) *This ineligible enrollment was listed as a protocol deviation.*
        - (b) (6) *This ineligible enrollment was listed as a protocol deviation.*
    b. Protocol exclusion criterion # 16 excludes subjects with screening creatinine clearance < 60 ml/min. (b) (6) had a screening creatinine clearance < 60 ml/min. *This ineligible enrollment was not listed as a protocol deviation. The low creatinine clearance was listed as a protocol deviation. The subject's weight was mis-transcribed on the lab report, thereby causing the creatinine clearance to be miscalculated as > 60 ml/min.*
    c. Protocol exclusion criterion # 13 excludes subjects at risk for poor medication compliance during the run-in period, defined as outside 80 - 120%, unless a reason for non-compliance is judged acceptable by the Investigator. The following subjects did not return all bottles of run-in study medication at the randomization visit; thus, medication compliance could not be determined:
        - (b) (6)
        - (b) (6)
        - (b) (6)

    OSI Reviewer Comment: None of these were listed as a protocol deviation.

    d. The protocol specifies that patients should meet all protocol-defined criteria at the time of randomization. The protocol also states that a subject must not

be randomized unless medical history is confirmed for eligibility criteria. The following subjects were randomized prior to receiving and reviewing medical records confirming their eligibility:

- (b) (6)
- (b) (6)
- (b) (6)
- (b) (6)

OSI Reviewer Comment: There were several additional communications to all sites reminding them to obtain medical records prior to randomization. There are several monitoring letters acknowledging the lack of medical records being reviewed at the site prior to randomization. Dr. Ahmed stated that in 2013 he did not require medical records to randomize subjects per his standard operating procedure (SOP), but that the site has since changed it.

2) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, including pre-screening sheets relevant to inclusion/exclusion criteria.
    a. The site failed to maintain the Pre-Screening Sheet/Screening Sheet for all subjects. References to this document from the Monitoring Visit letters indicate that the documents contain information relevant to subject eligibility. *The FDA inspector asked for these documents and the site could not find them. The staff think they may have been lost with the site move.*

In addition, of the 16 subjects reviewed for inclusion/exclusion, three had a history of cocaine-abuse. While the study protocol does not explicitly exclude subjects with a history of substance abuse, enrollment of such subjects is concerning.

- (b) (6) Screening medical records document cocaine use in 2009 and homelessness in 2012. Dr. Ahmed randomized the subject on August 26, 2013. The subject's 2015 MACE event medical records show her NSTEMI was due to cocaine use.
- (b) (6) Screening medical records document a history of cocaine use "a couple months ago" in October 2013. Dr. Ahmed randomized the subject on November 21, 2013.
- (b) (6) Screening medical records document cocaine use in May 2013. Dr. Ahmed randomized the subject on January 4, 2014.

In May 2014, Ms. Ahmed emailed the DECLARE Study Project Manager, asking if (b) (6) with a history of cocaine use could continue in the study; the manager responded, "We generally advise against including such subjects, but the Investigator may make a decision otherwise if the patient will be a compliant study subject".

OSI Reviewer Comment: Recommend that the review team consider this additional information when assessing the outcome of these subjects.

On 4/30/2019, Dr. Ahmed provided a written response to the deficiencies and submitted a final formal response on May 20, 2019. The deficiencies had been brought to his attention during the trial and he had already put into place several Corrective and Preventive Actions (CAPAs), trainings, and additional standard operating procedures (SOPs). He had also fired the two clinical research coordinators who enrolled ineligible subjects at the start of the trial and hired a more experienced person. Dr. Ahmed also stated that the firm does not enroll substance abusers any more per CAPA Form dated July 7, 2017.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

The final EIR was available for review.

2) Harpreet Bajaj, M.D., 2979 Bovaird Drive East, Brampton, Ontario L6S 0C6 Canada Site 1045

Dates of inspection: June 24 – July 3, 2019

There were 257 subjects screened and 164 subjects enrolled into the study; 153 subjects completed the study. The site did not have any subjects lost to follow-up; however, 12 permanently discontinued study drug before the conclusion of the trial (Subjects (b) (6) . This correlates with the Dropouts/Discontinued listing). There were 38 subject records reviewed.

Dr. Bajaj is the principal investigator at LMC Manna Research- Brampton. LMC Manna Research was formed in 2015, after LMC Diabetes & Endocrinology (founded in 1997) and Manna Research (founded in 1996) merged clinical operations. There are currently 21 research clinics throughout Canada. In February 2018, site operations were relocated to their current address. Dr. Bajaj sees patients for routine diabetes and endocrinology care at this location. Approximately 10% of his time is dedicated to involvement in research. All subjects, aside from one, were recruited from within the site's routine diabetes and endocrinology clinic.

(b) (4) was the institutional review board of record. ICFs were provided to patients in either English, Hindi, or Punjabi. This foreign site was not under IND.

The study records were organized, legible, and available. Adverse events (AEs), serious adverse events (SAEs), and concomitant medications reported at visits were transcribed directly onto their appropriate log. The site however, revised these reporting forms several times over the course of the study. For continuing events, the entries were carried forward with each iteration of the form, causing some confusion as to whether the event was a duplicate entry. Source records were compared to the sponsor's data line listings. There were no discrepancies.

During review of subject records, the following subjects took Jardiance, an SGLT-2

inhibitor, while in the study: Subjects (b) (6) Per protocol section 5.6.1, Prohibited Medication: "Treatment with pioglitazone, rosiglitazone, and any SGLT2 inhibitors other than IP is not permitted for the duration of the study." It was noted that these subjects had discontinued investigational study drug but were still on the study for follow-up with the potential to restart drug at any time. The DECLARE Monitor's Newsletter- Issue No.34, dated 03 OCT 2016, stated that "For patients not actively taking study drug (i.e. permanent discontinuation or temporary cessation) it is not considered a major protocol deviation if a patient takes pioglitazone, rosiglitazone, and any SGLT2 inhibitors other than study drug as long as the patient is not concomitantly taking study drug"

There was some inconsistency with reporting adverse events (AEs). The protocol states that AEs leading to discontinuation from IP needed to be reported into the CRFs. There were a few situations where subjects stopped taking IP on their own because of an AE (such as a urinary tract infection); however, the investigator believed that this discontinuation was per subject decision since the subject was the one who stopped IP at home and the AE was not related to the IP. Most of these AEs were not recorded in the eCRFs, and the reason in the line listings was sometimes reported as "treatment stopped due to subject decision" for subjects who permanently discontinued the study drug.

Subject #	Date study drug was started:	Date study drug was stopped:	Reason study drug was stopped:	If AE, was it reported?	Subjects' status in eCRFs	Listed as discontinued as line listings & reason?
(b) (6)	21 OCT 2013	30 JAN 2015	AE- UTI	No	"Discontinued study drug but continuing on for follow up"	Yes; "Treatment stopped due to subject decision"
	21 JAN 2014	03 FEB 2017	AE- UTI	No	"Continuing on study drug"	No
	12 MAR 2014	25 MAR 2015	AE- Hypotension	No	"Continuing on study drug"	No
	11 SEP 2014	15 MAR 2015	AE- UTI	No	"Continuing on study drug"	No
	23 OCT 2013	07 JAN 2014	AE- UTI	Yes	"Continuing on study drug"	No
	24 APR 2014	02 AUG 2014	AE- Chronic Balanitis	Yes	"Continuing on study drug"	No
	29 OCT 2014	16 NOV 2016	Subject stopped coming in, ran out of SD.	N/A	"Continuing on study drug"	No
	06 AUG 2014	22 DEC 2014	AE- Polyuria	No	"Continuing on study drug"	No

The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3) Joao Borges, M.D., Rua Deputado Antonio Heill, Joinville, Santa Carina, Brazil Site 715

Dates of inspection: May 20 – May 30, 2019

There were 136 subjects screened and 90 subjects enrolled into the study; 85 subjects completed the study. There were 40 subject records reviewed.

Dr. Borges has been practicing in the current location since 1984. The research site was expanded in 2005 to include 5 physician offices. Dr. Borges has 39 years of experience in clinical research in both Brazil and the United States. His practice maintains a large database for recruitment of subjects for studies. The site also advertises on Facebook, Google and in newspapers for recruitment in studies.

This study was initially approved by Comite de Etica Em Pesquisa Do Centro Universitario de Brasilia Uniceub located in Brasilia. There were several instances where different signatures on the ICFs were noted by the monitors. This was well documented, and the subjects signed documents stating that it was their signature on each document. The site was not under IND.

There were stratification errors at the start of the study which were documented and reported. These errors were corrected and were not repeated throughout the remainder of the trial.

The study records were organized, legible, and available. Each subject record reviewed had medical records documenting inclusion and exclusion criteria. Source records were compared to the sponsor's data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The final EIR was available for review.

4) Carlos Ince, Jr., M.D., 3407 Wilkens Ave, Suite 300, Baltimore, MD 21229
Site 8166

Dates of inspection: June 10 – June 14, 2019

There were 149 subjects screened and 68 subjects enrolled into the study; 67 subjects completed the study. There were 20 subject records reviewed.

Dr. Ince is a partner with Maryland Cardiovascular Specialists and Chief of Cardiology at St. Agnes Hospital. Research is performed via Spectrum Clinical Research, a multi-specialty clinical research trial management firm based in Central Maryland. Subjects were seen at two separate locations; at the location above and at 5500 Knoll North Dr., Suite 250, Columbia, MD, 21045.

(b) (4) was the institutional review board of record. During the trial, multiple subjects were not consented with the most current consent version. Corrective actions were implemented, and subjects were contacted to be reconsented.

The study source documents were organized and the records for each subject were maintained in a separate file. Source documents were attributable, legible, contemporaneous, original, and accurate. Source records were compared to the sponsor's data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The final EIR was available for review.

5) Ewa Krzyżagórska, Praktyka Lekarska Ewa Krzyżagórska, Ul, Murawa 37A, Poznań, Wielkopolskie, 61-655 Poland
Site 5703

Dates of inspection: June 24 – July 3, 2019

There were 138 subjects screened and 95 subjects enrolled into the study; 65 subjects completed the study (20 discontinued IP and 10 died). There were 95 subject records reviewed. A translator was available throughout the inspection.

Dr. Krzyżagórska saw study subjects at the above address; she also has an outpatient clinic from which study subjects were recruited.

The countrywide ethics committee for this study site was Komisja Bioetyczna przy CMKP, 01-813, Warszawa, Poland. The site ethics committee was Komisja Bioetyczna przy CMKP, ul. Marymoncka 99/103, 01-813, Warszawa, Poland. The site was not under IND.

Subject study records were located in individual binders. Records were organized and legible. Source records were compared to the sponsor's data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The final EIR was available for review.

6) Beata Miklaszewicz, Cardiamed Beata Miklaszewicz i Dariusz, Ul. Grunwaldzka 7, Legnica 59-220 Poland
Site 5718

Dates of inspection: June 24 – June 27, 2019

There were 97 subjects screened and 67 subjects enrolled into the study; 46 subjects completed the study. There were 17 subject records reviewed.

All subjects were seen at the above location. The clinic is owned by Dr. Miklaszewicz and Dr. Dariusz Dabrowski, who was a sub-investigator in the trial. All subjects were from Cardiamed and no advertisements were used for the clinical trial.

The central ethics committee used for this clinical trial was Certurm Medyczne Ksztalcenia Podyplomowego, Ul. Marymoncka 99/103, 913 Warszawa, Poland. The site was not under IND.

Subject study records were organized and available. The documentation consisted of both sponsor-provided templates and site visit paper records. In addition, paper laboratory reports were contained in each file for each blood sample taken. Source records were compared to the sponsor's data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable.

Many subjects were stratified by the site into the incorrect group. According to Section 5.2.1 of all versions of the protocol, subjects would be "stratified by CV risk category… and baseline hematuria status." However, nowhere in the protocol does it state what is considered baseline, i.e., screening or randomization visit results from laboratory or urine analysis. Thus, stratification was not properly completed by the clinical site due to ambiguity in the protocol.

Subject (b) (6) (randomized to placebo) was enrolled, although the subject failed to meet the age requirement. According to all versions of the protocol, subjects were required to have an age greater than 55 and have additional risk factors to be eligible for the clinical trial.

Subject (b) (6) failed to meet all inclusion/exclusion criteria due to the subject being 53 at the age of enrollment with cardiovascular risk factors; the subject did not have an established cardiovascular disease diagnosis. This was discovered during the trial. The sponsor was made aware of the issue and approved the subject's continuation in the clinical trial.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

The final EIR was available for review.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

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cc:

Central Doc. Rm./ NDA 202293 and NDA 205649
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DMEP /Regulatory Project Manager/Richard Whitehead
OSI/DCCE/Division Director/Ni Aye Khin
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OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 7, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 202293/S-018 NDA 205649/S-011
Product Name and Strength:	Farxiga (dapagliflozin) tablet, 5 mg and 10 mg Xigduo XR (dapagliflozin and metformin HCL extended release) tablet, 2.5 mg/1,000 mg, 5 mg/500 mg, 5 mg/1,000 mg, 10 mg/500 mg, 10 mg/1,000 mg
Product Type:	Single Ingredient Product and Multi-Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca Pharmaceuticals LP
FDA Received Date:	December 18, 2018 and March 22, 2019
OSE RCM #:	2018-2812
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

AstraZeneca Pharmaceuticals submitted efficacy supplement 018 for Farxiga (dapagliflozin), under NDA 202293, and 011 for Xigduo XR (dapagliflozin and metformin extended release), under NDA 205649, (b) (4) The original NDAs for Farxiga and Xigduo XR were approved January 8, 2014 and October 29, 2014, respectively, as adjunctive therapy in patients with type 2 diabetes mellitus.

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the proposed changes to the prescribing information and medication guide to determine if they are acceptable from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

AstraZeneca submitted Prior Approval Supplements, which proposes changes to the Farxiga and Xigduo XR product labeling to expand the current approved indication (b) (4) Thus, the sponsor has proposed changes to the prescribing information (b) (4)

We performed a risk assessment of the revised labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement.

4 CONCLUSION

We defer to the review team for analysis of the proposed changes to the various sections of the prescribing information. The revised prescribing information for Farxiga and Xigduo XR are acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Farxiga and Xigduo submitted by AstraZeneca on March 22, 2019.

Table 2. Relevant Product Information for Farxiga and Xigduo XR		
Product Name	Farxiga	Xigduo XR
Initial Approval Date	January 8, 2014	October 29, 2014
Active Ingredient	dapagliflozin	dapagliflozin and metformin HCL extended-release
Current Indication	indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both dapagliflozin and metformin is appropriate
Additional Indication Proposed	indicated in adults with type 2 diabetes mellitus: (b) (4)	
Route of Administration	oral	oral
Dosage Form	tablets	tablets
Strength	5 mg and 10 mg	2.5 mg dapagliflozin/1,000 mg metformin HCl extended-release 5 mg dapagliflozin/500 mg metformin HCl extended-release 5 mg dapagliflozin/1,000 mg metformin HCl extended-release 10 mg dapagliflozin/500 mg metformin HCl extended-release

		10 mg dapagliflozin/1,000 mg metformin HCl extended-release
Dose and Frequency	The recommended starting dose is 5 mg once daily, taken in the morning with or without food, and can be increased to 10 mg once daily in patients tolerating Farxiga who require additional glycemic control	Individualized starting dose administered once daily in the morning with food, not to exceed a daily dose of 10 mg dapagliflozin/2,000 mg metformin HCl extended-release
	(b) (4)	
How Supplied	Bottles of 30 tablets	bottles of 30, 60, 90, 400, or 500 tablets (depending on product strength)
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].	

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 17, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms Farxiga and Xigduo. Our search identified 2 previous reviews for Farxiga[a] and 2 previous reviews for Xigduo XR[b], and we confirmed that our previous recommendations were implemented.

[a] Agustin A. Label, Labeling and Packaging Review for Farxiga, NDA 202293. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Nov 18. RCM No.: 2013-1640.

Conrad A. Labeling Review for Farxiga, NDA 202293/S-016. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Feb 15. RCM No.: 2018-2089.

[b] Vee S. Label and Labeling Review for Xigduo XR (NDA 205649). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Oct 30. RCM No.: 2013-2529.

Conrad A. Label and Labeling Review for Xigduo XR (NDA 205649/S-008). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jul 27. RCM No.: 2017-1454.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Farxiga labels and labeling submitted by AstraZeneca Pharmaceuticals LP.

- Prescribing Information for Farxiga received on March 22, 2019
    - \\cdsesub1\evsprod\nda202293\0558\m1\us\nonannotated-draft-label-declare-label-updates-with-derive.pdf
- Prescribing Information for Xigduo XR received on March 22, 2019
    - \\cdsesub1\evsprod\nda205649\0162\m1\us\nonannotated-draft-label-xigduo-xr-cvot.pdf

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

ARIANE O CONRAD
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s018

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202293 SUPPL # S-018 HFD # 510

Trade Name FARXIGA 5mg and 10mg Tablets

Generic Name dapagliflozin

Applicant Name AstraZeneca

Approval Date, If Known October 18, 2019

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1), SE1

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3-years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA#	202293	Farxiga (dapagliflozin)
NDA#	205649	Xigduo XR
NDA#	209091	Qtern (dapagliflozin and saxagliptin)
NDA#	210874	Qternmet XR (dapagliflozin, saxagliptin, and metformin hydrochloride) extended-release

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability

studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

IND 068652- DECLARE (Study D1693C00001) study, entitled “Dapagliflozin Effect on Cardiovascular Events: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes”

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 (DECLARE) YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 (DECLARE) YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

IND 068652- DECLARE (Study D1693C00001) study, entitled “Dapagliflozin Effect on Cardiovascular Events: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients with Type 2 Diabetes”

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 068652 YES ☒ ! NO ☐
! Explain:
Date: 4/02/2012 SDN# 457

Investigation #2

IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Richard Whitehead, M.S.
Title: RPM
Date: 10/10/2019

Name of Division Director signing form: Patrick Archdeacon, M.D.
Title: Associate Director for Therapeutics (Acting)

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