CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202293Orig1s020

Trade Name:	FARXIGA
Generic or Proper Name:	dapagliflozin tablets
Sponsor:	AstraZeneca Pharmaceuticals LP
Approval Date:	May 5, 2020
Indication:	This Prior Approval supplemental new drug application provides for revisions to the prescribing information (PI) to provide for inclusion of a new indication for the use of FARXIGA to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

CENTER FOR DRUG EVALUATION AND RESEARCH

202293Orig1s020

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 202293/S-020

SUPPLEMENT APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Craig Zecher
Regulatory Affairs Director
One Medimmune Way
Gaithersburg, MD 20878

Dear Mr. Zecher:

Please refer to your supplemental new drug application (sNDA) dated November 6, 2019, received November 6, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for FARXIGA (dapagliflozin) 10 mg tablet.

This Prior Approval supplemental new drug application provides for revisions to the prescribing information (PI) to provide for inclusion of a new indication for the use of FARXIGA to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 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]

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

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. There is not a good understanding of the mechanism of dapagliflozin's clinical benefits in adults with heart failure. Given the differences in etiologies of heart failure in adults and children, we have neither a strong expectation that these benefits should apply to pediatric patients nor a suitable biomarker with which to bridge to pediatric patients.

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, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, & Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Medication Guide

[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/

NORMAN L STOCKBRIDGE
05/05/2020 08:18:15 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s020

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 (1.1)	10/2019
Indications and Usage (1.2)	05/2020
Dosage and Administration (2.1)	10/2019
Dosage and Administration (2.2, 2.3, 2.4)	05/2020
Contraindications (4)	05/2020
Warnings and Precautions (5.1)	05/2020
Warnings and Precautions (5.2)	01/2020
Warnings and Precautions (5.4)	10/2019
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 in adults for:

Type 2 Diabetes Mellitus

- as an adjunct to diet and exercise to improve glycemic control. (1.1)
- 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. (1.1)

Heart Failure

- to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA class II-IV). (1.2)

Limitations of use:

- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.3)

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

Assess renal function before initiating and then as clinically indicated. (2.1)

Type 2 Diabetes Mellitus:

- 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 in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors, the recommended dose is 10 mg once daily. (2.2)
- FARXIGA is not recommended for glycemic control when the eGFR is less than 45 mL/min/1.73 m^2. (2.4)

Heart Failure

- The recommended dose of FARXIGA is 10 mg once daily. (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) in patients who are being treated for glycemic control without established cardiovascular disease or cardiovascular risk factors. (4)
- Patients on dialysis. (4)

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

- *Volume depletion* Before initiating FARXIGA, assess volume status and renal function 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 in Patients with Diabetes Mellitus* 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)
- *Urosepsis and Pyelonephritis* Evaluate for signs and symptoms of urinary tract infections and treat promptly, if indicated. (5.3)
- *Hypoglycemia* Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination with FARXIGA. (5.4)
- *Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)* Serious, life-threatening cases have occurred in patients with diabetes, 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. (5.5)
- *Genital Mycotic Infections* Monitor and treat if indicated. (5.6)

---------- 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 hypotension. (5.1, 8.5)
- *Renal Impairment* Higher incidence of adverse reactions related to hypotension and renal function. (5.1, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 05/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Type 2 Diabetes Mellitus

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.

1.2 Heart Failure

FARXIGA is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

1.3 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 then as clinically indicated *[see Warnings and Precautions (5.1)]*.

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 Type 2 Diabetes Mellitus

To improve glycemic control, the recommended starting dose of FARXIGA is 5 mg orally 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 in patients with type 2 diabetes mellitus and established CVD or multiple CV risk factors, the recommended dose of FARXIGA is 10 mg orally once daily.

2.3 Heart Failure

The recommended dose of FARXIGA is 10 mg orally once daily.

2.4 Patients with Renal Impairment

Table 1. FARXIGA Dosing Recommendations for Patients Based on Renal Function

Treatment/ Patient Population	Recommended Dosage based on eGFR (mL/min/1.73 m^2, CKD-EPI)			
	45 or above	30 to less than 45	less than 30	ESRD/Dialysis
Use for glycemic control in patients with T2DM	No dose adjustment	Not recommended	Contraindicated	
To reduce risk of hHF in patients with T2DM, with CVD or multiple CV risk factors	No dose adjustment	Insufficient data to support a dosing recommendation.		Contraindicated
To reduce risk of CV death and hHF in patients with HFrEF, with or without T2DM	No dose adjustment		Insufficient data to support a dosing recommendation.	Contraindicated

eGFR: Estimated glomerular filtration rate, CKD-EPI: Chronic kidney disease epidemiology collaboration equation, T2DM: Type 2 diabetes mellitus, hHF: hospitalization for heart failure, HFrEF: Heart failure with reduced ejection fraction, CVD: Cardiovascular disease, CV: Cardiovascular, ESRD: End Stage Renal Disease

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)]*.
- Patients who are being treated for glycemic control without established CVD or multiple CV risk factors with severe renal impairment, (eGFR less than 30 mL/min/1.73 m^2) *[see Use in Specific Populations (8.6)]*.
- Patients on dialysis *[see Use in Specific Populations (8.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Volume Depletion

FARXIGA can cause intravascular volume depletion which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been post-marketing reports of acute kidney injury, some requiring hospitalization and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including FARXIGA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating FARXIGA in patients with one or more of these characteristics, assess volume status and renal function. Monitor for signs and symptoms of hypotension, and renal function after initiating therapy.

5.2 Ketoacidosis in Patients with Diabetes Mellitus

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 (1.3)]*.

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, 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.

For patients who undergo scheduled surgery, consider temporarily discontinuing FARXIGA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3)]*.

Consider monitoring for ketoacidosis and temporarily discontinuing FARXIGA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting FARXIGA.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue FARXIGA and seek medical attention immediately if signs and symptoms occur.

5.3 Urosepsis and Pyelonephritis

Serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization have been reported 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)]*.

5.4 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.

5.5 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.

5.6 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:

- Volume Depletion *[see Warnings and Precautions (5.1)]*
- Ketoacidosis in Patients with Diabetes Mellitus *[see Warnings and Precautions (5.2)]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions (5.3)]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions (5.4)]*
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene) *[see Warnings and Precautions (5.5)]*
- Genital Mycotic Infections *[see Warnings and Precautions (5.6)]*

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.

FARXIGA has been evaluated in clinical trials in patients with type 2 diabetes mellitus and in patients with heart failure. The overall safety profile of FARXIGA was consistent across the studied indications. Severe hypoglycemia and diabetic ketoacidosis (DKA) were observed only in patients with diabetes mellitus.

Clinical Trials in Patients with Type 2 Diabetes Mellitus

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

The data in Table 1 is derived from 12 glycemic control placebo-controlled studies in patients with type 2 diabetes mellitus 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 2 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 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control 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

Table 2: Adverse Reactions in Placebo-Controlled Studies of Glycemic Control 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
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 glycemic control placebo-controlled study pool in patients with type 2 diabetes mellitus. 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 a reduction in intravascular volume. Adverse reactions related to volume depletion (including reports of dehydration, hypovolemia, orthostatic

hypotension, or hypotension) in patients with type 2 diabetes mellitus for the 12-study and 13-study, short-term, placebo-controlled pools and for the DECLARE study are shown in Table 3 *[see Warnings and Precautions (5.1)]*.

Table 3: Adverse Reactions Related to Volume Depletion* in Clinical Studies in Patients with Type 2 Diabetes Mellitus 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=13935 (0.4%)	N=11457 (0.6%)	N=11939 (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=551 (1.8%)	n=400	n=313 (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=1072 (1.9%)	n=1071 (0.9%)	n=891 (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=2761 (0.4%)	n=2161 (0.5%)	n=2043 (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 in patients with type 2 diabetes mellitus *[see Clinical Studies (14.1)]* is shown in Table 4. Hypoglycemia was more frequent when FARXIGA was added to sulfonylurea or insulin *[see Warnings and Precautions (5.4)]*.

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	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)

Table 4: Incidence of Severe Hypoglycemia* and Hypoglycemia with Glucose < 54 mg/dL† in Controlled Glycemic Control Clinical Studies in Patients with Type 2 Diabetes Mellitus

	Placebo/Active Control	FARXIGA 5 mg	FARXIGA 10 mg
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

In the glycemic control trials, 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. In glycemic control studies, 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 Patients with Diabetes Mellitus

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 SGLT2 inhibitors, including FARXIGA causes a small increase in serum creatinine and decrease in eGFR. In patients with normal or mildly impaired renal function at baseline, these changes in serum creatinine and eGFR generally occur within weeks of starting therapy and then stabilize. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Warnings and Precautions (5.1)]*. The acute effect on eGFR reverses after treatment discontinuation, suggesting acute hemodynamic changes may play a role in the renal function changes observed with FARXIGA.

Increase in Hematocrit

In the pool of 13 placebo-controlled studies of glycemic control, 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 of glycemic control, 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)]*.

DAPA-HF Heart Failure Study

No new adverse reactions were identified in the DAPA-HF heart failure study.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of FARXIGA in patients with diabetes mellitus. 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 and untreated heart failure 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 in type 2 diabetes mellitus. 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 for glycemic control had adverse reactions of hypotension *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

In the DAPA-HF study, 2714 (57%) out of 4744 patients with HFrEF were older than 65 years. Safety and efficacy were similar for patients age 65 years and younger and those older than 65.

8.6 Renal Impairment

FARXIGA was evaluated in two glycemic control studies that included patients with type 2 diabetes mellitus 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 mellitus. 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 diabetes and renal impairment using FARXIGA 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.

Use of FARXIGA for glycemic control in patients without established CV disease or CV risk factors is not recommended when eGFR is less than 45 mL/min/1.73 m^2 *[see Dosage and Administration (2.4)]* and is contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) *[see Contraindications (4)]*.

In the DAPA-HF study *[see Clinical Studies (14.3)]* that included patients with eGFR equal to or above 30 mL/min/1.73 m^2, there were 1926 (41%) patients with eGFR below 60 mL/min/1.73 m^2 and 719 (15%) with eGFR below 45 mL/min/1.73 m^2. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function. No dose adjustment is recommended for HFrEF patients with eGFR 30 mL/min/1.73 m^2 and above *[see Dosage and Administration (2.4)]*.

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)]*.

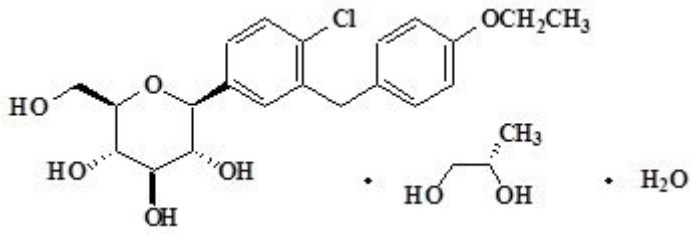
10 OVERDOSAGE

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

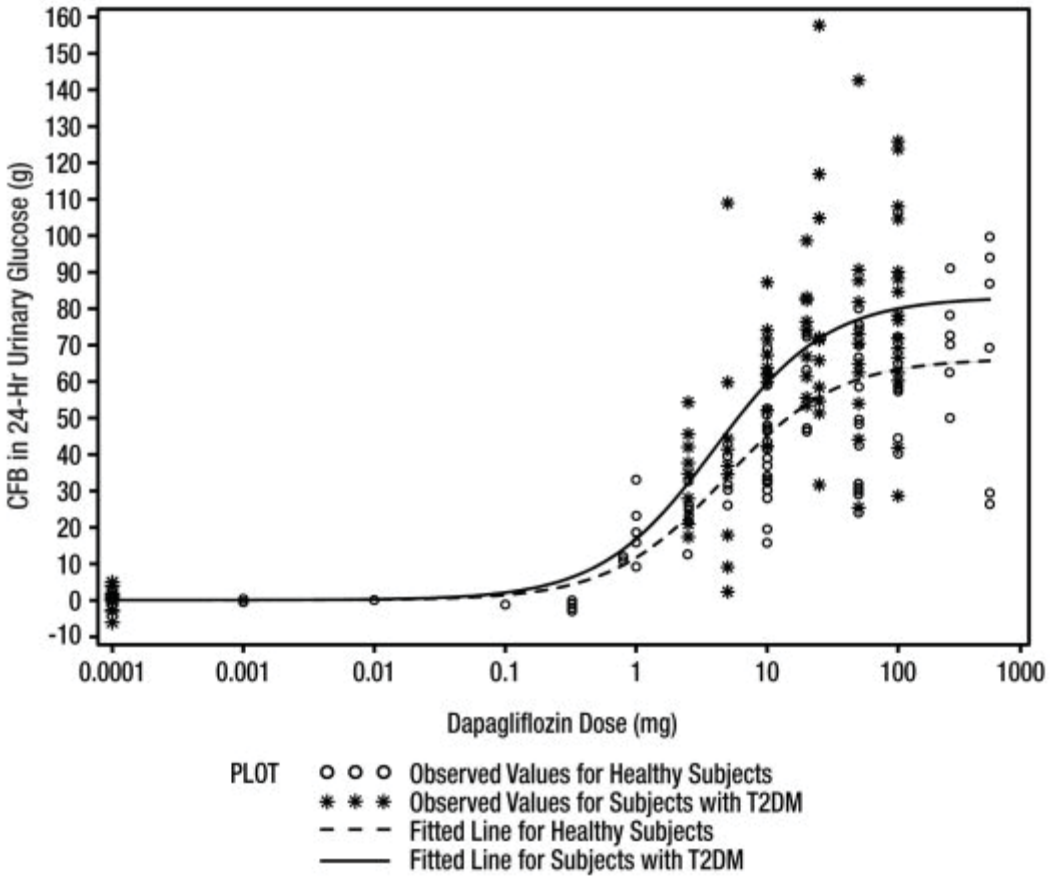
Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers 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)]*. After discontinuation of dapagliflozin, on average, the elevation in urinary glucose excretion approaches baseline by about 3 days for the 10 mg dose.

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 mellitus 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 mellitus and mild, moderate, and severe renal impairment was 42%, 80%, and 90% lower, respectively, than in patients with type 2 diabetes mellitus with normal renal function. The impact of hemodialysis on dapagliflozin exposure is not known *[see Dosage and Administration (2.4), Warnings and Precautions (5.1), 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 5 shows the effect of coadministered drugs on the pharmacokinetics of dapagliflozin. No dose adjustments are recommended for dapagliflozin.

Table 5: 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%, ↑11%]	↓22% [↓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 6 shows the effect of dapagliflozin on other coadministered drugs. Dapagliflozin did not meaningfully affect the pharmacokinetics of the coadministered drugs.

Table 6: 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	↔	↔

Table 6: 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†
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, 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 in Patients with Type 2 Diabetes Mellitus

Overview of Clinical Studies of FARXIGA for Type 2 Diabetes Mellitus

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 mellitus 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 mellitus 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 7).

Table 7: Results at Week 24 (LOCF[*]) in a Placebo-Controlled Study of FARXIGA Monotherapy in Patients with Type 2 Diabetes Mellitus (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

Table 7: Results at Week 24 (LOCF*) in a Placebo-Controlled Study of FARXIGA Monotherapy in Patients with Type 2 Diabetes Mellitus (Main Cohort AM Doses)

Efficacy Parameter	FARXIGA 10 mg N=70†	FARXIGA 5 mg N=64†	Placebo N=75†
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 mellitus (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 8 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 8: 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.

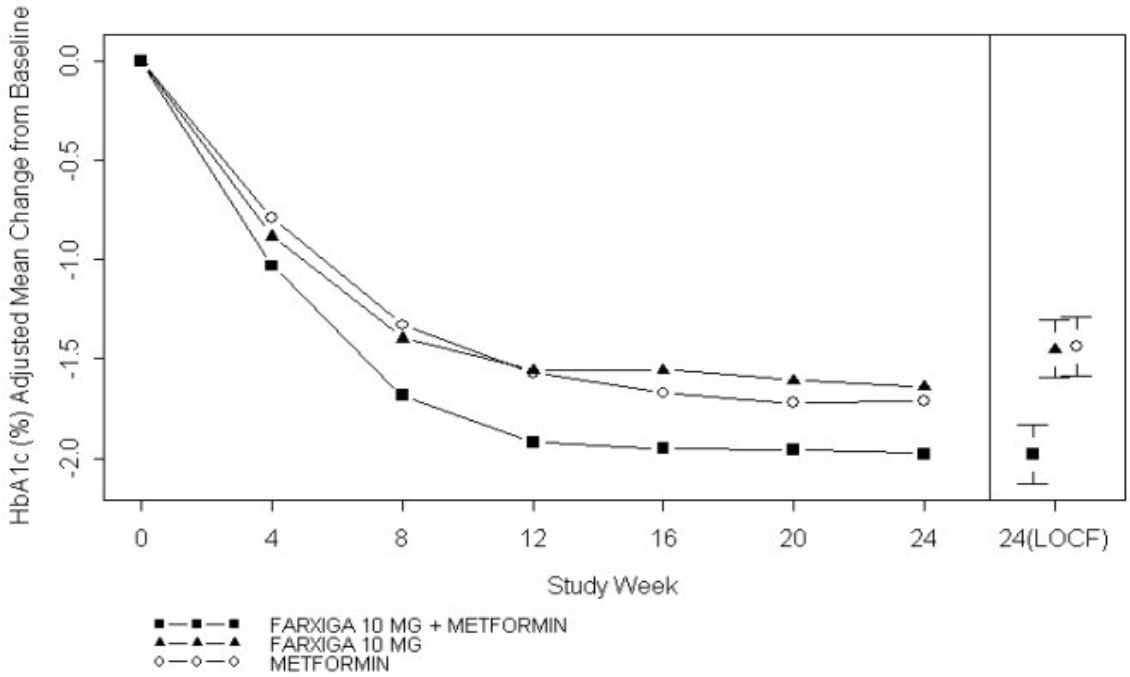
‡ Least squares mean adjusted for baseline value.

§ 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 9).

Table 9: 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

Table 9: 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†
Difference from FARXIGA (adjusted mean‡) (95% CI)	−0.9§ (−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 mellitus 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 10 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 10: 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.

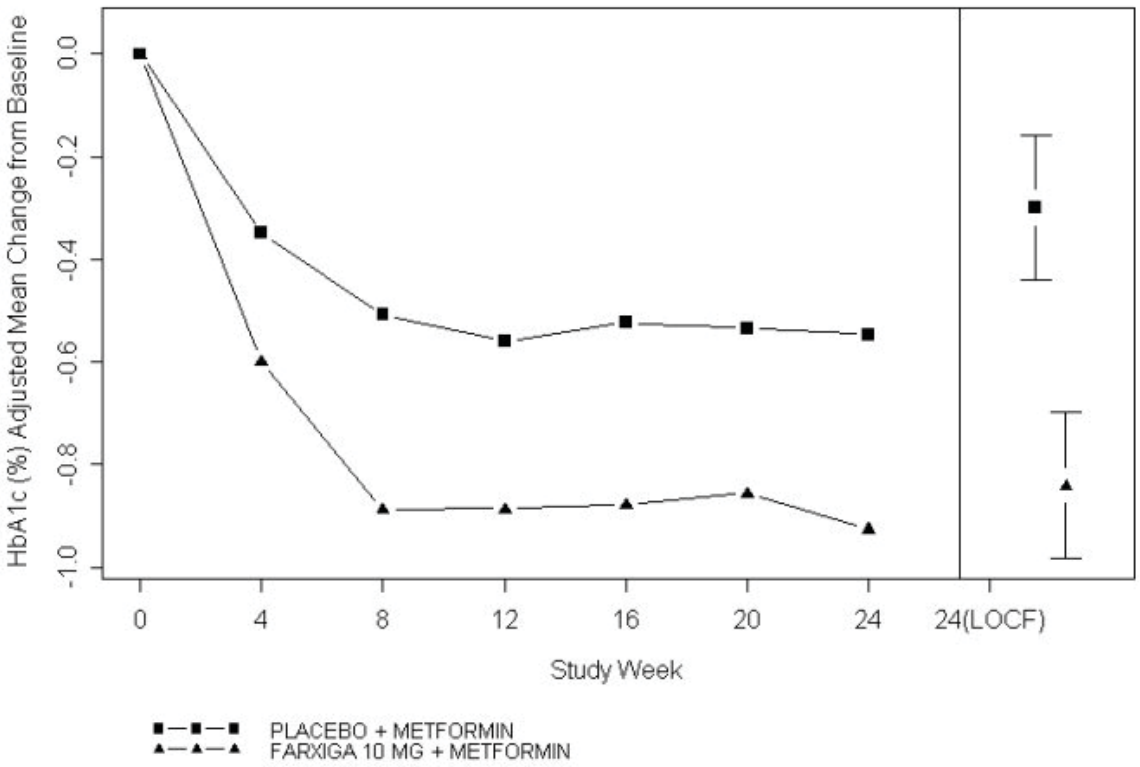
† All randomized patients who took at least one dose of double-blind study medication during the short-term double-blind period.

‡ 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 mellitus 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 11). 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 11: 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 mellitus 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 12). 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 mellitus 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 12). A statistically significant ($p < 0.05$) mean change from baseline in systolic blood pressure relative to placebo in combination with metformin and a sulfonylurea 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 mellitus 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 12) 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 mellitus 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 12). 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 mellitus 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 12); 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 12: 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 12: 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 12: 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	NT[à]	170.0
Change from baseline (adjusted mean[‡])	−21.7	NT[à]	3.3
Difference from placebo (adjusted mean[‡]) (95% CI)	−25.0[§] (−34.3, −15.8)	NT[à]	
Body Weight (kg)			

Table 12: 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 mellitus 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 Mellitus and Moderate Renal Impairment

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

Patients with type 2 diabetes mellitus 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 13).

Table 13: Results at Week 24 of Placebo-Controlled Study for FARXIGA in Patients with Type 2 Diabetes Mellitus 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 14 and Figures 4 and 5).

Table 14: 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)

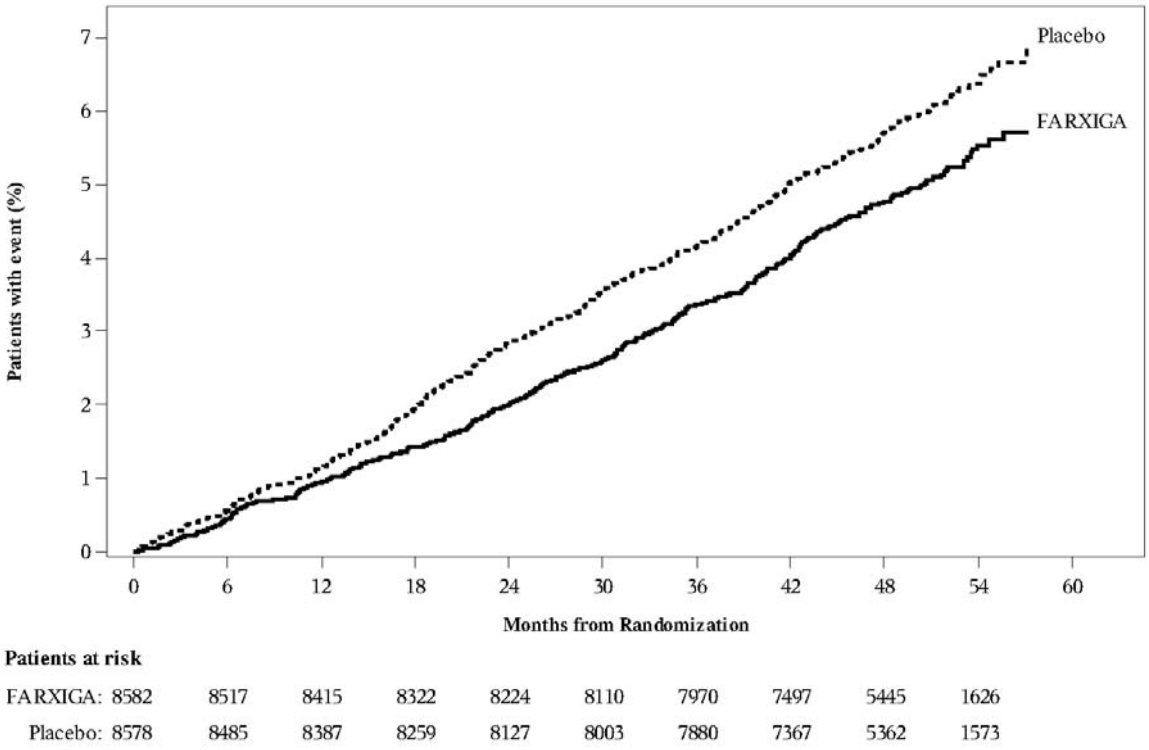
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, MI=Myocardial infarction.

* Full analysis set.

† p-value =0.005 versus placebo.

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

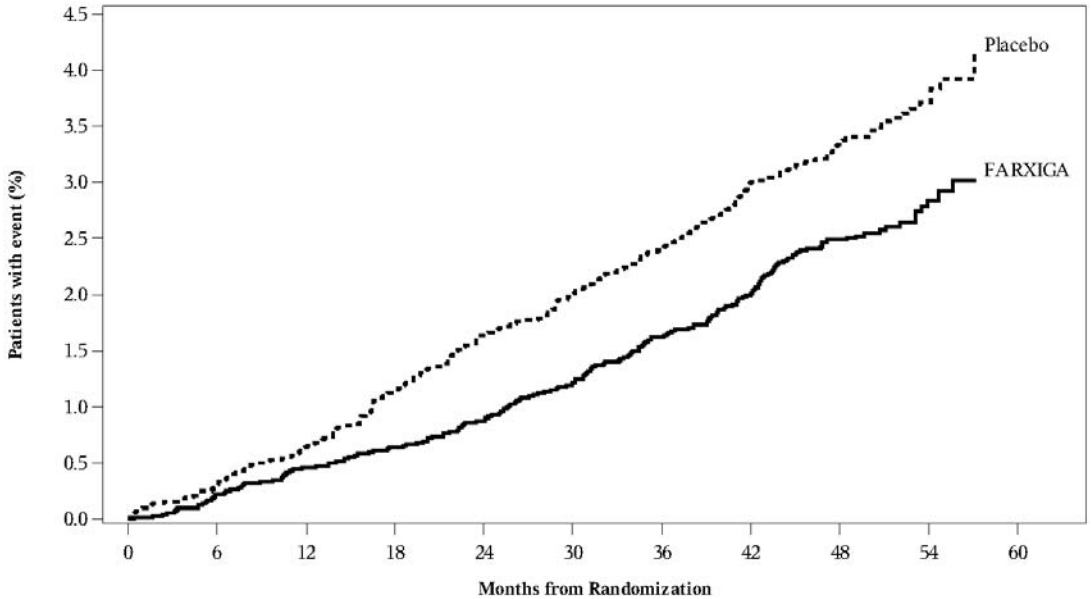
Figure 4: Time to First Occurrence of Hospitalization for Heart Failure or CV Death in the DECLARE Study



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

14.3 Heart Failure with Reduced Ejection Fraction

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF, NCT03036124) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] 40% or less) to determine whether FARXIGA reduces the risk of cardiovascular death and hospitalization for heart failure.

Of 4744 patients, 2373 were randomized to FARXIGA 10 mg and 2371 to placebo and were followed for a median of 18 months. The mean age of the study population was 66 years, 77% were male and 70% were White, 5% Black or African-American, and 24% Asian.

At baseline, 68% patients were classified as NYHA class II, 32% class III, and 1% class IV; median LVEF was 32%. History of type 2 diabetes mellitus was present in 42%, and an additional 3% had type 2 diabetes mellitus based on a HbA1c ≥6.5% at both enrollment and randomization.

At baseline, 94% of patients were treated with ACEi, ARB or angiotensin receptor-neprilysin inhibitor (ARNI, including sacubitril/valsartan 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic, and 26% had an implantable device.

FARXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85]; p<0.0001). All three components of the primary composite endpoint individually contributed to the treatment effect. The FARXIGA and placebo event curves separated early and continued to diverge over the study period (Table 15, Figures 6A, 6B and 6C).

Table 15: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FARXIGA 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value†**
Composite of Hospitalization for Heart Failure, CV Death or Urgent Heart Failure Visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	<0.0001
Composite of CV Death or Hospitalization for Heart Failure	382 (11.4)	495 (15.3)	0.75 (0.65, 0.85)	<0.0001
Components of the composite endpoints				
CV Death	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)	

Table 15: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

	Patients with events (event rate)			
Efficacy Variable (time to first occurrence)	**FARXIGA 10 mg N=2373**	**Placebo N=2371**	**Hazard ratio (95% CI)**	**p-value†**
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)	
All-Cause Mortality	276 (7.9)	329 (9.5)	0.83 (0.71, 0.97)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.

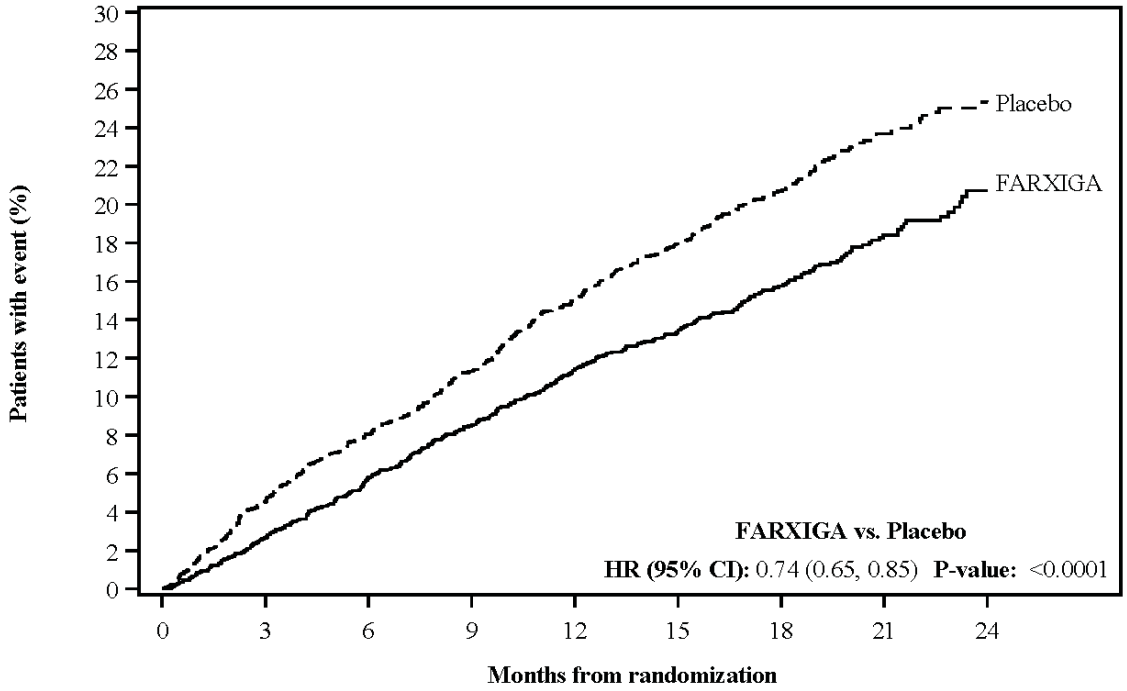
* Full analysis set.

† Two-sided p-values.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

Figure 6: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure 6A: Time to the First Occurrence of the Composite of Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit

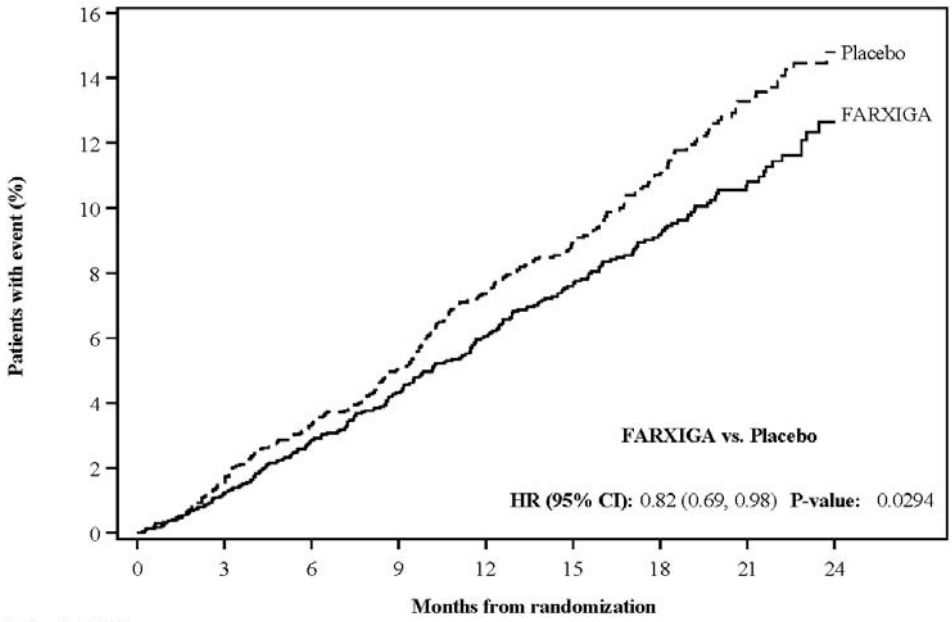


Patients at risk

FARXIGA:	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo:	2371	2258	2163	2075	1917	1478	1096	593	210

NOTE: An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics).
Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio, CI=Confidence interval.

Figure 6B: Time to the First Occurrence of Cardiovascular Death

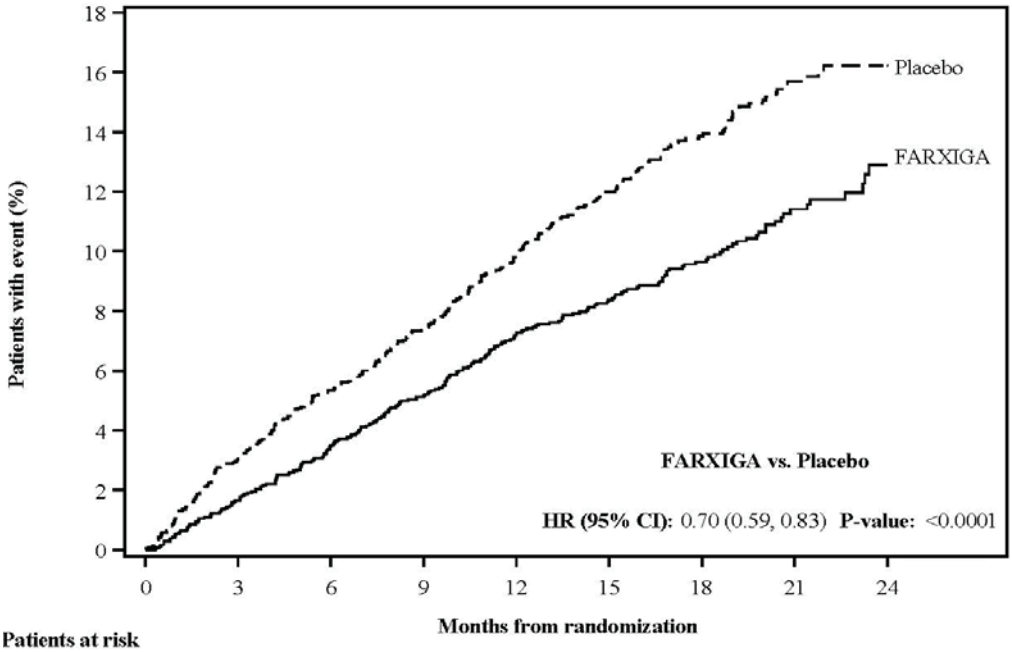


Patients at risk

FARXIGA:	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo:	2371	2330	2279	2230	2091	1636	1219	664	234

Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio, CI=Confidence interval.

Figure 6C: Time to the First Occurrence of Heart Failure Hospitalization



Patients at risk

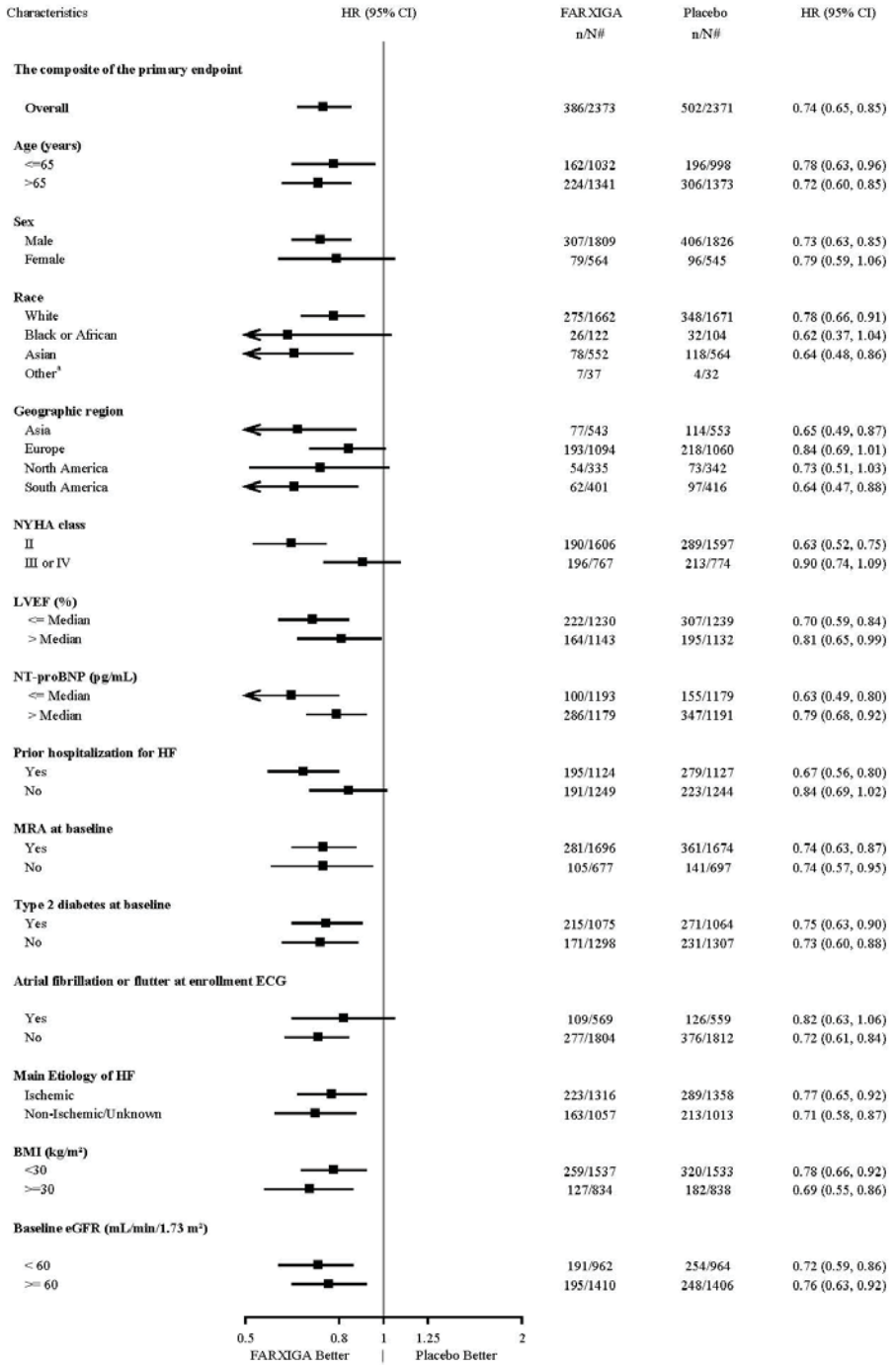
FARXIGA:	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo:	2371	2264	2168	2082	1924	1483	1101	596	212

Patients at risk is the number of patients at risk at the beginning of the period.
HR=Hazard ratio, CI=Confidence interval.

FARXIGA reduced the total number of hospitalizations for heart failure (first and recurrent) events and CV death, with 567 and 742 total events in the FARXIGA-treated vs placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

The results of the primary composite endpoint were consistent across the subgroups examined, including heart failure patients with and without type 2 diabetes mellitus (Figure 7).

Figure 7: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) Subgroup Analysis (DAPA-HF Study)



[a] Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide, HF = Heart failure, MRA = mineralocorticoid receptor antagonist, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate.

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

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 16.

Table 16: 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).

Volume Depletion

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 with diabetes mellitus that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of FARXIGA with diabetes mellitus, sometimes associated with illness or surgery among other risk factors. 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 attention immediately *[see Warnings and Precautions (5.2)]*.

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 (5.3)]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

Inform patients that necrotizing infections of the perineum (Fournier's Gangrene) have occurred with FARXIGA in patients with diabetes mellitus. 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 (5.5)]*.

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 (5.6)]*.

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 (5.6)]*.

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

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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). There have been reports of sudden kidney injury in people with Type 2 diabetes who are taking FARXIGA. You may be at a higher risk of dehydration if you:
  - 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

  Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.
- **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 in people who also have known cardiovascular disease or multiple cardiovascular risk factors
- **Heart failure when the heart is weak and cannot pump enough blood to the rest of your body to:**
  - reduce the risk of cardiovascular death, 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 and are taking FARXIGA to lower your blood sugar
- 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. Your doctor may stop your FARXIGA before you have surgery. Talk to your doctor if you are having surgery about when to stop taking FARXIGA and when to start it again.
- are eating less or there is 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.
- 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.
- 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.
- If you have diabetes
  - 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.
  - 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.

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 in people with diabetes mellitus (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 has also happened in people with diabetes who were sick or who had surgery 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**.**
- **Dehydration (loss of body water and salt).** Dehydration leading to symptoms of low blood pressure and changes in kidney function have happened in people who are taking FARXIGA. Call your healthcare provider right away if you:
  - reduce the amount of food or liquid you drink, for example if you 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) in patients with diabetes mellitus.** 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 with diabetes mellitus 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 05/2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s020

SUMMARY REVIEW

Clinical and Statistical Review

Table 1. Administrative Application Information

Category	Application Information	
Application type	Efficacy Supplement	
Application number(s)	sNDA 202993 FARXIGA® (Dapagliflozin)	
Priority or standard	Priority	
Submit date(s)	11/6/2019	
Received date(s)	11/6/2019	
PDUFA goal date	5/6/2020	
Division/office	Division of Cardiovascular and Renal Products (DCaRP)	
Review completion date	See DARRTS electronic signature date	
Established name	Dapagliflozin	
(Proposed) trade name	FARXIGA	
Pharmacologic class	SGLT2 inhibitor	
Code name	BMS-512148-05	
Applicant	AstraZeneca	
Dose form/formulation(s)	5 mg and 10 mg oral tablet	
Dosing regimen	Indication	Dosing Recommendation
	To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA Class II-IV)	Use 10 mg once daily
Applicant proposed indication(s)/population(s)	To reduce the risk of cardiovascular death and [redacted] (b) (4) in adults with heart failure with reduced ejection fraction	
Proposed SNOMED indication	Heart failure with reduced ejection fraction	
Regulatory action	Approval	
Approved indication(s)/population(s) (if applicable)	To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure with reduced ejection fraction (NYHA Class II-IV).	
Approved SNOMED indication	Heart failure with reduced ejection fraction	

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AF	atrial fibrillation
AKI	acute kidney injury
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BA	bioavailability
BE	bioequivalence
BID	twice daily
BLA	biologics license application
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDF	cumulative distribution function
CDISC	clinical data interchange standards consortium
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEA	Clinical Event Adjudication
CEAC	Clinical Event Adjudication Committee
CEC	Clinical Events Committee
CI	confidence interval
CKD	chronic kidney disease
CMC	chemistry, manufacturing, and controls
CMH	Cochran Mantel Haenszel
CMWPC	clinically meaningful within-patient change
CRF	case report forms
CRO	contract research organization
CRT-D	cardiac resynchronization therapy-defibrillator
CSR	clinical study report
CV	cardiovascular
CVOT	cardiovascular outcome

DAE	discontinuation of study drug due to adverse events
DAPA	dapagliflozin
DCRP	Division of Cardiology and Nephrology
DKA	diabetic ketoacidosis
DMC	data monitoring committee
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
EQ-5D-5L	EuroQol five-dimensional five level questionnaire
ER	event rate
ESRD	end stage renal disease
FDA	Food and Drug Administration
FMQ	FDA Medical Dictionary for Regulatory Activities Query
GCP	good clinical practice
GMP	good manufacturing practice
HF	heart failure
HHF	hospitalization for heart failure
HR	heart rate
ICD	implantable cardioverter-defibrillator
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intention-to-treat
KCCQ	The Kansas City Cardiomyopathy Questionnaire
KCCQ-TSS	KCCQ total symptom score
KCCQ-OS	KCCQ overall summary
LDL	low-density lipoprotein cholesterol
LVEF	left ventricle ejection fraction
LVOT	left ventricular outflow tract
MAED	MedDRA Adverse Event Diagnosis
MI	multiple imputation
MRA	Mineralocorticoid receptor antagonist
NDA	new drug application
NLI	National Lead Investigator Committee
NME	new molecular entity
NT-proBNP	N terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OCS	Office of Computational Science
OSE	Office of Surveillance and Epidemiology
PACD	primary analysis censoring date
PDF	probability density function
PGIC	Patient Global Impression of Change

PGIS	Patient global impression of severity
PK	pharmacokinetics
PSP	pediatric study plan
PT	preferred term
PTDV	Premature Treatment Discontinuation Visit
RD	risk difference
ROC	Receiver operating characteristic
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCV	study closure visit
SD	standard deviation
SMQ	standard MedDRA query
T2DM	type 2 diabetes mellitus
TVI	time velocity integral
WBDC	The Rave Web Based Data Capture
WR	win ratio

I. Executive Summary

1. Summary of Regulatory Action

The review team recommends approval for the use of dapagliflozin in adult patients with heart failure (HF) with reduced left ventricular (LV) function. Evidence of efficacy and safety is based on DAPA-HF, a randomized trial (n=4744) comparing dapagliflozin 10 mg daily vs. placebo in patients with NYHA class II-IV HF and LV ejection fraction <40%. In DAPA HF, dapagliflozin reduced the risk of CV death and HF hospitalization (including urgent HF visit) compared to placebo (HR 0.74, 0.65, 0.85 95% CI). The finding was robust for all components, and the reduction in risk was consistently seen in almost all prespecified subgroups, including patients with and without diabetes.

The major review issue involved assessing whether a clinically significant effect of dapagliflozin on symptoms was demonstrated in the trial (as assessed by the Kansas City Cardiomyopathy Questionnaire-Total Symptom Score). In DAPA-HF, a statistically significant, but small, increase in KCCQ-TSS score at month 8 was observed in the dapagliflozin group compared to placebo (~2.8 points). The clinical significance of this finding is questionable as it corresponds to a 1 unit change on a single item on the KCCQ-TSS. Further, the cumulative distributions (see Clinical Outcomes Assessment Review Figure 5) of scores for the dapagliflozin group were almost superimposed. The data from DAPA-HF does support a threshold of ≥15 points for improvement in KCCQ-TSS as a clinically meaningful within patient change. An analysis of the number of subjects who experienced an increase of ≥15 points in each group at month 8 (53.7% dapagliflozin vs. 47.7% placebo) reflects the small difference between groups, but does not indicate an identifiable responder population, given the large within-subject variability in the score. (b) (4) (b) (4).

Other specific areas of review included:

- An observed attenuation of effect on the primary endpoint in NYHA class III-IV patients. The finding was likely spurious, given beneficial effects seen in patient subgroups with other markers of severe disease (low EF, high NT-BNP).
- Effects of dapagliflozin on the risk of acute kidney injury (AKI). AKI events were not more frequent in the dapagliflozin arm. In fact, renal adverse events, in general, were less frequent in the treatment arm. The label was modified to remove the specific warning about AKI based on data from DAPA-HF. The hypotension warning (5.1) was modified to more appropriately describe intravascular volume depletion.

The safety review of DAPA-HF did not reveal any new safety concerns. In fact, except for intravascular volume depletion/hypotension, diabetic ketoacidosis (DKA) and genital mycotic

infections, the dapagliflozin-associated risks included in the current Warnings and Precautions section (based on glycemic control experience) were not observed more frequently in the dapagliflozin group. Notably, there was no excess of serious hypoglycemic events in the dapagliflozin group in DAPA-HF; three adjudicated cases of DKA were described, all in patients with diabetes.

The Dosing and Administration and Contraindications section of labeling were modified to harmonize and clarify dosing in renal impairment for the different indications. Labeling recommendations from the Office of Prescription Drug Promotion and the Patient Labeling group were considered and incorporated, as appropriate.

The Office of Pharmaceutical Quality reviewed this efficacy supplement (including the sponsor's request for a categorical exclusion from the need to prepare an environmental assessment) and recommended approval. The supplement contained three non-GLP studies to evaluate dapagliflozin's effects on cardiac structure and function in mouse models of type 2 diabetes which were reviewed but did not have impact on labeling for this supplement.

In conclusion, the application provides substantial evidence of dapagliflozin's effectiveness in reducing the risk of CV death and hospitalization for HF. Labeling describes dapagliflozin's risks and is considered sufficient to ensure that the benefits of dapagliflozin in this population outweigh the risks.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Heart failure (HF) is a chronic debilitating disease with increased risk for death. It affects over 5.8 million adults in the United States with an annual incidence of > 650,000. About half of these cases are HF with reduced ejection fraction (HFrEF). Despite available therapies, the rate of cardiovascular (CV) death and HF hospitalization remain high at about 20%; recurrent hospitalizations for HF are frequent. The 5-year mortality rate of HF is approximately 66% in patients aged over 60 years.	Heart failure (HF) is a chronic condition with significant morbidity and mortality.
Current Treatment Options	Treatment options for patients with HFrEF include pharmacologic and device therapies. Approved pharmacologic therapies that • reduce HF hospitalization and mortality are angiotensin converting enzyme inhibitors / angiotensin receptor blockers / angiotensin receptor blocker with neprilysin inhibitor, beta-blockers, mineralocorticoid receptor antagonists, and hydralazine with isosorbide dinitrate • reduce HF hospitalization is ivabradine • improve HF symptoms are digoxin and diuretics Approved device therapies to treat patients with HF are implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D).	Despite available treatment options, there is a continued unmet need to reduce morbidity and mortality in patients with HFrEF.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Dapagliflozin reduced the rate of HF hospitalization, urgent HF visit, and cardiovascular (CV) death in patients with HFrEF, when used on top of standard of care, regardless of T2DM status, in DAPA-HF trial. DAPA-HF trial was an international, prospective, randomized, placebo-controlled, event driven trial of 10 mg of dapagliflozin with the primary composite endpoint of time to CV death, HF hospitalization or urgent HF visit. DAPA-HF also demonstrated a statistically significant difference in change in KCCQ-TSS favoring dapagliflozin - KCCQ-TSS change at 8 months from baseline in dapagliflozin group was 6.1±18.6 and in placebo group was 3.3±19.2 with a difference of 2.8 points (95% CI 1.6, 4.0), P-value <0.001. Although statistically significant, anchor-based analyses in DAPA-HF did not indicate the difference in KCCQ-TSS change to be clinically meaningful.	DAPA-HF provided substantial evidence of efficacy of dapagliflozin in reduction of HF hospitalization, urgent HF visit, and cardiovascular (CV) death in patients with HFrEF, when used on top of standard of care, regardless of T2DM status. 

Risk and Risk Management	• Dapagliflozin is currently approved as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and to reduce the risk of hospitalization for heart failure in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors. The approved dapagliflozin label contains: – Warnings and Precautions for hypotension, diabetic ketoacidosis (DKA), acute kidney injury, urosepsis and pyelonephritis, hypoglycemia, necrotizing fasciitis of the perineum (Fournier's gangrene) and genital mycotic infections. – The label describes increases in serum creatinine, hematocrit, and low-density lipoprotein cholesterol (LDL) and decreases in eGFR and serum bicarbonate • Safety assessment of dapagliflozin in DAPA-HF focused on SAEs and predefined AEs of special interest (AESIs) based on the potential risks in the same class. – For the most part, the incidence of death, SAEs, AESIs and AEs leading to discontinuation was similar between the dapagliflozin arm and the placebo arm. – The incidence of AEs related to volume depletion was slightly higher in the dapagliflozin arm (7.2%) vs. the placebo arm (6.5%) with the most common reported AEs of hypotension and hypovolemia. – There were 3 events of diabetic ketoacidosis (DKA) in the dapagliflozin arm and none in the placebo arm; all 3 patients had T2DM at baseline. – There was also no difference between treatment arms in fractures (2.1% of patients in each arm) and amputations (0.5% of patients in each arm) – Genital infection AE was not prospectively assessed; though higher incidence was reported in the dapagliflozin arm vs. placebo arm (0.8% vs. 0.1%) and higher percent of patients discontinued study drug due to genital infection in the dapagliflozin arm (0.3% vs. 0). • Although the label carries a Warning and Precaution for acute kidney injury, the incidence of acute kidney injury was not greater in the dapagliflozin arm as compared to the placebo arm in DAPA-HF (6.0% versus 6.7% of patients or 42/1,000 patient- years versus 47/1,000	No new dapagliflozin-associated risks were identified in the DAPA-HF trial. Consistent with the trials of dapagliflozin for glycemic control, volume depletion and genital infections occurred more commonly in the dapagliflozin group. Labeling is considered sufficient to ensure that the benefits of dapagliflozin in the target population outweigh the risks. Severe hypoglycemia events were balanced between the arms and all occurred in patients with T2DM. There were three DKA events, all occurred in the dapagliflozin arm and in patients with T2DM. The risk of acute kidney injury was not greater in the dapagliflozin as compared to the placebo arm in DAPA-HF. Labeling should reflect this finding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patient-years, dapagliflozin versus placebo, respectively). • There was no difference between treatment arms in major hypoglycemic events (0.2%) and all patients with major hypoglycemic events had T2DM at baseline. • Consistent with findings in other trials, a small mean increase in hematocrit was observed following initiation of dapagliflozin therapy. The difference between arms started early and then plateaued after month 4 (~2.5% increase). Initiation of therapy was also associated with a small mean increase in creatinine and decrease in eGFR probably attributed to a hemodynamic effect on renal function. No corresponding clinical findings were found associated with the small differences in hematocrit and creatinine. Serum bicarbonate and LDL were not collected in DAPA-HF.	

Conclusions Regarding Benefit-Risk

Dapagliflozin is an oral sodium-glucose cotransporter 2 (SGLT2) that is approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (2014) (5 and 10 mg once daily), and 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 (2019) (10 mg once daily). On 11/6/2019, AstraZeneca submitted an efficacy supplement for dapagliflozin for the proposed indication to [redacted] (b) (4)

In support of the proposed indication, the applicant conducted a single, phase 3, international, prospective, randomized, placebo-controlled, event driven trial, DAPA-HF, comparing dapagliflozin 10 mg once daily with placebo, administered on top of standard of care therapy in adult patients with chronic heart failure with reduced ejection fraction of $\leq 40\%$ (NYHA class II-IV) and eGFR ≥ 30 ml/min/m^2. DAPA-HF randomized 4,744 patients (14.3% in North America) at 410 centers in 20 countries. The study population comprised primarily of white (70% with 16% Hispanic; 23% Asian, 4.8% Black, 1.4%) males (77%) with a mean age of 66 years (range, 22 to 94 years). Majority of patients were NYHA class II (68%) with a baseline median ejection fraction of 32%, baseline median NT-proBNP level of 1437 pg/mL (IQR, 857–2650 pg/mL), and 56% of the patients did not have type 2 diabetes mellitus. The baseline median blood pressure was 121/73 mm Hg, and pulse rate was 70 beats per minute. Main etiology of HF was ischemic (56% with 36% non-ischemic and 8% unknown). Patients received standard of care therapies for HF including ACEi/ARB/ARNI (94%), beta-blocker (96%), mineralocorticoid receptor antagonist (71%), diuretics (93.4%), and ivabradine (4.8%). The mean duration of follow up was approximately 17 months (range, 0 to 28 months). The ascertainment rate for vital status was 99.9%.

Incidence of the primary composite endpoint of CV death or a HF event (hospitalization for HF or urgent HF visit) was 16.3 versus 21.2% in dapagliflozin versus placebo group with a HR 0.74 (95% CI 0.65, 0.85), p<0.0001 in favor of dapagliflozin.

There were 386 and 502 patients with CV death or HF events in the dapagliflozin and placebo groups, respectively, corresponding to an event rate of 11.6 and 15.6 per 100 patient-years. The absolute risk reduction and number needed to treat are 4 and 26 (95% CI 18, 46). All the three components of the primary composite endpoint contributed to the overall treatment effect.

Key Review Issue: Is the observed change in KCCQ-TSS in DAPA-HF clinically meaningful?

DAPA-HF evaluated the secondary efficacy endpoint of change in KCCQ-TSS from baseline to 8 months as a measure of symptom improvement in patients with HFrEF. KCCQ-TSS includes the symptom frequency and burden domains of KCCQ. To define a clinically meaningful within-patient change (CMWPC) in KCCQ-TSS in DAPA-HF, the applicant implemented an anchor-based approach utilizing patient-reported outcome (PRO) of patient global impression of severity (PGIS). Rank ANCOVA, adjusted for baseline KCCQ score and stratified by T2DM status at randomization demonstrated a statistically significant change in KCCQ-TSS favoring dapagliflozin - KCCQ-TSS change at 8 months from baseline in dapagliflozin group was 6.1±18.6 and in placebo group was 3.3±19.2 with a least mean squares difference of 2.8 points (95% CI 1.6, 4.0), P-value <0.001. The proportion of deaths and missing data were balanced across the two groups. At 8 months, a stable PGIS correlated with a mean KCCQ-TSS change of 3.23 ± 15.51, and a median KCCQ-TSS change of 1.0 (minimum -63.5, maximum 82.3). At 8 months, a small improvement in PGIS correlated with a mean KCCQ-TSS change of 9.52 ± 17.42, and a median KCCQ-TSS change of 8.3 (minimum -49.0, maximum 80.2). A background variation of < 5 points in KCCQ score in patients with HFrEF has been reported in literature. The observed between-group difference in change in KCCQ-TSS of 2.8 falls within the background variation rate reported in literature (Green 2000) and that observed in DAPA-HF trial. The observed difference likely represents minimal improvement in HF symptoms. Hence, we do not believe that DAPA-HF results represent a clinically meaningful difference in KCCQ-TSS change at 8 months from baseline.

Key Safety Findings in the Target Population

The risks observed with the use of dapagliflozin in DAPA-HF trial were consistent with the known risk profile of dapagliflozin from the trials of glycemic control and cardiovascular outcomes in patients with T2DM. The incidence of death, SAEs, AESIs and AEs leading to discontinuation was similar between the dapagliflozin and placebo arms. The incidence of AEs related to volume depletion was slightly higher in the dapagliflozin (7.2%) vs. placebo arm (6.5%) with the most common reported AEs of hypotension and hypovolemia. The incidence of acute kidney injury was not greater in the dapagliflozin arm (6.0%) as compared to the placebo arm (6.7%) in DAPA-HF. Subgroup analyses indicate that the risk of volume depletion and acute kidney injury was in general similar regardless of T2DM status at baseline. There were 3 events of DKA in the dapagliflozin arm and none in the placebo arm; all 3

patients had T2DM at baseline. There was also no difference in the incidence of fractures (2.1% of patients in each arm) and amputations (0.5% of patients in each arm) between the two treatment arms.

Conclusions Regarding Risk-Benefit

The submitted data provide substantial evidence of efficacy of dapagliflozin in reducing HF hospitalization, urgent HF visit, and CV death in patients with HFrEF, with or without T2DM, when added to standard of care, and a compelling evidence that the clinical benefit outweighs potential risk with dapagliflozin. Hence, the review team recommends approval of the efficacy supplement.

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted a single, phase 3 trial (DAPA-HF) in support of supplemental new drug application (sNDA) for FARXIGA (dapagliflozin) for the following new indication:

> "*FARXIGA is indicated in adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and* (b) (4) "

Dapagliflozin is approved in US for the following indications:

i. as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (2014) (5 and 10 mg once daily)
ii. 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 (2019) (10 mg once daily)

Dapagliflozin is a sodium-glucose cotransporter 2 (SGLT2) inhibitor. The mechanism of action of dapagliflozin is inhibition of renal SGLT2 leading to reduced reabsorption of glucose and sodium from the glomerular filtrate in the proximal renal tubule, thereby, increasing urinary excretion of glucose and osmotic diuresis. The degree of glucosuria is proportional to plasma glucose level and explains the hypoglycemic effect of dapagliflozin. Other observed effects of SGLT2 inhibition include reduction in blood pressure and body weight and increase in hematocrit. The precise mechanism of cardiorenal benefit with SGLT2 inhibitors is not well understood.

Heart failure (HF) is a chronic condition with significant morbidity and mortality. HF affects 1 to 2% of the population worldwide, with higher prevalence in the elderly, ≥10% in those age ≥65 years. The annual incidence of HF in the US is > 650,000[1] and it is the leading cause of recurrent hospitalizations and early readmissions.[2] About half of these cases are HF with reduced ejection fraction (HFrEF), with a 5-year mortality of approximately 66% in patients aged over 60 years.[3]

[1] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.
[2] The Burden of Iron Deficiency in Heart Failure. Bruno M.L. Rocha, Gonçalo J.L. Cunha, Luiz F. Menezes Falcão. J Am Coll Cardiol. 2018 Feb, 71 (7) 782-793.
[3] Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. JACC Heart Fail. 2018;6(8):678-85.

Treatment of patients with HFrEF is targeted towards reduction of morbidity/mortality, symptom relief, and adequate management of comorbidities such as hypertension, atrial fibrillation, sleep apnea, obesity, etc. FDA approved drugs to reduce morbidity/mortality in patients with HFrEF include angiotensin converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)/angiotensin receptor blocker with neprilysin inhibitor (ARNI), beta blockers, mineralocorticoid receptor antagonists, hydralazine/isosorbide dinitrate, digoxin, and Ivabradine.[4] Diuretics are used to provide symptomatic relief. In addition, device therapies such as internal cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) are used in appropriate patients with HFrEF to further reduce morbidity/mortality. Despite these therapies, the rate of cardiovascular (CV) death and HF hospitalization remain high at about 20%.[5]

3.1. Approach to the Review

This was a joint clinical and statistical review. Charu Gandotra and Fanhui Kong focused on the data supporting efficacy, and Tzu-Yun McDowell focused on the data supporting safety. A Clinical Outcomes Assessment consult was obtained to help evaluate the efficacy endpoint of heart failure symptom improvement measured by KCCQ-TSS.

The Applicant did not conduct additional clinical pharmacology studies to support the proposed indication. There were no relevant nonclinical data for review.

[4] See table in appendices for details of approved treatments for chronic heart failure.
[5] McMurray, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

Table 3. Clinical Trial Submitted in Support of Efficacy and Safety Determinations for dapagliflozin (Source: Reviewer compilation)

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Patients Randomized[2]	Number of Centers and Countries
D1699C00001	Adults (≥18 years), with HFrEF (NYHA class II-IV for ≥2 months), LVEF of ≤40% within the last 12 months, eGFR ≥30 mL/min/1.73 m2	Control Type: Placebo Randomization: Randomized Blinding: Double-blind	Drug: Dapagliflozin / Placebo Dose: 10 mg Number treated: 2373 Duration: 18.2 mo	Primary: Composite of CV death, hospitalization for HF or urgent HF visit Secondary: 1.CV death or hospitalization for HF 2.First and recurrent hospitalization for HF and CV death 3. Change from baseline to 8 months in KCCQ-TSS 4. Renal composite of ≥50% sustained decline in eGFR; reaching End Stage Renal Disease; sustained eGFR <15 mL/min/1.73m2 or, chronic dialysis treatment or, receiving a renal transplant, or renal death 5. All-cause mortality	4744	410 and 20

Abbreviations: HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; LVEF: left ventricle ejection fraction; eGFR: estimated glomerular filtration rate; CV: cardiovascular; HF: heart failure; KCCQ-TSS: Kansas City Cardiomyopathy Questionnaire Total Symptom Score

4. Patient Experience Data

DAPA-HF trial collected data on patients' perception of their heart failure symptoms at baseline and at various timepoints during the trial by using KCCQ, PGIS, and PGIC questionnaires. These are discussed in detail in sections 5.7.1. and 15.

5. Evidence of Benefit (Assessment of Efficacy)

5.1. Assessment of Dose and Potential Effectiveness

The DAPA-HF trial evaluated a single dose of 10 mg of dapagliflozin as the 10 mg dose has been demonstrated to be safe and effective for glycemic control and prevention of heart failure

hospitalization in patients with T2DM. Additionally, the pharmacokinetic and pharmacodynamic data indicated that the 10 mg dose will achieve a near maximal inhibition of SGLT2.

5.2. Design of Clinical Trials Intended to Support Efficacy

In support of the proposed indication, the applicant conducted a single phase 3 trial (D1699C00001) titled "Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients with Chronic Heart Failure with Reduced Ejection Fraction (DAPA-HF)." The first Global Clinical Study Protocol Version 1 dated 10/26/2016 was amended once. The protocol overview provided here is based on Version 1 with amendments noted.

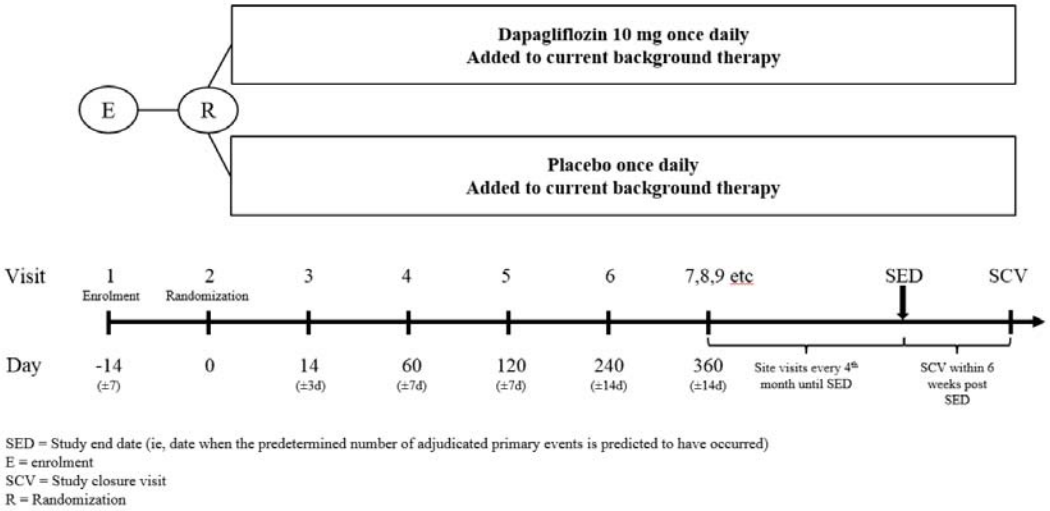
Study D1699C00001, referred to as DAPA-HF in this review, was a phase 3, international, multicenter, prospective, randomized, double-blind, placebo-controlled, event driven trial. DAPA-HF evaluated the effect of 10 mg of dapagliflozin, compared to placebo, administered once daily, on top of standard of care therapy in adult patients with chronic heart failure with reduced ejection fraction (HFrEF), New York Heart Association (NYHA) class II-IV, with and without T2DM.

Sample Size: DAPA-HF was an event driven trial with 844 primary events needed to achieve 90% power for a hazard ratio (HR) of 0.80 to demonstrate superiority of dapagliflozin over placebo. Findings from the EMPA-REG trial informed the assumption of a HR of 0.80. The planned sample size, assuming an annual event rate of 11% in the placebo group, was 4500 patients (2250 patients in each treatment group) to achieve 844 primary events. The estimated recruitment and average follow-up periods were 18 and 24 months, respectively.

Randomization: An Interactive Voice/Web Response System (IxRS) was used to randomize eligible patients to dapagliflozin versus placebo in 1:1 ratio (balanced blocks), stratified by T2DM status. The protocol allowed for capping randomization to ensure at least 30% patients with and without T2DM, each. However, capping was not needed. Randomization was monitored based on geographic region, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, and atrial fibrillation (AF) status to ensure adequate representation of these patient subgroups. Figure 1 displays the study design. Table 27 in the appendices displays the schedule of study visits and assessments.

Study Drug Dose Modification Approach: Study patients were randomized to 10 mg of dapagliflozin or placebo. However, if a patient experienced adverse effect(s) of volume depletion, hypotension, or transient worsening of kidney function, the study protocol allowed a temporary study drug dose reduction to 5 mg or dose interruption, if modification or discontinuation of concomitant non-essential medication doses did resolve the adverse effect.

Figure 1. Study Design of DAPA-HF Trial (Source: Sponsor Material)



SED = Study end date (ie, date when the predetermined number of adjudicated primary events is predicted to have occurred)
E = enrolment
SCV = Study closure visit
R = Randomization

Study Objectives

Primary efficacy objective: To determine if dapagliflozin is superior to placebo, when added to standard of care, in reducing the incidence of CV death or an HF event (hospitalization for HF or equivalent HF event, i.e., an urgent HF visit).

Secondary efficacy objectives:

1. To compare the effect of dapagliflozin versus placebo on CV death or hospitalization for HF
2. To compare the effect of dapagliflozin versus placebo on total number of recurrent HF hospitalizations and CV death
3. To compare the effect of treatment with dapagliflozin versus placebo on the KCCQ total symptom score for HF symptoms and physical limitations.[6]
4. To determine if dapagliflozin compared with placebo reduces the incidence of a composite endpoint of worsening renal function
5. To determine whether dapagliflozin, compared with placebo, reduces the incidence of all-cause mortality

[6] Clarification: The original KCCQ endpoint was 'clinical symptom score for HF symptoms and physical limitations'. Based of FDA feedback, the KCCQ endpoint was amended to 'total symptom score for HF symptoms' for CSP version 2.0 (Section 2.2). In CSP version 2.0 "physical limitations" was not removed as planned. The endpoint is correctly defined in SAP version 3.0 (Section 9.9.2).

Safety objective is as follows:

1. To evaluate the safety and tolerability of dapagliflozin in this patient population.

Exploratory objectives:

1. To compare the effect of dapagliflozin versus placebo on an expanded composite outcome reflecting worsening of HF
2. To determine whether dapagliflozin compared with placebo will have effect on NYHA class
3. To determine whether dapagliflozin compared with placebo will reduce the incidence of diagnosis of atrial fibrillation (AF) in patients without history of AF at baseline
4. To determine whether dapagliflozin compared with placebo will result in a reduction of the incidence of hyper – and hypokalemia
5. To determine whether dapagliflozin compared with placebo affected the number of events of doubling of serum creatinine
6. To determine whether dapagliflozin compared with placebo reduced the incidence of diagnosis of T2DM in patients without diabetes at baseline
7. To determine whether dapagliflozin compared with placebo had effect on HbA1c in T2DM sub-group
8. To determine whether dapagliflozin compared with placebo had an effect on systolic BP
9. To determine whether dapagliflozin compared with placebo had an effect on body weight
10. To determine whether dapagliflozin compared with placebo reduced the incidence of myocardial infarction
11. To determine whether dapagliflozin compared with placebo reduced the incidence of any stroke (ischemic, hemorrhagic, or undetermined)
12. To compare the effect of dapagliflozin versus placebo on health status assessed by Patient Global Impression of Change (PGIC) and Patient global impression of severity (PGIS) questionnaires
13. To compare the effect of dapagliflozin versus placebo on health status assessed by EuroQol five-dimensional five level questionnaire (EQ-5D-5L) to support health economic analysis and health technology assessment
14. To collect and analyze pharmacokinetic (PK) samples for dapagliflozin concentration
15. To assess cardiac structure and function with echocardiography at baseline and 8-months follow-up
16. To collect and store samples of plasma and serum for future exploratory biomarker research

Study Endpoints

Primary efficacy endpoint:

1. Time to the first occurrence of any of the components of this composite:
    a. CV death
    b. Hospitalization for HF
    c. An urgent HF visit

Secondary efficacy endpoints:

1. Time to the first occurrence of either of the components of this composite:
    a. CV death
    b. Hospitalization for HF
2. Total number of (first and recurrent) HF hospitalizations and CV death
3. Change from baseline measured at 8 months in the total symptom score of the KCCQ, a specific HF patient reported outcome questionnaire
4. Time to the first occurrence of any of the components of this composite:
    a. ≥50% sustained* decline in eGFR
    b. Reaching End Stage Renal Disease (ESRD)
        i. Sustained* eGFR <15 mL/min/1.73m2 or,
        ii. Chronic* dialysis treatment or,
        iii. Receiving a renal transplant
    c. Renal death

    *As defined in the Clinical Event Adjudication (CEA) charter
5. Time to death from any cause

Safety endpoint:

1. Serious Adverse Events (SAEs)
2. Discontinuation of study drug due to Adverse Events (DAEs)
3. Changes in clinical chemistry/hematology parameters
4. AEs of special interest (volume depletion, renal events, major hypoglycemic events, fractures, DKA, AEs leading to amputation and AEs leading to a risk for lower limb amputation)

Exploratory endpoints:

1. Time to the first occurrence of any of the components of the expanded composite worsening HF outcome:
    a. CV death
    b. Hospitalization for HF
    c. An urgent HF visit

   d. Documented evidence of worsening HF symptoms/signs leading to initiation of a new treatment for HF sustained for at least 4 weeks or augmentation of existing oral therapy for HF (e.g., increase in dose of diuretic) sustained for at least 4 weeks
2. Change in NYHA class from baseline
3. Proportion of patients without history of AF at baseline with a new diagnosis of AF during the study
4. Time to the first occurrence of each of any of the following central lab levels of serum potassium:
   a. >6.0 mmol/L
   b. >5.5 mmol/L
   c. <3.5 mmol/L
   d. <3.0 mmol/L
5. Number of events with doubling of serum creatinine (compared with the most recent laboratory measurement)
6. Proportion of patients without T2DM at baseline with a new diagnosis of T2DM during the study
7. Changes in HbA1c from baseline
8. Change in systolic BP from baseline
9. Change in body weight from baseline
10. Time to first fatal or non-fatal MI
11. Time to first fatal or non-fatal stroke of any cause
12. Changes in health status measured by PGIC and PGIS
13. Changes in health status measured by EQ-5D-5L

Reviewer Comments: The primary efficacy endpoint of a composite of CV death, hospitalization for HF (HHF), and urgent HF visit is a clinically significant and well-defined endpoint.

Study committees:

1. Executive Committee (EC): The EC was comprised of international academic leaders and non-voting members of the sponsor and operated under an Executive Committee charter. EC was responsible for the final overall study design, and recommendations to the sponsor regarding early stopping or modifications of the study based on information received from the Data Monitoring Committee (DMC).
2. National Lead Investigator Committee (NLI): The NLI Committee comprised national leaders from each country where the study was conducted and supervised by the Executive Committee. Members of the committee were responsible for providing clinical guidance on study implementation, recruitment and study conduct in their respective country.
3. Data Monitoring Committee (DMC): An independent DMC monitored the trial to ensure patient safety, performed the interim efficacy analysis, and reported to the EC. The DMC operated under the DMC charter to ensure maintenance of blinding and integrity of the study.

4. Clinical Event Adjudication Committee (CEAC): The CEAC conducted adjudication of potential endpoints in the trial.
5. Diabetic Ketoacidosis Adjudication Committee (DKA-AC): The DKA-AC provided independent blinded adjudication of potential cases of DKA by expert endocrinologists. This was coordinated by the TIMI Study Group Clinical Events Committee (CEC) Department.

5.3. Eligibility Criteria

DAPA-HF enrolled patients with and without T2DM. T2DM was defined as an established diagnosis of T2DM or HbA1c ≥ 6.5% reported by the central laboratory test at enrolment. Patients had to meet the following eligibility criteria at enrolment:

Inclusion criteria

- Male or female adults (≥18 years)
- Established diagnosis of HFrEF (New York Heart Association [NYHA] class II-IV for ≥2 months)
- Left ventricular ejection fraction (LVEF) of ≤40% within the last 12 months; if patients underwent any surgical, device or pharmacological intervention (e.g. initiation of a beta-blocker) that might improve LVEF must have a measurement of LVEF at least 3 months after the intervention in order to be eligible
- Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2 (CKD-EPI formula)
- Have received local standard of care for HFrEF and treated appropriately; medical and/ or device therapy (except diuretic dose) should have been optimized at least 4 weeks prior to enrolment.
- NT-proBNP >600 pg/ml (or if hospitalized for heart failure within the previous 12 months, NT-proBNP ≥400 pg/ml) at enrolment; if concomitant atrial fibrillation at Visit 1, NT-proBNP must be ≥900 pg/ml (irrespective of history of heart failure hospitalization)

Exclusion criteria

- SGLT2 inhibitor therapy within 8 weeks prior to enrolment
- History of intolerance to SGLT2 inhibitor
- Type 1 diabetes mellitus (T1D)
- HF due to restrictive cardiomyopathy, active myocarditis, constrictive pericarditis, hypertrophic (obstructive) cardiomyopathy or uncorrected primary valvular disease
- Women of child-bearing potential (i.e., those who are not chemically or surgically sterilized or who are not post-menopausal) who are not willing to use a medically accepted method of contraception that is considered reliable in the judgment of the investigator OR women who have a positive pregnancy test at enrolment or randomization OR women who are breast-feeding

5.4. Data Sources

The sponsor's electronic data sources were stored in the directories of \\CDSESUB1\evsprod\NDA202293\0654 of the Center's electronic document room of the Agency. Data sources include all material reviewed, i.e., study reports, raw data sets in SDTM format, analysis data sets in ADAM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets are stored in the directory of \\CDSESUB1\evsprod\NDA204042\0654\m5\datasets\. The analysis software is also stored in the same directory.

Reviewer Comments: *The data sets and variable names were well-defined, and instructions were clear. The statistical reviewer could reproduce the primary analysis datasets, in particular those related to the analyses of the primary and secondary endpoints.*

5.5. Data quality

The sponsor developed the study protocol for the study and data management. The quality of study data was ensured through monitoring of investigational sites, providing training for study personnel, and use of data management procedures. In the Clinical Study Protocol, the applicant defined quality control procedure to ensure that all data were reliable and had been processed correctly. This included: to contact and visit the study site to monitor the study regularly by an AstraZeneca representative, to build quality into the design, conduct, analysis, and reporting of the study, to perform data management according to the Data Management Plan (DMP), to save data to a central database, and to review, query, and update data as needed. When all data have been coded, validated, signed and locked, a clean file would be declared. The final database would therefore be locked.

Applicant undertook a GCP audit program to ensure compliance with its procedures and to assess the adequacy of its quality control measures. Audits, by a Global Quality Assurance group operating independently of the study monitors, were directed towards all aspects of the clinical study process and its associated documentation.

5.5.1. Statistical Analysis Plan

Plan to control type I error rate: One interim analysis was planned to be performed when approximately 75% of the primary events had been adjudicated, using the Haybittle-Peto rule. The significance level for the final analysis was determined by the Haybittle-Peto function based on the actual number and timing of interim analyses. The Sponsor and Investigators remained blinded to the results. At the interim analysis, the primary composite endpoint was planned to be tested at the pre-specified alpha level of 0.001, resulting in a significance level of 0.02496 (corresponding to 0.04992, 2-sided) at the final analysis. If superiority was achieved for the primary endpoint, then the superiority of dapagliflozin to placebo on CV deaths would be tested at a one-sided level of 0.001. If CV death was significant, then an action will be triggered whereby the DMC would evaluate the totality of the efficacy data and safety data, to determine if benefit was unequivocal and overwhelming such that the DMC would recommend ending the study. The DMC had the flexibility

to conduct additional interim analysis if deemed necessary. The significance level for the final analysis would account for actual number and timing of interim analyses. The primary and secondary endpoints included in confirmatory analysis were tested in a hierarchical sequence at the 0.04992 significance level.

Analysis sets:

Full analysis set (FAS) included all randomized patients irrespective of treatment actually received, protocol adherence, and continued participation. FAS was used for analyses of primary, secondary, and exploratory efficacy variables.

Safety analysis set (SAS) included all patients who received at least one dose of the study medication. SAS was used for primary analysis of all safety variables according to treatment actually received.

Primary analysis: The primary analysis was based on the intention-to-treat (ITT) principle using the FAS, including events with onset on or prior to the primary analysis censoring date (PACD), individually adjudicated and confirmed by the Clinical Event Adjudication committee. In the analysis of the primary composite endpoint, treatments (dapagliflozin versus placebo) were compared using a Cox proportional hazards model with a factor for treatment group, stratified by T2DM status at randomization, and adjusting for history of hospitalization for HF. The Efron method for ties and p-value based on the score statistic was used. Event rates per 100 patient years, p-value, HR, and 95% confidence interval were reported. Kaplan-Meier estimates of the cumulative proportion of patients with event were calculated and plotted for the composite endpoint and for the individual components.

The contribution of each component of the primary composite endpoint to the overall treatment effect was examined. In the analysis of the components, all first events of the given type were included irrespective of any preceding non-fatal composite event of a different type. Methods similar to those described for the primary analysis were used to separately analyze the time from randomization to the first occurrence of each component of the primary composite endpoint.

Censoring: The time-to-event analysis using the Cox regression depended on the assumption of non-informative or ignorable censoring, corresponding to the missing-at-random assumption. The analysis used withdrawal of consent, non-cardiovascular (CV) death, date of last clinical event assessment or PACD for censoring of patients without any primary event.

Secondary endpoint analyses: The analysis of secondary time to first event endpoints (the composite of CV death or hospitalization for HF, the renal composite endpoint and all-cause mortality) were based on the ITT principle and stratified by T2DM status. The composite of CV death or hospitalization for HF was adjusted for history of hospitalization for HF. The renal composite endpoint was adjusted for baseline eGFR. The total number of HF hospitalizations (first and recurrent) and CV death was analyzed in a semiparametric proportional rates model.

KCCQ Analyses: Change from baseline at 8 months in the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) was analyzed using the rank ANCOVA method. In addition, to quantify the treatment effect, a win ratio and supporting analyses of thresholds of meaningful change from baseline were presented. Missing values in the KCCQ TSS, due to reasons other than death, at timepoints included in the analysis were imputed under Missing at Random

assumption, using predictive mean matching multiple imputation model. The applicant also performed supportive responder analyses.

Changes to planned analyses: Version 1.0 of the SAP was dated January 31, 2017. Two subsequent SAP amendments were prepared: version 2.0 was published February 19, 2019 and version 3.0 was published July 23, 2019. According to the Applicant, all amendments were made after the completion of patient recruitment and before study unblinding.

In SAP version 2.0, revised on February 19, 2019, it was clarified that the significance level was determined based on the exact actual proportion of primary endpoints included in the interim analysis. The analysis of the KCCQ endpoint was changed to a composite rank-based method. In SAP version 3.0 revised on July 23, 2019, details of statistical methods, assumptions and references for the joint frailty model of recurrent HF events and CV death were added; details about Ghosh and Lin plot were added. Additional details regarding responder analysis of KCCQ TSS were added. Clarification was added regarding the variable representing the number of HF events in multiple imputation of missing TSS values. Appendix B in SAP describing the estimation of clinically meaningful thresholds for KCCQ-TSS was added.

5.6. Results of Analyses of Clinical Trials / Studies Intended to Demonstrate Benefit to Patients

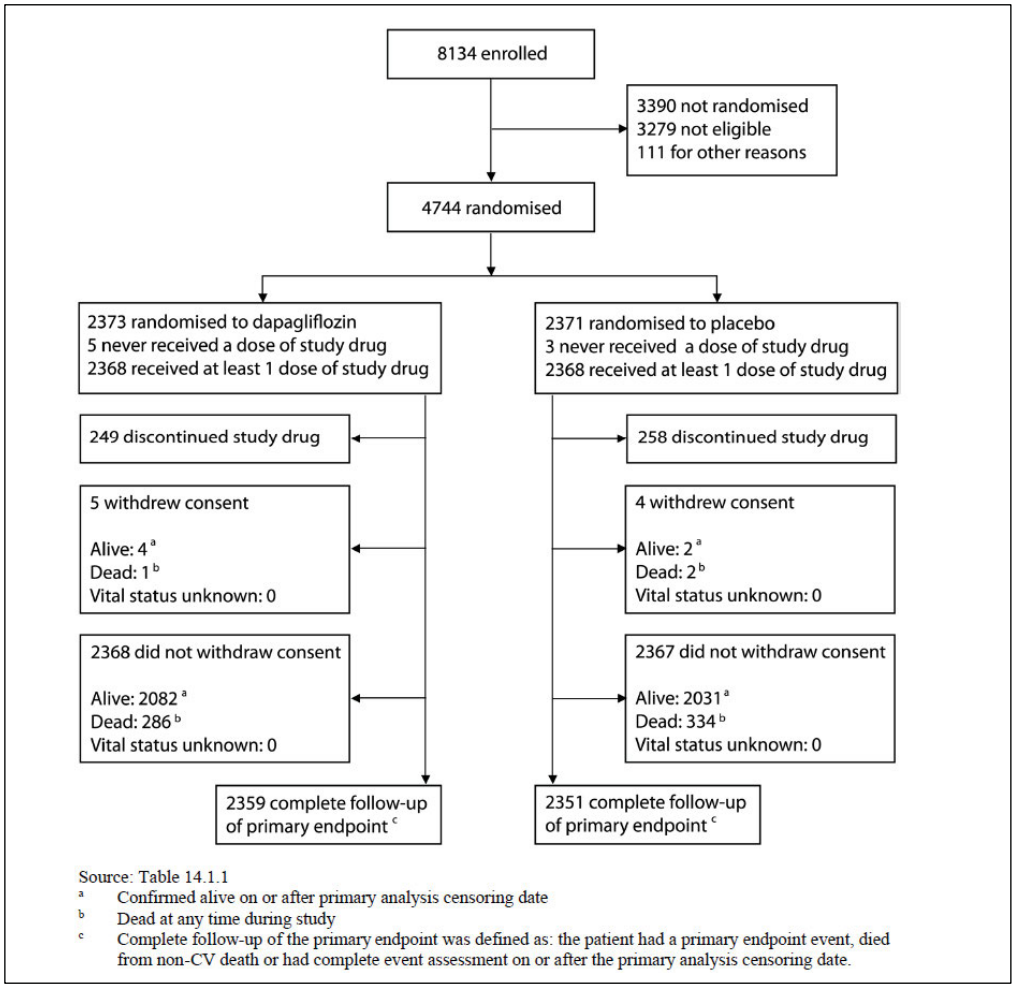
Patient Disposition

8134 patients were enrolled, and 4744 patients were randomized at 410 study sites in 20 countries; 2373 in the dapagliflozin treatment group and 2371 in the placebo group. Of the 3390 enrolled patients who were not randomized, 3279 (96.7%) failed to meet the eligibility criteria. The most common failed eligibility criterion was NT-proBNP >600 pg/ml (≥400 if HF hospitalization within 12 months, ≥900 if Atrial fibrillation at visit 1), not met by 2570 patients.

A total of 507 (10.7%) patients discontinued study treatment; 10.5% in the dapagliflozin treatment group and 10.9% in the placebo group. Vital status was known for all 9 patients who withdrew consent. Vital status was not known for 2 patients who were lost to follow-up. Of the 4744 randomized patients, 99.3% had complete follow-up of the primary endpoint. Figure 2 displays patient disposition in DAPA-HF.

Baseline demographics, patient characteristics, and heart failure therapies were well balanced between the dapagliflozin and placebo arms. 54.9% of patients did not have T2DM. Tables 4, 5, and 6 display baseline demographic characteristics, clinical characteristics, and concomitant heart failure therapies for patients enrolled in DAPA-HF trial, respectively.

Figure 2. Patient Disposition in DAPA-HF Trial (Source: Sponsor material, CSR Figure 2)



Source: Table 14.1.1

[a] Confirmed alive on or after primary analysis censoring date

[b] Dead at any time during study

[c] Complete follow-up of the primary endpoint was defined as: the patient had a primary endpoint event, died from non-CV death or had complete event assessment on or after the primary analysis censoring date.

Table 4. Baseline Demographic Characteristics of FAS, DAPA-HF (Source: Sponsor material)

Characteristic		Dapa 10 mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Sex, n (%)	Male	1809 (76.2)	1826 (77.0)	3635 (76.6)
	Female	564 (23.8)	545 (23.0)	1109 (23.4)
Age, years	Mean (SD)	66.2 (11.0)	66.5 (10.8)	66.3 (10.9)
	Median (min, max)	67 (22, 93)	67 (25, 94)	67 (22, 94)
Age groups (years), n (%)	≥18 to ≤ 65	1032 (43.5)	998 (42.1)	2030 (42.8)
	>65 to ≤ 75	825 (34.8)	886 (37.4)	1711 (36.1)
	> 75	516 (21.7)	487 (20.5)	1003 (21.1)
Race, n (%)	White	1662 (70.0)	1671 (70.5)	3333 (70.3)
	Asian	552 (23.3)	564 (23.8)	1116 (23.5)
	Black/African American	122 (5.1)	104 (4.4)	226 (4.8)
	Other	37 (1.5)	32 (1.3)	69 (1.4)
Ethnicity, n (%)	Hispanic	381 (16.1)	387 (16.3)	768 (16.2)
	Non-Hispanic	1992 (83.9)	1984 (83.7)	3976 (83.8)
Region of participation, n (%)	Asia/Pacific	543 (22.9)	553 (23.3)	1096 (23.1)
	Europe	1094 (46.1)	1060 (44.7)	2154 (45.4)
	North America	335 (14.1)	342 (14.4)	677 (14.3)
	South America	401 (16.9)	416 (17.5)	817 (17.2)

Dapa Dapagliflozin, n Number, SD Standard Deviation, min Minimum, max Maximum

Table 5. Baseline Clinical Characteristics of FAS, DAPA-HF (Source: Sponsor material)

Characteristic		Dapa 10 mg (N=2373)	Placebo (N=2371)	Total (N=4744)
Clinical characteristics				
Type 2 diabetes mellitus, n (%)		993 (41.8)	990 (41.8)	1983 (41.8)
Body Mass Index (kg/m2),	Mean (SD)	28.2 (6.0)	28.1 (5.9	28.2 (6.0)
Systolic blood pressure (mm Hg)	Q1, Median, Q3	109.7, 121.3, 132.3	109.3, 120.7, 131.7	109.7, 121.0, 132.0
Diastolic blood pressure (mm Hg)	Q1, Median, Q3	66.7, 73.3, 80.0	66.7, 72.7, 80.0	66.7, 73.0, 80.0
Pulse rate (Beats/min)	Q1, Median, Q3	63.3, 70.3, 78.3	63.0, 70.0, 78.3	63.3, 70.0, 78.3
Prior HF hospitalization, n (%)		1124 (47.4)	1127 (47.5)	2251 (47.4)
No prior HF hospitalization, n (%)		1249 (52.6)	1244 (52.5)	2493 (52.6)
Time from last HF hospitalization to randomization				
	0 - 3 Months	198 (8.3)	170 (7.2)	368 (7.8)
	>3 - 6 Months	190 (8.0)	220 (9.3)	410 (8.6)
	>6 - 12 Months	250 (10.5)	273 (11.5)	523 (11.0)
	>1 - 2 Years	180 (7.6)	168 (7.1)	348 (7.3)
	>2 - 5 Years	167 (7.0)	168 (7.1)	335 (7.1)
	>5 Years	139 (5.9)	128 (5.4)	267 (5.6)
NYHA class at enrolment, n (%)	NYHA class II	1606 (67.7)	1597 (67.4)	3203 (67.5)
	NYHA class III	747 (31.5)	751 (31.7)	1498 (31.6)
	NYHA class IV	20 (0.8)	23 (1.0)	43 (0.9)
LVEF at enrolment (%)	Q1, Median, Q3	26, 32, 37	25, 32, 36	26, 32, 37
Main Etiology of HF, n (%)	Ischemic	1316 (55.5)	1358 (57.3)	2674 (56.4)
	Non-ischemic	857 (36.1)	830 (35.0)	1687 (35.6)
	Unknown	200 (8.4)	183 (7.7)	383 (8.1)
Atrial Fibrillation or Flutter at enrolment ECG n (%)		569 (24.0)	559 (23.6)	1128 (23.8)
History of Atrial Fibrillation, n (%)		916 (38.6)	902 (38.0)	1818 (38.3)
History of Atrial Flutter, n (%)		107 (4.5)	119 (5.0)	226 (4.8)
QRS duration n (%)	≥150 msec	546 (23.2)	499 (21.2)	1045 (22.2)
	≥130 msec	839 (35.6)	798 (33.8)	1637 (34.7)
NT-proBNP (pg/mL)	Q1, Median, Q3	857, 1428, 2655	857, 1446, 2641	857, 1437, 2650
eGFR (ml/min/1.73 m2)	Q1, Median, Q3	51, 64.0, 80	51, 64, 79	51, 64, 80
Hemoglobin (g/L)	Q1, Median, Q3	125, 136, 146	126, 136, 146	125, 136, 146
Anemia n (%)	Men: Hemoglobin <130 g/L	519 (28.9)	493 (27.2)	1012 (28.1)
	Women: Hemoglobin <120 g/L	144 (25.8)	146 (26.9)	290 (26.4)

Dapa Dapagliflozin, n Number, SD Standard Deviation, Q1 1st quartile, Q3 3rd quartile, NYHA New York Heart Association, LVEF Left Ventricle Ejection Fraction, HF Heart failure, NT-proBNP N-terminal pro b-type natriuretic peptide

Table 6. Baseline Concomitant Heart Failure Therapy of FAS, DAPA-HF (Source: Sponsor material)

Characteristic		Dapa 10 mg (N=2373)	Placebo (N=2371)	Total (N=4744)
HF concomitant medication use n (%)	ACEi	1332 (56.1)	1329 (56.1)	2661 (56.1)
	ARB	675 (28.4)	632 (26.7)	1307 (27.6)
	ARNI	250 (10.5)	258 (10.9)	508 (10.7)
	ACEi, ARB or ARNI	2235 (94.2)	2207 (93.1)	4442 (93.6)
	Beta-Blocker	2278 (96.0)	2280 (96.2)	4558 (96.1)
	MRA	1696 (71.5)	1674 (70.6)	3370 (71.0)
	Diuretics	2216 (93.4)	2217 (93.5)	4433 (93.4)
	Ivabradine	119 (5.0)	109 (4.6)	228 (4.8)
Cardiac pacemaker, n (%)		348 (14.7)	316 (13.3)	664 (14.0)
ICD, n (%)		467 (19.7)	486 (20.5)	953 (20 1)
ICD or CRT-D, n (%)		622 (26.2)	620 (26.1)	1242 (26.2)

Dapa Dapagliflozin, n Number, ACEi Angiotensin Converting Enzyme inhibitor, ARB Angiotensin receptor blocker, ARNI Neprilysin inhibitor/ARB, MRA Mineralocorticoid receptor antagonist, ICD Implantable cardioverter defibrillator, CRT-D Cardiac resynchronization therapy defibrillator

Exposure

The median follow-up time until primary analysis censoring date (PACD) was 18.2 months (range 0 to 27.8 months) and the median exposure was 17.8 months and 17.6 months in the dapagliflozin and placebo groups, respectively. In total, there were 3310 patient-years of exposure to dapagliflozin in the study.

Treatment compliance

Treatment compliance was high and similar between treatment groups.

Study drug was discontinued due to an AE in 111 (4.7%) and 116 (4.9%) patients in dapagliflozin and placebo arms, respectively. Study drug was modified due to an AE in 320 (13.5%) and 367 (15.5%) patients in dapagliflozin and placebo arms, respectively. The number of patients by treatment arm, who had study drug discontinuation or modification due to an AE of volume depletion or renal impairment, two adverse events of interest further described in the safety review section, was low and is displayed in Table 7.

Table 7. Study Drug Dose Changes Due to Adverse Events of Volume Depletion or Renal Impairment (Source: Reviewer analysis)

	Volume depletion Adverse Event		Renal impairment Adverse Event	
	Dapagliflozin (N=2368)	Placebo (N=2368)	Dapagliflozin (N=2368)	Placebo (N=2368)
Dose reduced n (%)	25 (1.1)	17 (0.7)	6 (0.3)	3 (0.1)
Dose interrupted n (%)	19 (0.8)	29 (1.2)	19 (0.8)	30 (1.3)
Dose withdrawn n (%)	(0.4)	8 (0.3)	8 (0.3)	9 (0.4)

Conclusions on study subjects

Of the 4744 randomized patients, 99.3% had complete follow-up of the primary endpoint. Treatment compliance was generally high and balanced between treatment groups while discontinuation of study treatment was low and balanced between treatment groups. Demographic and baseline patient characteristics, including standard of care HF treatment and medical history, were generally balanced between treatment groups.

Interim Analysis

An interim analysis, conducted with 664 events (79% of the 844 targeted number of events), demonstrated a hazard ratio of 0.76 (95% CI 0.65,0.88; p-value 0.0002) for the primary composite endpoint and 0.90 (95% CI 0.74, 1.11; p-value 0.17) for CV death. The predefined stopping rule for CV death to reach a p-value of 0.001 was not met. Hence, the trial was not stopped. Table 8 displays the results of interim analysis of DAPA-HF.

Table 8. Interim Analysis of DAPA-HF Trial (Source: Sponsor material, table 43, page 1152 of cmte charters and meeting minutes part a)

Endpoint[a]	*Adjusted Hazard ratio*[c] *(95% CI)*	*Events*[d]	*One-sided p-value*	
			Stopping boundary[e]	*Observed result*
Primary composite[b]	0.76 (0.65, 0.88)	664	0.001	0.0002
CV death	0.90 (0.74, 1.11)	359	0.001	0.17

a. Endpoint events are confirmed by a CEA committee.
b. The primary composite endpoint is time to first event of CV death, hospitalization for HF, or urgent HF visit.
c. Analysis is stratified by Type 2 Diabetes status at randomization and is adjusted for a history of hospitalization for HF.
d. Number of patients with at least one CEA-confirmed event.
e. Haybittle-Peto boundary

Data received: CRF: 01MAR19
Presentation manually compiled. (page 1 of 1)

Primary Composite Endpoint in the Full Analysis Set

The total number of patients in the FAS and adjudicated primary endpoint events were 4744 (2373 patients in the dapagliflozin treatment group and 2371 patients in the placebo group) and 888, respectively. The incidence of the primary composite endpoint of CV death or a HF event (hospitalization for HF or urgent HF visit) was 16.3% versus 21.2% in dapagliflozin versus placebo group with a HR 0.74 (95% CI 0.65, 0.85), p<0.0001 in favor of dapagliflozin. There were 386 and 502 patients with CV death or HF events in the dapagliflozin and placebo groups, respectively, corresponding to an event rate of 11.6 and 15.6 per 100 patient-years. All the three components of the primary composite endpoint contributed to the overall treatment effect. The incidence of CV death, hospitalizations for HF, and urgent HF visits was lower in dapagliflozin group compared to placebo. Table 9 summarizes the analysis of the primary composite endpoint and its components in the FAS. These analyses were reproduced by the statistical reviewer. The Kaplan-Meier curves for

the primary composite endpoint and its components in the FAS in DAPA-HF trial displayed in figure 3 diverged early and continued to separate over the course of the trial.

The treatment effect observed with dapagliflozin continued to be statistically significant after the following prespecified sensitivity analyses for the primary endpoint were performed:

- Deaths adjudicated as undetermined were excluded from the primary endpoint but treated as censoring events (HR 0.72, 95% CI 0.63, 0.83; p-value < 0.0001)
- A "worst case scenario" analysis that considered patients censored before PACD, including those censored due to non-CV death, as having experienced the composite endpoint (HR 0.85, 95% CI 0.74, 0.96; p-value = 0.0103)

Table 9. Analysis of primary composite endpoint and components (FAS) (Source: Sponsor material, CSR, Table 14.2.2.1)

Variable	Subjects with events (Event rate)		HR (95% CI)	p-value
	Dapa 10 mg (N=2373)	Placebo (N=2371)		
Comp of CV death, HF hosp, and urgent HF visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	< 0.0001
Comp of CV death and HF hosp	382 (11.4)	495 (15.3)	0.75 (0.65, 0.85)	< 0.0001
CV death	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)	0.0294
HF hosp or urgent HF visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)	< 0.0001
HF hosp	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)	< 0.0001
Urgent HF visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)	0.0213

The number of events for the individual components are the actual number of first events for each component and their sum exceeds the number of events for the composite endpoint.

Event rates are presented as the number of subjects with event per100 patient-years of follow-up.

Hazard ratio for Dapa 10mg vs placebo, confidence intervals and 2-sided p-value are calculated from Cox proportional hazards model (score test) stratified by T2DM status at randomization, with factors for treatment group and history of HF hospitalization.

CI - Confidence interval, Dapa - Dapagliflozin, FAS - Full analysis set, HF - Heart failure, HR - Hazard ratio, N - Number of subjects in treatment group, T2DM - Type 2 diabetes mellitus, hosp - hospitalization

Figure 3. Kaplan-Meier Curves of the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Event (C) in DAPA-HF trial (FAS)

Figure 3A

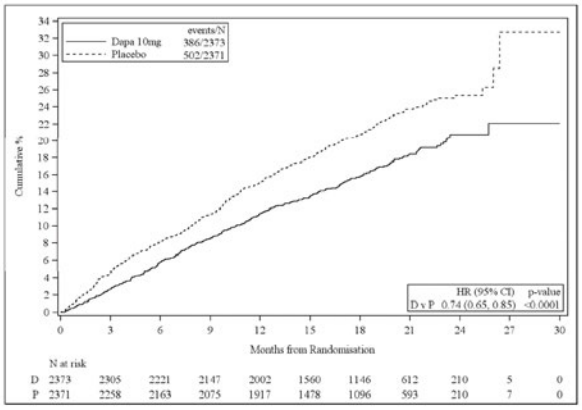


Figure 3B

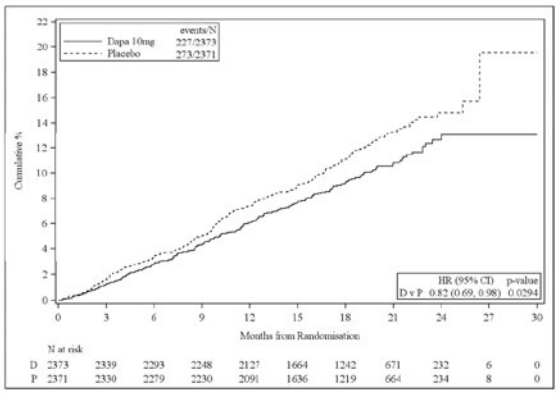
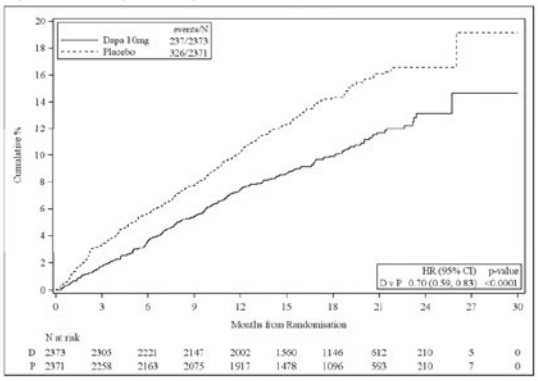


Figure 3C



N at risk is the number of subjects at risk at the beginning of the period 1 month corresponds to 30 days 2-sided p-value is displayed

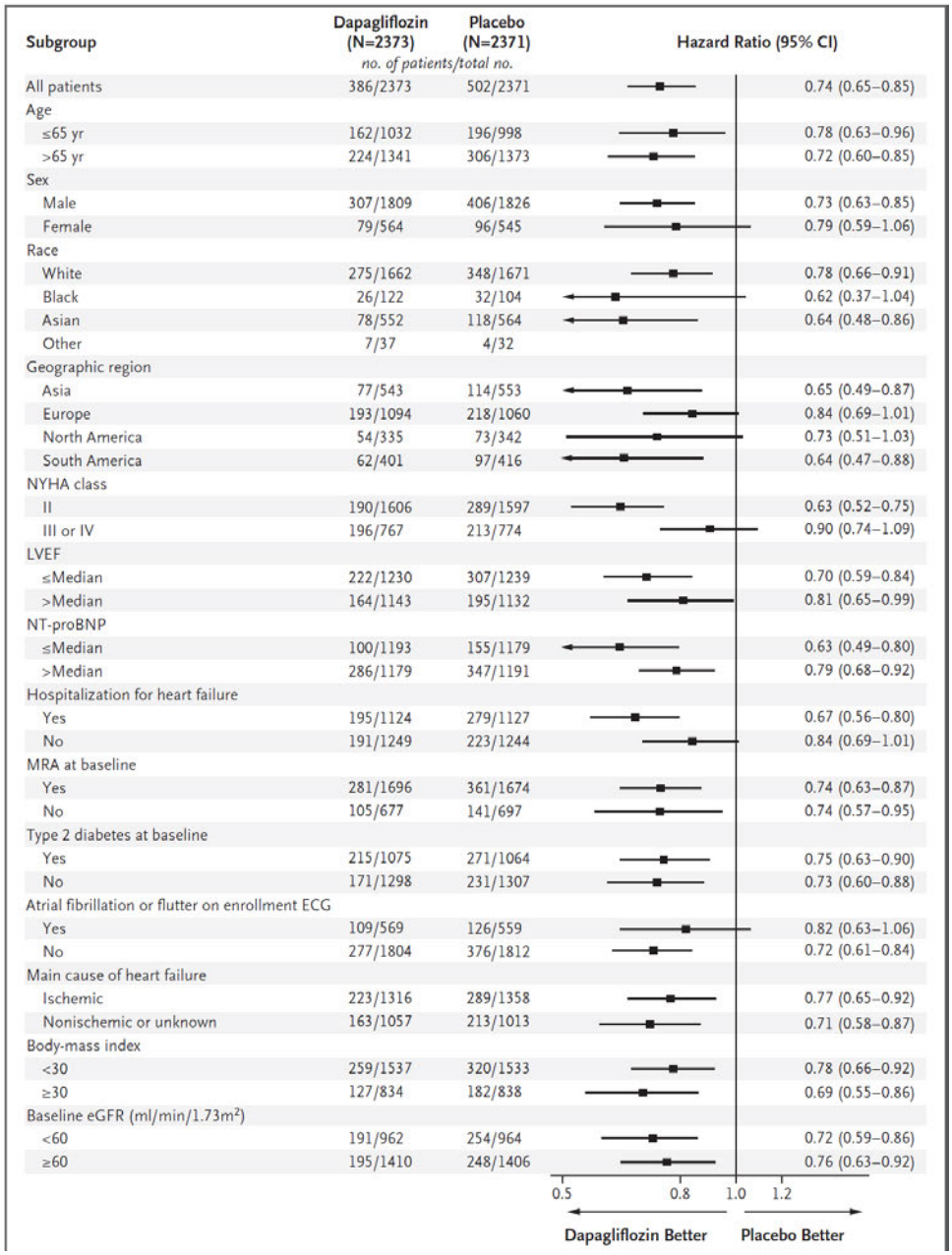
HR, CI and p-value are from the Cox proportional hazard model CI Confidence interval Dapa Dapagliflozin D Dapa 10 mg FAS Full analysis set HF Heart failure HR Hazard ratio N Number of subjects P Placebo

Pre-specified Subgroup Analyses

Subgroup analyses were performed for the primary efficacy endpoint for age, sex, race, and geographic regions and were generally consistent with results in the FAS. Analyses by geographic region are included in the appendix.

Sub-group analysis by NYHA class showed that the treatment effect in patients with NYHA class III/IV was lower than in patients with NYHA class II (Figure 4). This is discussed in greater detail under review issue #2.

Figure 4. Subgroup analyses for the primary composite endpoint (CV Death/HF hospitalization/Urgent HF visit) (FAS) (Source: Sponsor NEJM DAPA HF publication)[7]



Shown is the primary outcome of the trial — a composite of hospitalization for heart failure, an urgent visit resulting in intravenous therapy for heart failure, or death from cardiovascular causes — according to subgroups that were prespecified in the protocol. Race was reported by the investigators. The body-mass index is the weight in kilograms divided by the square of the height in meters. ECG denotes electrocardiography, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, MRA mineralocorticoid receptor antagonist, NT-proBNP N-terminal pro–B-type natriuretic peptide, and NYHA New York Heart Association.

[7] McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019b.

Secondary and other relevant endpoints

CV death and HF hospitalization

The treatment effect of dapagliflozin was demonstrated on some secondary endpoints. Treatment with dapagliflozin was superior to placebo in delaying the time to the first event of CV death or HF hospitalization (HR 0.75 [95% CI 0.65, 0.85], p < 0.0001), and the composite of CV death and recurrent HF hospitalization (Rate Ratio 0.75 [95% CI 0.65, 0.88], p=0.0002).

Renal Endpoints

Although not statistically significant, fewer patients experienced renal composite endpoint events (≥ 50% sustained decline in eGFR, ESRD or Renal death) in the dapagliflozin treatment group than in placebo, (HR 0.71 [95% CI 0.44, 1.16] p=0.1681). In addition, compared with placebo, the dapagliflozin treatment group reduced the events of doubling of serum creatinine, an exploratory endpoint; 43 (1.8%) versus 77 (3.2%). Although not formally tested for significance, treatment with dapagliflozin reduced the risk of all-cause mortality, compared with placebo (HR 0.83 [95% CI 071, 0.97]).

HF Symptoms

Treatment with dapagliflozin compared to placebo statistically significantly improved symptoms of HF, as measured by the KCCQ-TSS (total symptom score), using a composite endpoint, including death, analyzed by rank ANCOVA. KCCQ TSS change from baseline to 8 months was transformed to a composite endpoint with fractional ranks, using the mean method for ties and stratified by T2DM status at randomization. Deaths prior to the 8-month assessment were assigned the worst ranks within each stratum. Of the patients who died, the relative ranking was based on their last value of change from baseline in TSS (TSS was also collected at 4 months) while alive before deriving fractional ranks. This composite endpoint was analyzed using the rank ANCOVA method (Stokes et al, 2012), adjusted for ranked baseline TSS value. The superiority of dapagliflozin over placebo was demonstrated using the Cochran Mantel Haenszel (CMH) test, stratified for the T2DM status at randomization, in improving symptoms of HF as measured by the KCCQ-TSS at Month 8 (p <0.0001).

At 8 months, the KCCQ compliance was 88.7% and 87.6% in the dapagliflozin and placebo treatment group, respectively; 254 (11.3%) and 278 (12.4%), respectively, had missing data due to reasons other than death. In addition, 121 (5.1%) and 136 (5.7%), respectively, had missing data due to death. The proportions of death and patients with missing data were balanced across the two treatment arms. The win ratio (WR) test was conducted to show the superiority of dapagliflozin over placebo. The method makes use of the missing data caused by deaths prior to 8-month assessment. The patients who were alive at 8-month and had missing baseline or 8-month KCCQ assessments had their missing TSS values imputed using the multiple imputation (MI) methodology, under the missing at random assumption. This method confirmed the statistical superiority. The treatment with dapagliflozin was statistically superior to placebo in improving symptoms of HF, as measured by the KCCQ-TSS (Win ratio 1.18 [95% CI 1.11, 1.26], p<0.0001). Additional discussion on KCCQ-TSS results and its interpretation is presented in section 5.5.1. titled Important Review Issue #1 Relevant to Benefit.

***Reviewer comments*:** *In the statistical analyses of the change from baseline of KCCQ-TSS at Month 8, the rank ANCOVA included deaths prior to the 8-month assessment. Missing data due to reasons other than death were 11.3% and 12.4% in the dapagliflozin and placebo, respectively. The missing data were moderate, and the missing percentages were balanced across the two treatment arms. Although missing mechanism is not clear, under such circumstances, statistical methods demonstrate good robustness using different imputation strategies, including no imputation, see Lederer et al (2015). Besides, the statistical superiority of dapagliflozin to placebo in improving symptoms of HF, as measured by the KCCQ-TSS, was confirmed by the win ratio method with multiple imputation for missing data.*

5.7. Review Issues Relevant to the Evaluation of Benefit

5.7.1. Important Review Issue #1 Relevant to Benefit

Is the observed change in KCCQ-TSS in DAPA-HF clinically meaningful?

KCCQ is a 23-item, patient-reported questionnaire used to evaluate HF- specific symptoms, function, and quality of life over a 2-week period. KCCQ domains include symptom frequency and burden, physical limitation, quality of life, social limitation, and self-efficacy. Each domain score is scaled between 0 and 100, with higher scores representing better health status. A 5-point difference in KCCQ-Overall Symptom Score (KCCQ-OS, includes all domains) has been associated with increased risk for CV death and HF hospitalization in patients with HFpEF and HFrEF.[12]

KCCQ-TSS includes the symptom frequency and burden domains. To define what constitutes a clinically meaningful within-patient change (CMWPC) in KCCQ-TSS in DAPA-HF, the applicant implemented an anchor-based approach utilizing patient-reported outcome (PRO) of patient global impression of severity (PGIS) and concluded the following:

- CMWPC in KCCQ-TSS at 8 months is 5 to10 points
- An improvement of ≥15 points is moderate or large improvement
- A deterioration of ≥10 points is a large deterioration

See appendices for additional details on KCCQ, and the applicant's approach to anchor-based and KCCQ-TSS analyses in DAPA-HF.

DAPA-HF evaluated the secondary efficacy endpoint of change in Kansas City Cardiomyopathy Questionnaire Total Symptom score (KCCQ-TSS) from baseline to 8 months as a measure of symptom improvement. Rank ANCOVA, adjusted for baseline KCCQ score and stratified by T2DM

status at randomization demonstrated a statistically significant change in KCCQ-TSS favoring dapagliflozin - KCCQ-TSS change at 8 months from baseline in dapagliflozin group was 6.1±18.6 and in placebo group was 3.3±19.2 with a least mean squares difference of 2.8 points (95% CI 1.6, 4.0), P-value <0.001. Review of median change in KCCQ score by various domains (Table 35 in the appendices) indicated that the domains of physical limitation, symptom frequency, and social limitation showed slight improvement (about 4 points) in dapagliflozin arm compared to placebo.

Supportive results from win ratio and responder analyses demonstrated a Win ratio for KCCQ-TSS at 8 months of 1.18 (95% CI 1.11, 1.26), P-value <0.0001 with 2252 patients for dapagliflozin and 2235 for placebo group, including missing due to death, and 57.4% (n=1198) patients showed a 5 point improvement in KCCQ-TSS at 8 months in dapagliflozin arm versus 50.0% (n=1030) in the placebo arm.

A background variation of < 5 points in KCCQ score in patients with HFrEF has been reported in literature. For example, Green (2000)[14] reported a mean change in KCCQ score of 0.8 to 4.0 points on a 100-point scale over three months of observation. In DAPA-HF, the placebo group demonstrated a mean change in KCCQ-TSS of 3.3 ± 19.2. At 8 months, a stable PGIS correlated with a mean KCCQ-TSS change of 3.23 ± 15.51, and a median KCCQ-TSS change of 1.0 (minimum -63.5, maximum 82.3). At 8 months, a small improvement in PGIS correlated with a mean KCCQ-TSS change of 9.52 ± 17.42, and a median KCCQ-TSS change of 8.3 (minimum -49.0, maximum 80.2).

The observed between-group difference in change in KCCQ-TSS of 2.8 falls within the reported background variation rate (Green 2000) and that observed in DAPA-HF trial. Although this difference is statistically significant, it likely represents minimal improvement in HF symptoms.

The Clinical Outcomes Assessment team reviewed these data and reached the following conclusions:

- While the change in KCCQ-TSS at Month 8 showed a statistically significant between group difference, the result appears to be driven by the large sample size as the magnitude of the between-group change was quite small as demonstrated by nearly overlapping empirical cumulative distribution function (eCDF) curves and probability density function (PDF) curves for dapagliflozin vs. placebo. The between-group separation is slight throughout the entire distribution including at the clinically meaningful responder thresholds (i.e., ≥15 points). [Of note, anchor-based analyses within DAPA-HF suggest that ≥15-point change in the KCCQ-TSS is the most appropriate cut-off for a clinically meaningful within-patient change.]
- The treatment effect does not appear to be clinically meaningful. (b) (4)

(b) (4)

- [redacted]

5.7.2. Important Review Issue # 2 Relevant to Benefit

Higher Rate of Cardiovascular Death in Dapagliflozin Arm in NYHA Class III Subgroup

In DAPA-HF, 32% of the randomized patients had NYHA class III symptoms at enrolment, compared to 68% with NYHA class II and 1% with NYHA class IV symptoms. A subgroup analysis of the primary composite endpoint by NYHA class demonstrated a lower magnitude of treatment effect in NYHA class III/IV (HR 0.90; CI 0.74, 1.09) compared to NYHA class II (HR 0.63; CI 0.52, 0.75) patients, with a p-value of 0.0087 for treatment by NYHA class interaction. With regard to the components of the primary composite endpoint i.e.; HF events and CV death, there was a lower incidence of HF events (15.6 vs. 18.3%), but a higher incidence of CV death (16.6 vs. 15.2%) in dapagliflozin versus placebo groups in NYHA class III patients. The magnitude HF event reduction with dapagliflozin was similar in the NYHA class II and III/IV patients. Tables 10 and 11 summarize the results of HF events and CV death by NYHA class, respectively.

The baseline characteristics were generally similar between NYHA class II and III/IV patients, except for a higher prevalence of patients with HF hospitalization in the last year; ischemic HF etiology; and history of atrial fibrillation in NYHA class III/IV compared to class II. Baseline LVEF was similar between NYHA class II and III/IV patients. Table 12 summarizes the key baseline subject characteristics by NYHA class. These findings raised a concern about a lack of benefit or potential harm with dapagliflozin in patients with NYHA class III, who represent a sicker cohort of HFrEF patients.

However, subgroup analyses did not suggest a difference in treatment effect based on other measures of HF severity such as LVEF and NT-pro-BNP. Figures 6 and 7 demonstrate that the HR across the continuum of LVEF and NT pro-BNP values at randomization remained less than 1. In addition, a better treatment effect was observed in patients with versus without prior history of HF hospitalization, HR of 0.67 (0.56, 0.81) versus 0.84 (0.69, 1.02), suggesting that sicker patients did derive benefit with dapagliflozin. Overall, all-cause mortality was lower in dapagliflozin versus placebo group with an event rate of 7.9 versus 9.5 per 100 patient years, which is also reassuring.

Table 10. Results of HF Events (Hospitalization for HF or Urgent Visit) by NYHA Class in DAPA-HF trial, FAS (Source: Reviewer compilation)

Subject Category	Dapagliflozin			Placebo						
	Number of patients	Patients with event n (%)	Event rate per 100 patient years	Number of patients	Patients with event n (%)	Event rate per 100 patient years	Hazard Ratio	95% CI	P-value	Interaction p-value
FAS	2373	237(10.0)	7.1	2371	326 (13.7)	10.1	0.70	(0.59, 0.83)	<0.0001	
NYHA class										
II	1606	117 (7.3)	5.0	1597	184 (11.5)	8.4	0.61	(0.48, 0.77)	<0.0001	0.0808
III or IV	767	120 (15.6)	11.8	774	142 (18.3)	13.9	0.82	(0.64, 1.05)	0.1114	
Hf Heart failure, FAS Full analysis set, NYHA New York Heart Association										

Table 11. Results of CV Death by NYHA Class in DAPA-HF Trial, FAS (Source: Reviewer compilation)

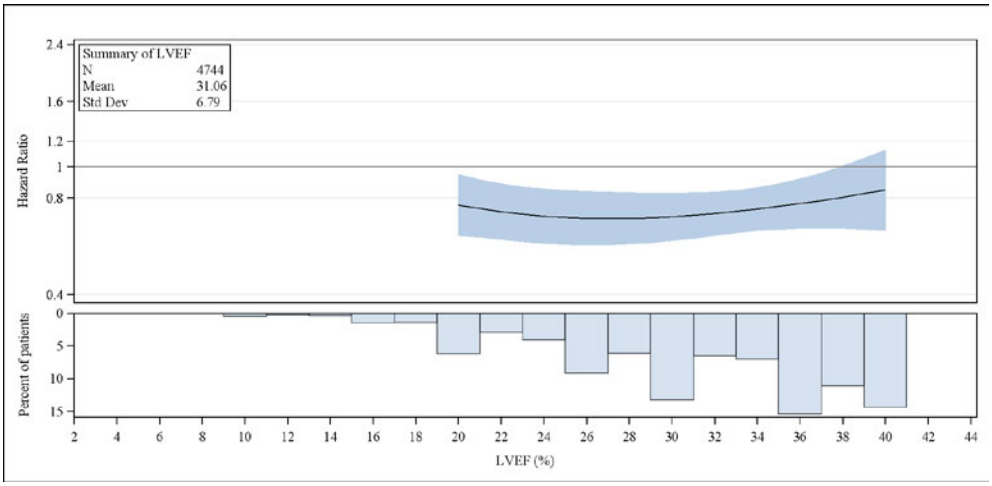
Subject Category	Dapagliflozin			Placebo						
	Number of patients	Patients with event n (%)	Event rate per 100 patient years	Number of patients	Patients with event n (%)	Event rate per 100 patient years	Hazard Ratio	95% CI	P-value	Interaction p-value
FAS	2373	227(9.6)	6.5	2371	273(11.5)	7.9	0.82	(0.69, 0.98)	0.0294	
NYHA class										
II	1606	100(6.2)	4.2	1597	155(9.7)	6.7	0.63	(0.49, 0.81)	0.0003	0.0023
III or IV	767	127 (16.6)	11.6	774	118 (15.2)	10.5	1.09	(0.85, 1.41)	0.4848	
CV Cardiovascular FAS Full analysis set, NYHA New York Heart Association										

Table 12. Key baseline subject characteristics by NYHA Class in DAPA-HF (Source: Reviewer compilation)

Characteristic		NYHA II (N=3203)	NYHA III/IV (N=1541)	Total (N=4744)
Time from last HF hospitalization to randomization				
	0 - 3 Months	210 (6.6)	158 (10.3)	368 (7.8)
	>3 - 6 Months	252 (7.9)	158 (10.3)	410 (8.6)
	>6 - 12 Months	340 (10.6)	183 (11.9)	523 (11.0)
	>1 - 2 Years	256 (8.0)	92 (6.0)	348 (7.3)
	>2 - 5 Years	250 (7.8)	85 (5.5)	335 (7.1)
	>5 Years	202 (6.3)	65 (4.2)	267 (5.6)
LVEF (%)	Mean (SD)	31.1 (6.8)	31.0 (6.8)	31.1 (6.8)
	Q1, Median, Q2	26, 32, 37	25, 32, 37	26, 32, 37
Main Etiology of HF, n (%)	Ischemic	1742 (54.4)	932 (60.5)	2674 (56.4)
	Non-ischemic	1189 (37.1)	498 (32.3)	1687 (35.6)
	Unknown	272 (8.5)	111 (7.2)	383 (8.1)
History of Atrial Fibrillation, n (%)		1140 (35.6)	678 (44.0)	1818 (38.3)
NT-proBNP (pg/mL)	Q1, Median, Q3	816, 1340, 2331	993, 1714, 3396	857, 1437, 2650

Dapa Dapagliflozin, n Number, SD Standard Deviation, Q1 1st quartile, Q3 3rd quartile, NYHA New York Heart Association, LVEF Left Ventricle Ejection Fraction, HF Heart failure, NT-proBNP N-terminal pro b-type natriuretic peptide

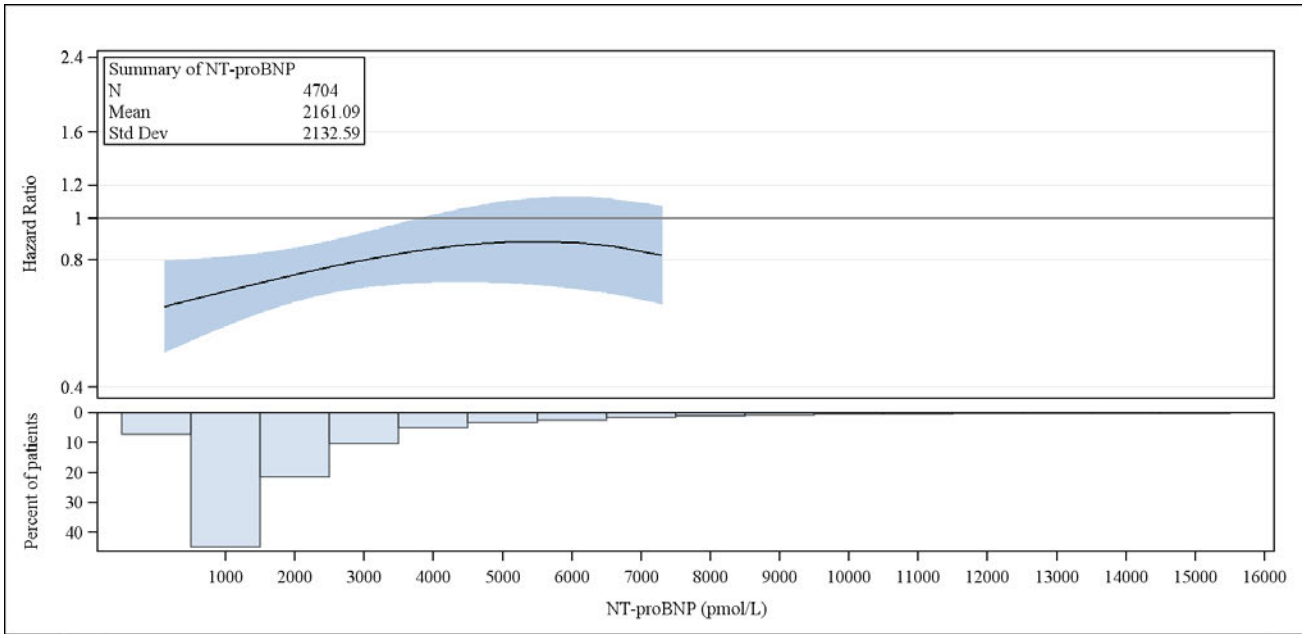
Figure 4. Hazard ratio of the Primary Endpoint by Baseline LVEF (%) (FAS) (Source: Sponsor material)



Hazard ratios for Dapa 10mg vs placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for history of HF hospitalization, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with three knots at 5th, 50th and 95th percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model.

Dapa Dapagliflozin. FAS Full analysis set. HF Heart failure. T2DM Type 2 diabetes mellitus. LVEF Left Ventricular Ejection Fraction.

Figure 5. Hazard Ratio of the Primary Endpoint by Baseline NT-proBNP (pmol/L) (FAS) (Source: Sponsor material)



Hazard ratios for Dapa 10mg vs placebo at each point of continuous variable are calculated from Cox proportional hazards model stratified by T2DM status at randomization, with factors for history of HF hospitalization, the relevant continuous variable, the treatment group and the interaction between treatment group and the continuous variable. The continuous variable was transformed using a restricted cubic spline with three knots at 5th, 50th and 95th percentiles of the range before including in the model. Band on the plot shows 95% confidence interval calculated using the same model. Values greater than 16000 pmol/L were not used in the model.

Dapa Dapagliflozin. FAS Full analysis set. HF Heart failure. T2DM Type 2 diabetes mellitus. NT-proBNP N terminal pro b-type natriuretic peptide.

Reviewer comments: *In a subgroup analysis, there was a marginally increased rate of CV death, but a lower rate of hospitalization for HF, in patients with NYHA class III on dapagliflozin versus placebo. NYHA class is a subjective determination based on functional capacity of patients with HF and changes over time. Treatment effect, in favor of dapagliflozin, was observed in the overall study cohort and in other subgroups that reflect HF severity such as, LVEF, pro-BNP, and history of prior HF hospitalization. All-cause mortality also trended in favor of dapagliflozin. Analyses of adverse events and deaths in the safety population (see Tables 16 and 17) did not show any imbalances of concern. Even though the mechanism of action of dapagliflozin in patients with HFrEF is not elucidated, there is no reason to believe that dapagliflozin will reduce hospitalization for HF in patients with HFrEF with NYHA class II, III, and IV, and decrease CV death in patients with NYHA class II, but will increase CV death in patients with NYHA class III patients. Hence, the observed difference in the rate of CV death between dapagliflozin and placebo, in an under powered subgroup analysis, is most likely a chance finding and may not reflect a lack of treatment effect or evidence of potential harm.*

6. Risk and Risk Management

6.1. Potential Risks or Safety Concerns Based on Nonclinical Data

No additional nonclinical studies were conducted to support the proposed indication. According to the dapagliflozin label:

- 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 rates at exposure multiples less than or equal to 1708-times and 998-times the maximum recommended human dose in males and females, respectively.
-

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

Warnings and Precautions for approved members of the pharmacologic class (SGLT2 inhibitors) include:

- Hypotension (intravascular volume contraction)
- Ketoacidosis (including fatal cases)
- Acute kidney injury (AKI) (including hospitalization and dialysis) and renal impairment
- Urosepsis and pyelonephritis requiring hospitalizations
- Necrotizing fasciitis of the perineum (Fournier's gangrene) including hospitalizations, multiple surgeries and death
- Hypoglycemia with concomitant insulin and insulin secretagogues
- Genital mycotic infections

Warnings and Precautions for specific SGLT2 inhibitors include:

- Hypersensitivity (canagliflozin and empagliflozin; also described in Section 6.1 of labeling for dapagliflozin)
- Increase in LDL cholesterol (canagliflozin and empagliflozin; also described in section 6.1 of labeling for dapagliflozin)
- Lower limb amputations (canagliflozin)
- Bone fracture risk (canagliflozin)
- [redacted] (b) (4) (canagliflozin)

6.3. Potential Safety Concerns Identified Through Postmarket Experience

Acute pancreatitis, a potential safety signal observed during post-marketing setting for SGLT2 inhibitors was evaluated in DAPA-HF (see Section 6.6.6.1). Overall, the incidence of acute pancreatitis AEs was similar between the arms and no safety signal of concern was raised.

6.4. FDA Approach to the Safety Review

The safety review of dapagliflozin focused on previously identified risks of SGLT2 inhibitors and included a review of data quality[8], adverse event (AE), laboratory and vital sign datasets. Adverse events were primarily analyzed by MedDRA (version 22.0) preferred term (similar to the Applicant's analyses) and by pooling similar adverse events (referred to as the MedDRA SMQ or FDA Medical Dictionary for Regulatory Activities [MedDRA] Query [FMQ]). The FMQ analysis is similar to a customized MedDRA query. Adverse events of special interest (AESI) in dapagliflozin included AEs suggestive of volume depletion, renal AEs including acute renal injury, diabetes ketoacidosis (DKA), major hypoglycemic events, fractures, AEs leading to amputation (AEs that indicate an amputation), AEs leading to a risk of lower limb amputation (events that might precede an amputation). For AESIs, the applicant grouped a pre-defined list of preferred terms, similar to a customized MedDRA query.

In addition to the DAPA-HF clinical study report (CSR), the documents shown in the table below were reviewed.

Table 13. Documents Reviewed

Document	Period Covered or Submission Date	Report Date
FDA DMEP Clinical review of efficacy supplement 18 – dapagliflozin for T2DM patients with established cardiovascular disease (cardiovascular outcome trials, DECLARE)	Submission date 12/18/2018	9/16/2019

Reviewer's Table

[8] Data quality was examined using JumpStart Service -Data Fitness Analysis.

Safety analyses were performed on the treated population (received at least one dose of study drug) and were primarily presented for the on-treatment data period. For AESIs such as fractures, and amputations, the on and off treatment period was used. Definitions of data periods for analyses are shown in table 14.

Table 14. Definitions and Data Periods for Safety Analyses

Analysis Set	Analysis Population	Dapagliflozin Patients	Placebo Patients	Data Period
On-treatment	Treated patients	2368	2368	Between first dose of treatment and 30 days after last dose of treatment
On and Off treatment	Treated patients	2368	2368	After first dose of study drug regardless whether patients were on or off study treatment at the time of event

Reviewer's Table

SAS version 9.4 and the Office of Computational Science table builder tool were used for most analyses; MedDRA Adverse Event Diagnosis (MAED) and JMP Clinical were also used. Results are presented as percent of patients (%) and rate per 1,000 patient years

6.5. Adequacy of the Clinical Safety Database

The median duration of dapagliflozin exposure in DAPA-HF was 17.8 months (or 1.5 years). This exposure in combination with the extensive prior clinical experience, is considered adequate to characterize safety. See table 15 for additional information on duration of treatment in DAPA-HF.

Table 15. Duration of Exposure, Safety Population, DAPA-HF

Parameter	Dapa 10 mg N=2368	Placebo N=2368
Duration of treatment (months)		
Mean (SD)	16.8 (6.3)	16.6 (6.5)
Median (Min, Max)	17.8 (0.03, 28.0)	17.6 (0.03, 28.3)
Patients treated, by duration, n (%)		
Any duration (at least one dose)	2368 (100)	2368 (100)
<1 month	52 (2.2)	51 (2.2)
≥1 month	2316 (97.8)	2317 (97.8)
≥3 months	2247 (94.9)	2246 (94.9)
≥6 months	2152 (90.9)	2137 (90.2)
≥12 months	1955 (82.6)	1905 (80.5)
≥18 months	1168 (49.3)	1133 (47.9)
≥24 months	261 (11.0)	255 (10.8)

Reviewer's table; Source: adsl & adex

6.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

The safety evaluation of dapagliflozin in DAPA-HF was adequate and acceptable for the proposed indication. There was generally a similar incidence of adverse events between treatment arms (slightly lower in the dapagliflozin arm for the most part), including deaths, SAEs, AESIs and study drug discontinuation due to AEs. About 5% of patients in each arm discontinued medication due to an AE. The most common reasons for medication discontinuation were congestive heart failure, volume depletion and renal impairment; the incidences were similar between treatment arms (all < 1% in either arm). Volume depletion occurred more frequently with dapagliflozin than placebo. AEs leading to a risk for lower limb amputation also were more frequent in the dapagliflozin group, largely driven by dehydration and volume depletion events.

To evaluate the appropriateness of the existing Warning and Precaution about acute kidney injury (AKI) in the dapagliflozin label, renal events (efficacy and AE) were examined. The incidence of renal adverse events was not greater in the dapagliflozin arm (6.0%) as compared to the placebo arm (6.7%) in DAPA-HF. There were fewer acute kidney injury events in the dapagliflozin arm. These findings were consistent with numerically favorable efficacy renal results in DAPA-HF- fewer patients experienced renal composite endpoint events (≥ 50% sustained decline in eGFR, ESRD or Renal death) in the dapagliflozin treatment group than in placebo, (HR 0.71 [95% CI 0.44, 1.16] p=0.1681). Renal safety was also previously evaluated in a large CV outcome trial in patients with T2DM (i.e., DECLARE) and similar results favorable to dapagliflozin were found. Overall, data from two large outcome trials do not support the current labeling regarding adverse renal effects of dapagliflozin and; therefore, the label will be modified.

The rate of lower limb amputations was similar between treatment arms (0.5% in both arms corresponding to ~ 0.4 per 100 patient-years.). There were 3 patients with adjudicated diabetic ketoacidosis in the dapagliflozin arm vs. 0 in the placebo arm; all with diabetes at baseline. The incidence of major hypoglycemic event was the same-4 patients (0.2%) in each arm; all with diabetes at baseline.

6.6.1. Overall Adverse Event Summary

The overall incidence of AE was similar between the dapagliflozin arm and the placebo arm as shown in the table below.

Table 16. Overview of Adverse Events,[1] DAPA-HF Safety Population, On-Treatment

Event	Dapa N=2368 n (%)	Placebo N=2368 n (%)
Any AE	1372 (57.9%)	1438 (60.7%)
Mild	758 (32%)	785 (33.2%)
Moderate	719 (30.4%)	778 (32.9%)
Severe	504 (21.3%)	587 (24.8%)
SAE	846 (35.7%)	951 (40.2%)
SAEs with fatal outcome	236 (10.0%)	268 (11.3%)
AE leading to discontinuation of study drug	111 (4.7%)	116 (4.9%)
AE leading to dose modification of study drug	320 (13.5%)	367 (15.5%)
AE leading to interruption of study drug	284 (12.0%)	349 (14.7%)
AE leading to reduction of study drug	43 (1.8%)	25 (1.1%)

Reviewer's table; Source: adsl & adae
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of patients in group; n, number of patients with at least one event.

6.6.2. Deaths

As discussed under efficacy, all-cause mortality was lower in the dapagliflozin as compared to the placebo arm. AEs that led to death during the whole study period (i.e., on and off treatment) based on the AE case report forms are shown in table 17.

Table 17. Deaths in Safety Population, Dapa-HF, On and Off Treatment

Deaths	Dapa N=2368 n (%)	Placebo N=2368 n (%)
Total AE with fatal outcome	286 (12.1%)	333 (14.1%)
Treatment-emergent deaths	236 (10.0%)	268 (11.3%)
Congestive heart failure[1]	76 (3.2%)	91 (3.8%)
Cardiac arryhthmia[2]	46 (1.9%)	53 (2.2%)
Myocardial infarction	15 (0.6%)	12 (0.5%)
Stroke and embolism	15 (0.6%)	14 (0.6%)
Renal injury	4 (0.2%)	1 (0.0)
Non-treatment emergent deaths[1]	50 (2.1%)	65 (2.7%)
Congestive heart failure[1]	15 (0.6%)	34 (1.4%)
Cardia arrythmia[2]	5 (0.2%)	8 (0.3%)
Myocardial infarction	3 (0.1%)	3 (0.1%)
Stroke and embolism	4 (0.2%)	2 (0.1%)

Reviewer's Table; Source: ads & adae

[1] Congestive heart failure based on cardiac failure (SMQ) includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiopulmonary failure, cardiogenic shock, acute pulmonary edema

[2] Cardiac arrhythmia based on cardiac arrythmia (SMQ) includes sudden cardiac death, sudden death, cardiac death, pulseless electrical activity, ventricular arrythmia, ventricular fibrillation, atrial fibrillation, cardio-respiratory arrest

Patients could be counted in more than one AE grouping leading to death

6.6.3. Serious Adverse Events

The overall incidence of SAE was lower in the dapagliflozin arm compared with the placebo arm: 846/2368 (35.7%) and 951/2368 (40.2%), respectively. There were no preferred terms that

occurred with a frequency of at least 0.5% greater in the dapagliflozin arm compared to the placebo arm. Table 18 summarizes actions taken as a result of SAEs and shows preferred term SAEs occurring in at least 2%. The incidence of more frequently reported SAEs was generally lower in patients treated with dapagliflozin than placebo. Because cardiac failure related AEs were the most frequently reported SAEs, MedDRA cardiac failure SMQ (narrow) was used to further summarize the results. Similar to MedDRA preferred terms analysis, there was no safety concern from the analyses pooling preferred terms that capture a similar medical concept using MedDRA SMQ and FMQs.

Table 18. Serious Adverse Events, Safety Population, DAPA-HF, On-Treatment

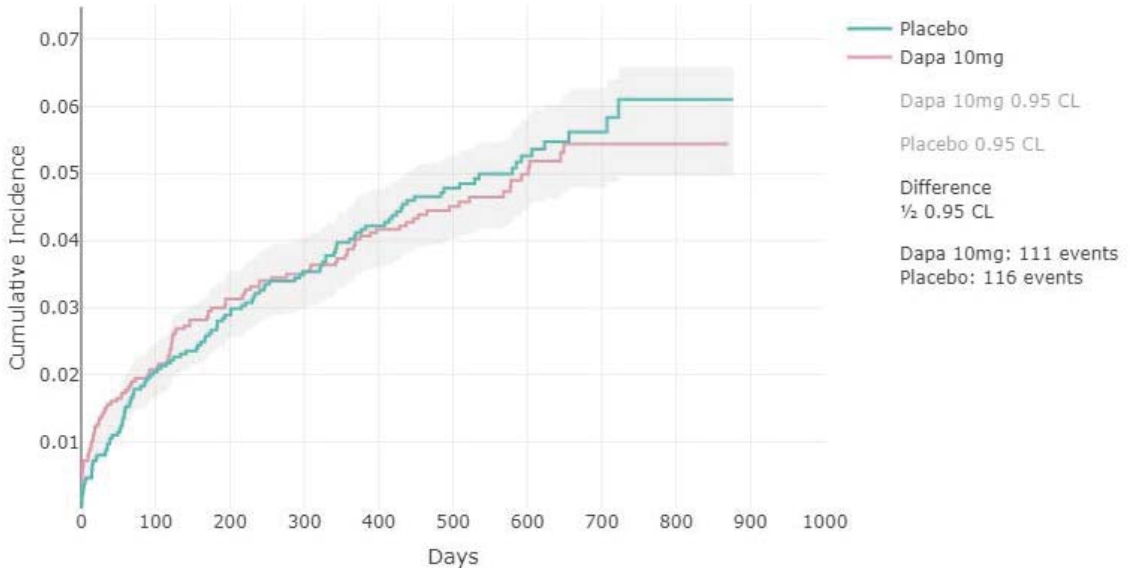
Serious Adverse Event[1]	Dapa N=2368 n (%)	Placebo N=2368 n (%)
Any SAE	846 (35.7%)	951 (40.2%)
Study drug withdrawn	51 (2.2%)	72 (3.0%)
Study drug interrupted	211 (8.9%)	255 (10.8%)
SAE preferred term in at least 2% of patients		
Cardiac failure	238 (10.1%)	325 (13.7%)
Pneumonia	70 (3.0%)	73 (3.1%)
Cardiac failure congestive	57 (2.4%)	65 (2.7%)
Cardiac failure acute	36 (1.5%)	51 (2.2%)
Ventricular tachycardia	32 (1.4%)	53 (2.2%)
SAE AE grouping		
Cardiac failure (SMQ, narrow)	353 (14.9%)	454 (19.2%)

Reviewer's table; Source: adsl & adae

6.6.4. Dropouts and/or Discontinuations Due to Adverse Events

The treatment discontinuation rate due to an AE was similar between treatment arms throughout the study (Figure 8). Approximately 5% of patients in both arms discontinued medication due to an AE, which is quite low. The most common reasons for medication discontinuation in the dapagliflozin arm were cardiac failure and adverse events related to volume depletion; the percentage of patients with discontinuations for such events was similar in the two arms. Results from the MedDRA Preferred Term Analysis and FDA MedDRA Query (FMQ) Analysis, discussed below, were generally consistent except for genital infection. There were 7 (0.3%) patients with AE leading to discontinuation due to genital infection in the dapagliflozin group and none in the placebo group.

Figure 6. Kaplan-Meier plot of the cumulative percentage of patients with permanent discontinuation of study drug due to an adverse event



Reviewer's Table: OCS The Adverse Event Temporal Visualization, datasets: adsl and adae

Table 19. Adverse Events Leading to Discontinuation, Safety Population, DAPA-HF

Adverse Event[1]	Dapa N=2368 n (%)	Placebo N=2368 n (%)
Patients with at least 1 AE leading to discontinuation	111 (4.7%)	116 (4.9%)
Congestive heart failure[2]	18 (0.8%)	17 (0.7%)
Volume depletion[3]	9 (0.4%)	8 (0.3%)
Renal impairment[3]	8 (0.3%)	9 (0.4%)
Genital infection[4]	7 (0.3%)	0 (0%)
Dizziness	4 (0.2%)	4 (0.2%)
Haemorrhage[5]	4 (0.2%)	4 (0.2%)

Reviewer's Table; Source: adsl & adae
[1] Coded as pooling MedDRA preferred that capture a similar medical concept
[2] Congestive heart failure includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiopulmonary failure, cardiogenic shock, acute pulmonary edema
[3] Sponsor's definition for AESI
[4] Genital infection includes balanitis candida, balanoposthitis, fungal balanitis, genital infection, genital infection fungal, penile infection, and vulvovaginal mycotic infection
[5] FMQ narrow haemorrhage
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in group; n, number of patients with adverse event ; PT, preferred term.

6.6.5. Adverse Events of Special Interest (AESI)

For non-serious AEs, only AESIs (some prespecified dapagliflozin and SGLT2 class related effects) and AEs leading to discontinuation or dose reduction were reported. AESIs (see section 7.4) are summarized in table 20. Overall, the incidence of these events was similar between the two arms. For AESIs occurring in at least 5% of treated patients (volume depletion, renal events and AEs leading to a risk for lower limb amputation) subgroup analyses were performed.

Table 20. Incidence of Adverse Events of Special Interest, Safety Population, DAPA-HF

AESI	Dapa 10 mg (N=2368)		Placebo (N=2368)	
	AE	SAE	AE	SAE
Volume depletion	170 (7.2)	23 (1.0)	153 (6.5)	38 (1.6)
Renal AEs	141 (6.0)	34 (1.4)	158 (6.7)	58 (2.4)
Diabetic ketoacidosis[a]	3 (0.1)	3 (0.1)	0	0
Major hypoglycemic events	4 (0.2)	0	4 (0.2)	1
Fractures[b]	49 (2.1)	29 (1.2)	50 (2.1)	26 (1.1)
Amputations[b]	13 (0.5)	12 (0.5)	12 (0.5)	11 (0.5)
AEs leading to a risk for lower limb amputation[b]	155 (6.5)	63 (2.7)	120 (5.1)	46 (1.9)

[a] There were 20 potential DKA events in 19 patients – 12 in the dapagliflozin and 7 in the placebo arms, sent for adjudication
[b] AEs were analyzed for the whole treatment period- on and off treatment
Reviewer's Table, datasets: adae and adsl

6.6.5.1. AEs suggestive of volume depletion

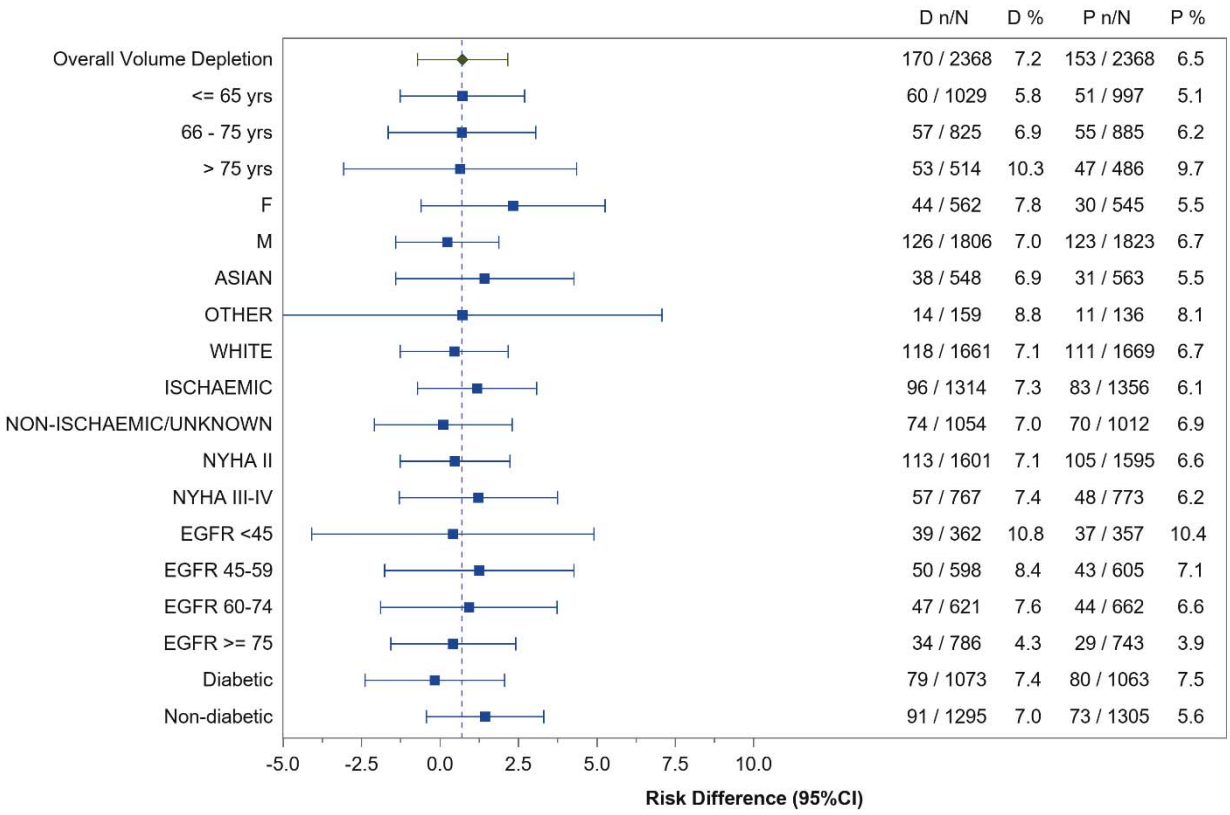
The incidence of AEs suggestive of volume depletion was 7.2% in the dapagliflozin treatment arm and 6.5% in the placebo arm, corresponding to event rate of 5.1 and 4.6 per 100 patient-years, respectively. The most commonly reported AE related to volume depletion is hypotension in both arms (Table 21). The results were also similar between two arms regarding the incidence of SAEs (Table 18). There was no fatal case in either arm. Subgroup analyses for AEs suggestive of volume depletion were performed by age, gender, race, NYHA class, eGFR and diabetes status at baseline (Figure 9). In general, the results were consistent across most of subgroups with a risk difference (RD) close to the overall point estimate of 0.7. Female patients and patients without diabetes in the dapagliflozin arm had slightly higher incidence compared to those in the placebo arm; though, the overall point estimate was included in the 95% CIs of these two subgroups.

Table 21. Incidence of AEs Suggestive of Volume Depletion by Preferred Terms, Safety Population, DAPA-HF, On-Treatment Period

	Dapa 10mg (N=2368)	Placebo (N=2368)
VOLUME DEPLETION	170 (7.2)	153 (6.5)
Hypotension	92 (3.9)	80 (3.4)
Hypovolemia	34 (1.4)	21 (0.9)
Dehydration	30 (1.3)	28 (1.2)
Syncope	12 (0.5)	21 (0.9)
Orthostatic hypotension	11 (0.5)	8 (0.3)
Blood pressure decreased	4 (0.2)	1 (0.0)
Circulatory collapse	1 (0.0)	4 (0.2)
Hypovolemic shock	0	4 (0.2)

Reviewer's Table, Source: datasets: adsl & adae. OCS Analysis Studio, Custom Table Builder.

Figure 7. Volume Depletion AEs by Subgroup, Safety Population, DAPA-HF, On-Treatment Period



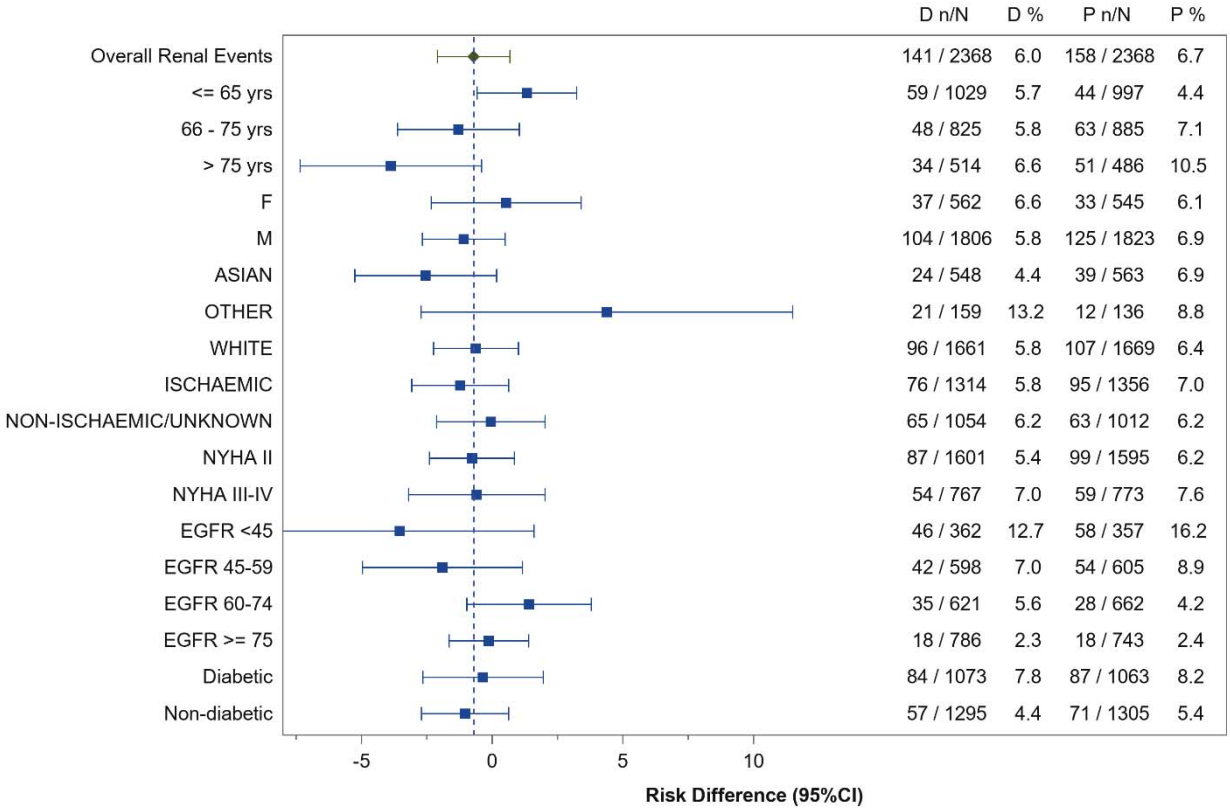
Reviewer's figure, Source: datasets: adae and adsl

6.6.5.2. Renal adverse events

The incidence of renal AEs was similar between the treatment arms: 6% in the dapagliflozin treatment arm and 6.7% in the placebo arm, corresponding to event rate of 4.2 and 4.8 per 100 patient-years, respectively. The results were also similar between two arms regarding the incidence of SAEs (Table 18) and DAEs (Table 19). There were 4 fatal cases in the dapagliflozin arm compared to 1 case in the placebo arm. All 4 fatal cases in the dapagliflozin arm were in white males with treatment exposure that ranged from 5.6 to ~12 months. There was one fatal renal insufficiency case that the investigator thought was possibly related to dapagliflozin. The patient was categorized as having NYHA class II HF with diabetes at baseline. His baseline serum creatinine was ~1.25 mg/dL with eGFR >60 mL/min/1.73m^2 and his renal function remained similar up to month 4 (Day 114) with serum creatinine of 1.3 mg/dL. However, he was admitted in hospital on Day 173 with confused behavior and renal failure was discovered with serum creatinine of ~9.6 mg/dl. The patient died on the same day. The cause of this rapid decline in renal function after the month 4 visit is unclear. The cause of death in the other 3 fatal cases was likely associated with patients' medical condition including chronic renal failure and was not related to dapagliflozin.

Subgroup analyses for renal AEs were performed by age, gender, race, NYHA class, eGFR and diabetes status at baseline. In general, the results were consistent across most of subgroups with a RD of < 0. Compared to the placebo, it is noted that the risk of having renal events in the dapagliflozin arm was slightly higher in the race group-other (i.e. majority were black), though this was a small subgroup.

Figure 8. Renal AEs by Subgroup, Safety Population, DAPA-HF, On-Treatment Period



Reviewer's figure, Source datasets: adsl, adae

The incidence of acute kidney injury (preferred term included in renal AEs) was lower in the dapagliflozin arm (1.8%) as compared to the placebo arm (2.6%) in DAPA-HF.

6.6.5.3. Diabetic Ketoacidosis

Potential DKA events were sent for adjudication in DAPA-HF. Overall, there were 20 potential DKA events, in 19 patients (12 in the dapagliflozin arm and 7 in the placebo arm), all of who had diabetes at baseline. Three events (0.1%) were adjudicated as definite DKA: all were SAEs in the dapagliflozin arm during the on-treatment period. The event rate for DKA was 0.09 per 100 patient-years. All 3 patients with definite DKA events had taken diabetic medication during the study, including 2 who were on insulin; all had been exposed to dapagliflozin for at least > 9 months before the occurrence of the event. There was one fatal case- a 70-year-old female who was hospitalized at Day 399, after being found unconscious at home. This patient had T2DM for

over 20 years and received biguanides and sulfonylureas during the study. She was suspected to have stopped her antidiabetic treatment for an unknown reason. Her primary cause of death was diabetic ketoacidosis hyperglycemic coma and the secondary cause of death was multiorgan failure.

6.6.5.4. Major Hypoglycemic Events

Major hypoglycemia was predefined in DAPA-HF as an event where all the following criteria were confirmed in a patient by the investigators: (1) symptoms of severe impairment in consciousness or behavior; (2) external assistance is needed; (3) intervention was needed; and (4) prompt recovery following the intervention.

The incidence of major hypoglycemic event was similar between the two arms – 4 (0.2%) patients in each arm, corresponding to an event rate of 0.12 per 100 patient-years. There was only one SAE, which was in the placebo arm. All patients with major hypoglycemic events had diabetes at baseline.

The results of a sensitivity analysis using the FMQ narrow hypoglycemia query are shown in Table 22. The incidence of hypoglycemia was slightly lower in the dapagliflozin arm compared to the placebo and majority of the events occurred in patients with diabetes at baseline. This analysis of less severe hypoglycemic events did not show a signal of concern.

Table 22. Incidence of FMQ Narrow Hypoglycemia, Safety Population, DAPA-HF, On-Treatment Period

	Dapa 10mg		Placebo	
	Diabetic (N=1073)	Non-diabetic (N=1295)	Diabetic (N=1063)	Non-diabetic (N=1305)
FDA N Hypoglycemia	12 (1.1)	2 (0.2)	25 (2.4)	1 (0.1)
HYPOGLYCAEMIA	11 (1.0)	2 (0.2)	25 (2.4)	1 (0.1)
POSTPRANDIAL HYPOGLYCAEMIA	1 (0.1)	0	0	0

Reviewer's table; Source: adsl & adae. OCS Analysis Studio, Custom Table Builder.

6.6.5.5. Fractures

The incidence of fracture AEs was assessed during on- and off- treatment and was about 2.1% in both arms corresponding to event rate of ~ 1.4 per 100 patient-years. The most common fractures in the dapagliflozin arm were lower limb fracture including ankle and hip fracture. The incidence of SAE (~1.2%) was also similar in the two arms.

6.6.5.6. Amputations

The number of patients who had at least 1 surgical amputation was similar between the two arms: 13 (0.5%) and 12 (0.5%) in the dapagliflozin and placebo arm, respectively, corresponding to event rate of ~ 0.4 per 100 patient-years. All amputations were lower limb amputations.

Reviewer Comments: *Because of the safety concern identified in another SGLT2 inhibitor – canagliflozin, amputations were also assessed in DECLARE (the CVOT trial in adults with T2DM). No imbalance in amputations was found in DECLARE. Overall, there is no evidence indicating that dapagliflozin is associated with an increased risk of amputation in high risk patients with T2DM or HF.*

6.6.5.7. Adverse events leading to a risk for lower limb amputation ("preceding events")

This group of adverse event terms was pre-specified by the sponsor to identify events that might precede amputation.

The incidence of AEs of "preceding events" was slightly higher in the dapagliflozin arm (6.5%) compared to the placebo arm (5.1%), corresponding to event rate of 4.4 and 3.4 per 100 patient-years, respectively. The most common AEs were dehydration and hypotension in both arms. The subgroup results are in general consistent with the overall results (Figure 11).

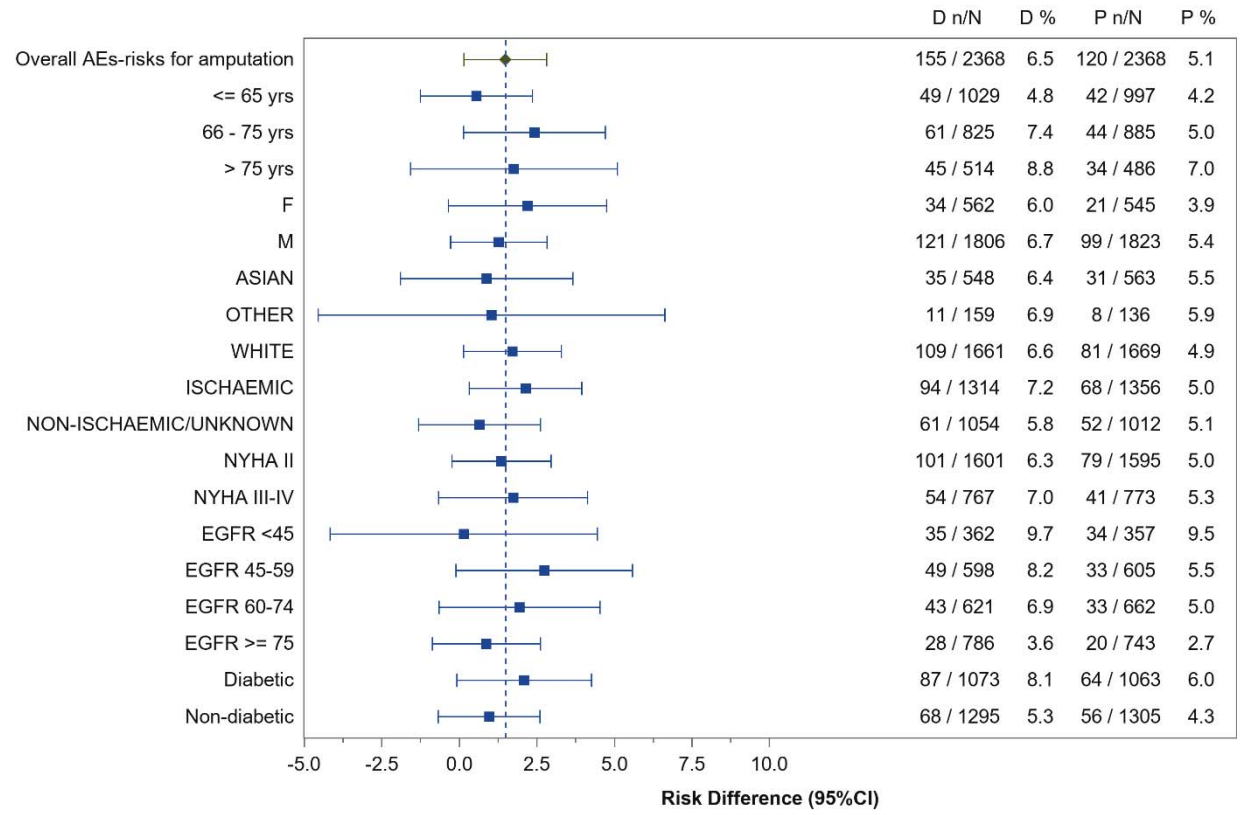
Table 23. Incidence of AEs related to Risk for Lower Limb Amputation, Safety Population, DAPA-HA

	Dapa 10mg (N=2368)	Placebo (N=2368)
EVENT RELATED TO RISK FOR LOWER LIMB AMPUTATION	155 (6.5)	120 (5.1)
Dehydration	35 (1.5)	29 (1.2)
Hypovolemia	34 (1.4)	23 (1.0)
Peripheral arterial occlusive disease	18 (0.8)	13 (0.5)
Cellulitis	17 (0.7)	22 (0.9)
Peripheral ischemia	10 (0.4)	5 (0.2)
Diabetic foot	8 (0.3)	3 (0.1)
Osteomyelitis	7 (0.3)	3 (0.1)
Skin ulcer	7 (0.3)	9 (0.4)
Wound infection	6 (0.3)	0
Paraesthesia	4 (0.2)	1 (0.0)

Reviewer's Table, Source: adsl & adae, OCS Analysis Studio, Custom Table Builder.

This table only includes AEs that occurred >0.2% in the dapagliflozin arm.

Figure 9. AEs leading to Risks for Amputation by Subgroup, Safety Population, DAPA-HF, On and Off Treatment Period



Review Figure Source: adsl & adae

6.6.6. Other Safety Events

6.6.6.1. Acute Pancreatitis

During the review, Office of Surveillance and Epidemiology (OSE) requested an evaluation of safety data on acute pancreatitis, a potential safety signal observed during post-marketing setting for SGLT2 inhibitors. Acute pancreatitis was not one of the pre-identified AESIs; thus, underreporting of these events is likely, but would not be biased between the arms. Table 24 shows the incidence of acute pancreatitis in DAPA-HF. Overall, the incidence of AE related to acute pancreatitis based on MedDRA SMQ (either broad or narrow) is similar between the two arms. The incidence of SAEs[9] is also similar between the two arms- 12 (0.5%) and 15 (0.6%) in the dapagliflozin and placebo arm, respectively. There was one fatal case from each arm. The fatal case in the dapagliflozin arm was a 72-year-old white male patient who had NYHA class III heart failure at baseline. The patient was hospitalized on Day 342 with the emergency of symptoms of pancreatitis (abdominal pain, nausea) and died in 2 days. No biopsy was done, and the cause of acute pancreatitis was unclear.

[9] The incidence of SAE listed here was based on MedDRA acute pancreatitis SMQ (broad). All AEs under acute pancreatitis SMQ (narrow) were SAE.

Table 24. Incidence of Acute Pancreatitis AEs based on MedDRA SMQ, Safety Population, DAPA-HF, On Treatment Period

MedDRA SMQ	Dapa 10mg (N=2368)	Placebo (N=2368)
Acute pancreatitis (broad SMQ)	42 (1.8)	41 (1.7)
Abdominal distension	1 (0.0)	5 (0.2)
Abdominal pain	8 (0.3)	12 (0.5)
Abdominal pain upper	7 (0.3)	3 (0.1)
Ascites	4 (0.2)	2 (0.1)
Ileus paralytic	1 (0.0)	1 (0.0)
Jaundice	0	1 (0.0)
Nausea	10 (0.4)	8 (0.3)
Pancreatitis	1 (0.0)	1 (0.0)
Pancreatitis acute	5 (0.2)	4 (0.2)
Vomiting	5 (0.2)	8 (0.3)
Acute pancreatitis (narrow SMQ)	6 (0.3)	5 (0.2)
Pancreatitis	1 (0.0)	1 (0.0)
Pancreatitis acute	5 (0.2)	4 (0.2)

Reviewer's Table, Source: adsl & adae, OCS Analysis Studio, Custom Table Builder.

6.6.6.2. Genital Infection / Fournier's Gangrene

Genital infection is an identified risk for dapagliflozin in patients with T2DM. In DAPA-HF, genital infection was not one of the pre-defined AESIs, thus non-serious events related to genital infection were only collected if events led to discontinuation, interruption or dose reduction of study drug. There were 20 (0.8%) patients (14 patients without diabetes) with reported genital infection AEs in the dapagliflozin arm and 2 (0.1%) in the placebo arm. No serious event was reported in the dapagliflozin arm and one in the placebo arm. A total of 7 (0.3%) patients (5 without diabetes) had genital infection AEs leading to drug discontinuous and none in the placebo arm.

All SAEs or DAEs indicating genital infections or necrotizing fasciitis were assessed by the sponsor to identify cases of Fournier's gangrene. None of these events was confirmed as Fournier's gangrene.

***Reviewer Comments**: Genial infection AE was not prospectively evaluated thus the incidence in the DAPA-HF was likely underestimated. Nevertheless, the results suggest that dapagliflozin-associated risk for genital infection was also present in patient with HF, with or without diabetes.*

6.6.7. Laboratory Findings

Section 6.1 Clinical Studies Experience of the current label describes increases in serum creatinine, hematocrit, LDL and decreases in eGFR and serum bicarbonate. In DAPA-HF, several laboratory parameters were collected at all visits including blood urea nitrogen, creatinine, HbA1c, hematocrit, potassium and sodium. Other parameters were collected at least at baseline visit and at the last study visit (i.e., either at premature treatment discontinuation visit or study closure visit). Overall, there were no clinically relevant changes in majority of laboratory parameters. Hematocrit (b) (4) and renal findings are described below.

Small mean increases in hematocrit were observed following the initiation of dapagliflozin. The difference between arms started early and then plateaued after month 4. Dapagliflozin had about 2.5 % increases in hematocrit compared to the placebo arm at month 4 onward. Slightly higher percent of patients in the dapagliflozin arm (3.5%) vs. the placebo arm (1.5%) had hematocrit > 55%.

In DAPA-HF, there was an initial small rise in serum creatinine and blood urea nitrogen by month 2 in the dapagliflozin arm (1.25±0.4 mg/dL and 24.1 ±10.3 mg/dL, respectively) compared to placebo (1.19±0.4 mg/dL and 23.4 ±10.0 mg/dL respectively). There were no obvious differences between the treatment arms in serum creatinine and urea nitrogen after month 8. Similarly, there was a small initial decrease in eGFR in the dapagliflozin arm and the differences between arms did not persist over time, mainly due to the decline in eGFR in the placebo arm over time.

The category analysis on renal parameters also did not reveal any safety concern (Table 25).

Figure 10. Hematocrit Over Time, Safety Population, DAPA-HF

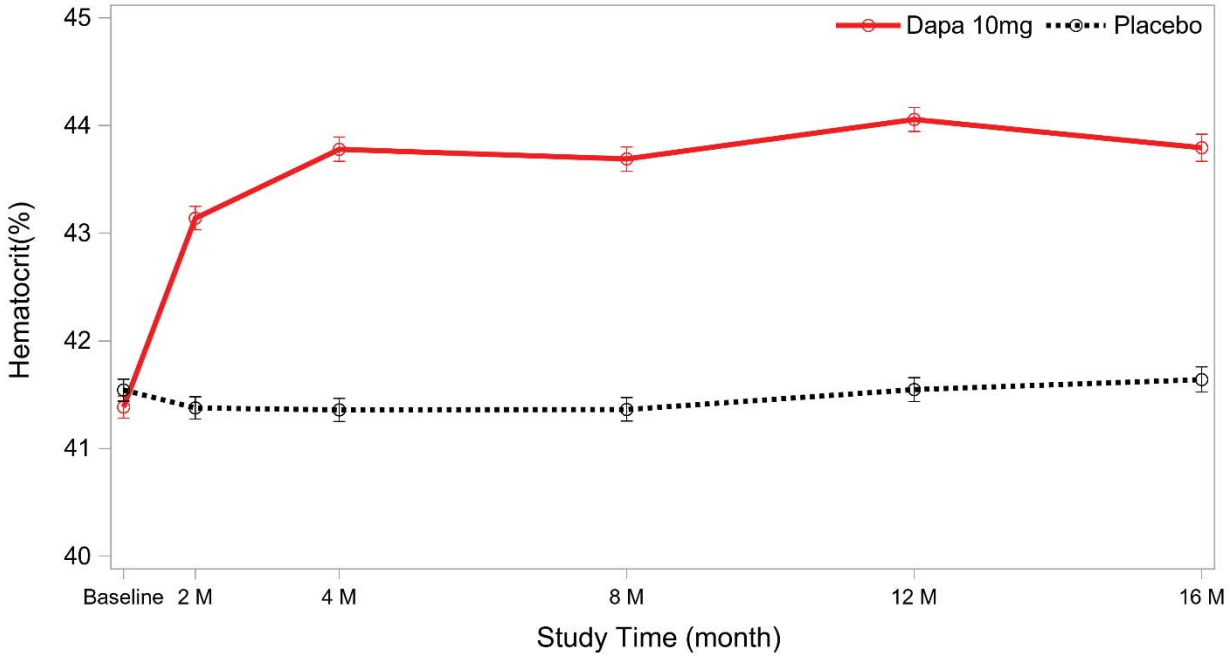
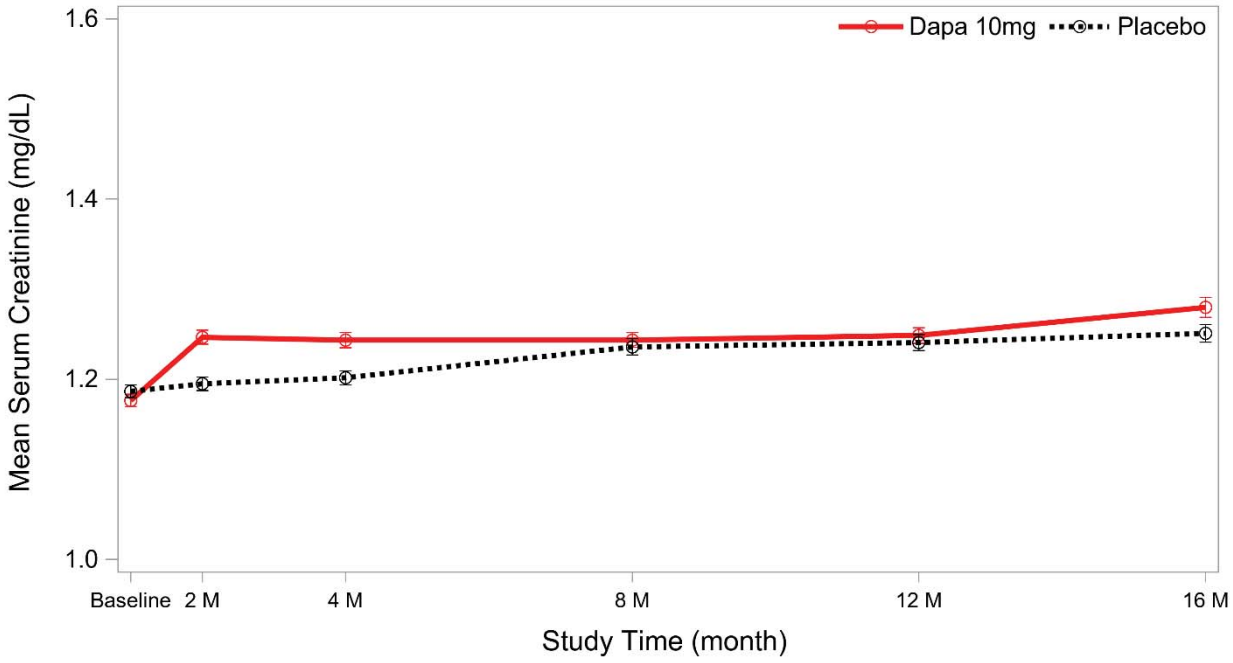
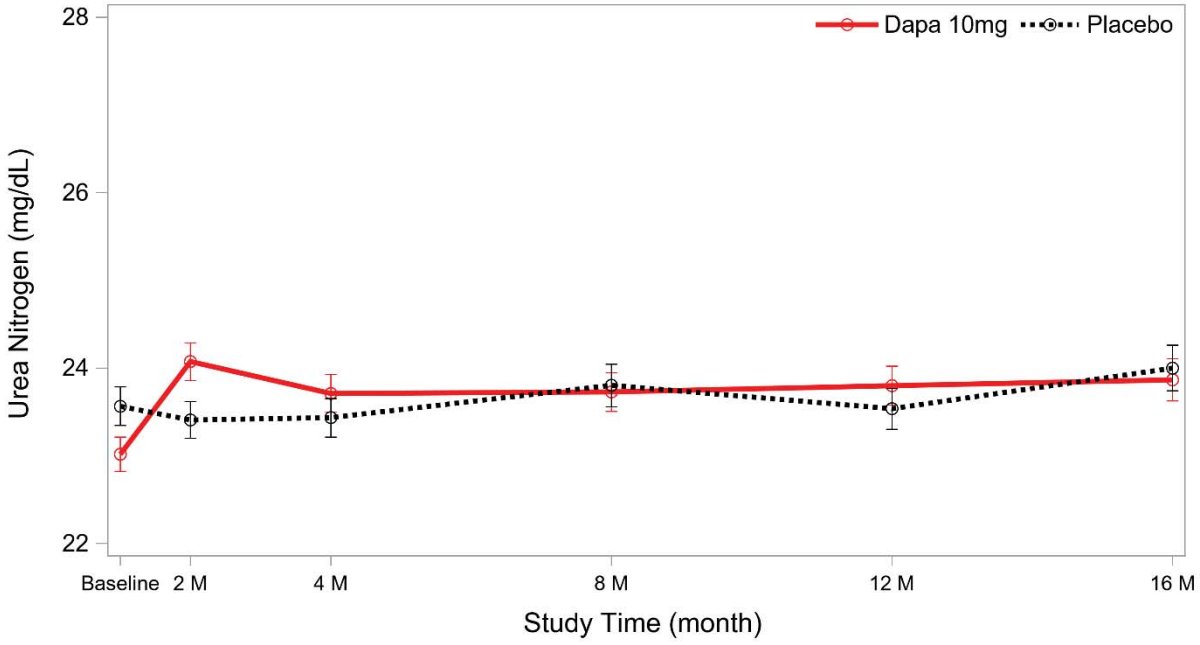


Figure 11. Serum Creatinine Over Time, Safety Population, DAPA-HF



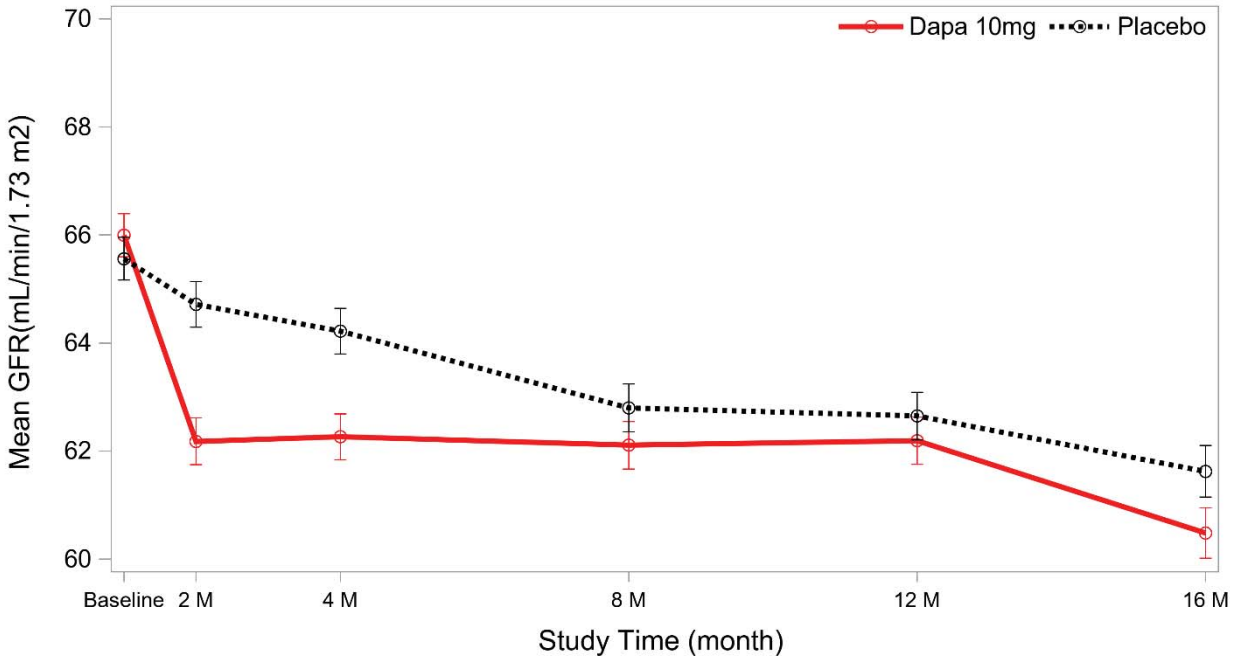
Reviewer's Figure, Source: adsl & adlb

Figure 12. Urea Nitrogen Over Time, Safety Population, DAPA-HF



Reviewer's Figure, Source: adsl & adlb

Figure 13. eGFR Over Time, Safety Population, DAPA-HF



Reviewer's Figures, Source: adsl & adlb

Table 25. Safety Criteria for Renal Parameters, Safety Population, DAPA-HF

Criteria	Dapa_10mg N = 2367[a]	Placebo N=2367 [a]
Serum creatinine increase		
> 50% increase from baseline	241/2367 (10.2)	251/2367 (10.6)
>0.5 mg/dL	344/2367 (14.5)	315/2367 (13.3)
>2.0 mg/dL	13/2367 (0.5)	18/2367 (0.8)
>2.5 mg/dL	7/2367 (0.3)	9/2367 (0.4)
eGFR decline		
> 25% decrease from baseline	833/2367 (35.2)	667/2367 (28.2)
> 50% decrease from baseline	66/2367 (2.8)	94/2367 (4.0)
> 30 mL/min/1.73m2	128/2367 (5.4)	128/2367 (5.4)

[a] Number of patients who had baseline and at least one post-baseline measurement

Reviewer's Table, Source: adsl & adlb

***Reviewer Comments**: The observed small early changes in laboratory parameters related to renal function in the dapagliflozin arm did not have corresponding clinical findings based on the AE data. The category analysis assessing outliers for renal parameters also did not reveal any safety concern.*

Increases in hemoglobin/hematocrit were observed consistently across the SGLT2 inhibitor class which may be related to the volume depletion class effects. Increases in hematocrit could theoretically increase the risk for thromboembolic events; however, in both DECLARE and DAPA-HF, these small increases in hematocrit did not result in any significant clinical findings.

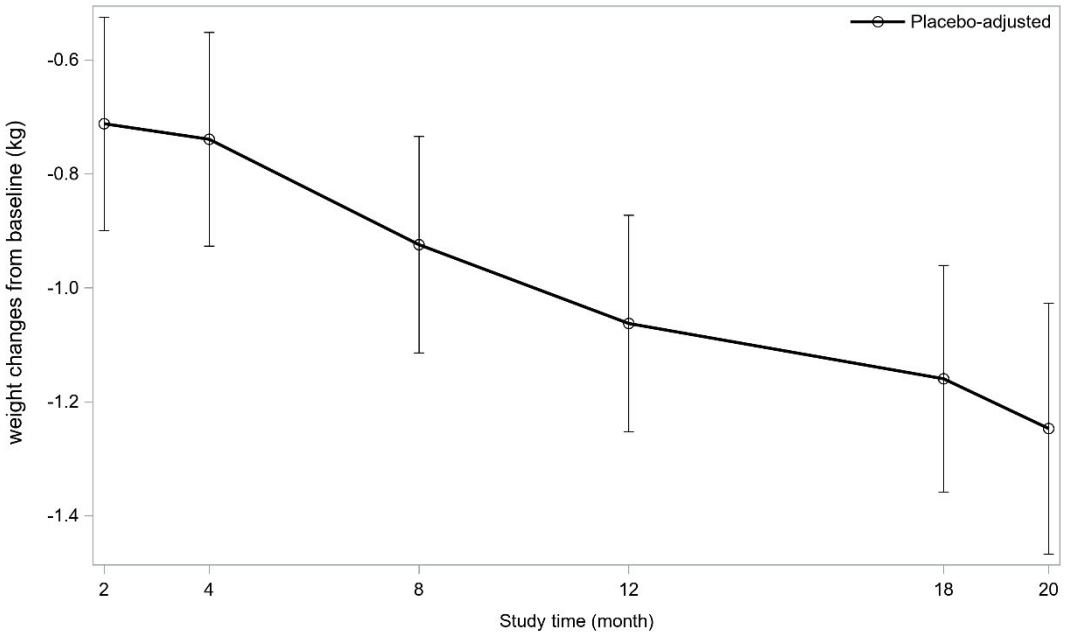
Of note, the Sponsor cited few references suggesting that increased hematocrit may provide systemic organ protection by enhancing myocardial and systemic tissue oxygen delivery and this mechanism of action could contribute to the beneficial effect of dapagliflozin. (b) (4)

6.6.8. Vital Sign Findings

There was a small decrease in body weight (~ 1.2 kg decrease at month 18) and systolic blood pressure (SBP) (~ 1.5 mmHg at month 18) in the dapagliflozin arm compared to the placebo arm. The placebo-adjusted differences for weight decline in the dapagliflozin arm gradually increased over time (Figure 14) while the SBP declines were at peak prior to month 2 (Figure 15). There were no meaningful differences between treatment arms in changes in diastolic blood pressure and heart rate over time.

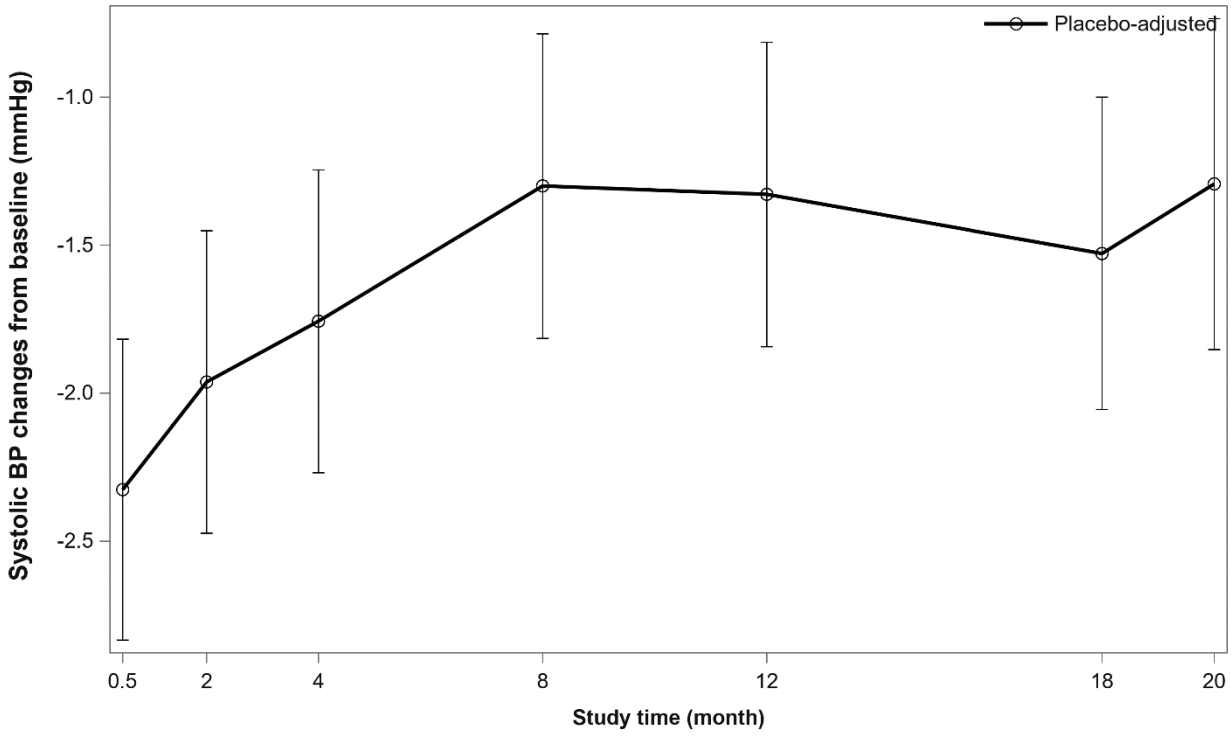
***Reviewer Comments**: The observed changes in vital sign are consistent with the diuretic effect of dapagliflozin.*

Figure 14. Placebo-adjusted body weight changes over time, Safety Population, DAPA-HF



Reviewer's Figure, datasource: adsl & adlb

Figure 15. Placebo-adjusted systolic blood pressure changes over time, Safety Population, DAPA-HF



Reviewer's Figure, datasource: adsl & adlb

6.7. Review Issues Relevant to the Evaluation of Risk

The adverse event profile in DAPA HF does not raise concerns about harmful renal effects of dapagliflozin. Renal adverse events trended lower in the dapagliflozin group compared to placebo; AKI events also trended lower in the dapagliflozin group. The Warnings and Precautions section of labeling will be modified to remove the individual warning about AKI and include it as a consequence of volume depletion.

7. Therapeutic Individualization

No additional clinical pharmacology studies regarding intrinsic factors and drug interactions were submitted as part of the application. See the label section 12.3 for factors that affect exposures.

Pregnancy and Lactation

Based on this efficacy supplement, no changes are proposed to the approved dapagliflozin label.

8. Product Quality

Not applicable.

8.1. Device or Combination Product Considerations

Not applicable.

9. Human Patients Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

DAPA-HF trial was conducted in accordance with the principles laid out in the Declaration of Helsinki, International Council for Harmonization (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples. The study treatment bottles were labelled in accordance with Good Manufacturing Practice (GMP). DAPA-HF trial was approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each investigational center prior to the start of the trial at that center.

10. Advisory Committee Summary

Not applicable.

III. Appendices

11. Summary of Regulatory History

Sponsor-FDA meetings related to the DAPA-HF Trial are listed below:

June 30, 2016, PIND 130631 Type B Meeting /EOP2

The sponsor met with FDA to discuss design of DAPA-HF trial. Relevant discussion points are listed below:

a. FDA agreed with the proposed definitions for heart failure hospitalization and urgent heart failure visit.

b. FDA clarified that a key consideration for the indication will be whether dapagliflozin appears effective in both diabetic and non-diabetic patients.
c. FDA indicated that the two proposed doses of dapagliflozin, 5 and 10 mg, were on the steep portion of the dose response relationship, and not separated by much. FDA recommended that the sponsor consider including a dose higher than 10 mg. The sponsor responded that patients with heart failure are expected to have a higher systemic dapagliflozin exposure and from a safety perspective, the 10 mg dose is most extensively studied. Hence, the sponsor proposed to study only the 10 mg dose.
d. FDA recommended that renal function should be assessed earlier than 1 month after initiation of study drug. In addition, clinically significant episodes of acute kidney injury should be specified as an adverse event of special interest.
e. Dapagliflozin has Warning and Precautions for increased LDL-C and bladder cancer. In addition, increases in serum phosphorus were observed in clinical trials. Consider monitoring related to these issues.
f. According to the dapagliflozin label, in a study of patients with an eGFR of 30 to <60 mL/min/1.73mz, 13 patients randomized to dapagliflozin experienced a fracture compared with 0 randomized to placebo, and eight of the 13 patients had an eGFR 30 to 45 mL/min/1.73m2. Consider specifying fracture as an adverse event of special interest for this population.
g. Consider specifying amputation as an adverse event of special interest.
h. Consider collecting sparse PK data to help provide more insight into the dose response relationship.

May 4, 2017, Written Responses to sponsor's Type C meeting request

The sponsor requested a type C meeting to obtain FDA advice on the Patient Reported Outcome (PRO) instrument – KCCQ, to be used in the DAPA-HF study. Relevant FDA recommendations are listed below:

a. While KCCQ TSS measures important symptoms of heart failure, concerns about translating the results of KCCQ TSS into a readily described treatment benefit remain.

b. (b) (4) FDA clarified that if dapagliflozin reduces mortality, imputation of a KCCQ TSS score of 0 following death is likely to drive success on the KCCQ TSS endpoint. (b) (4)

c. FDA asked the sponsor to justify the proposed threshold for meaningful within-patient change (improvement and worsening) on the KCCQ TSS using anchor-

based methods and cumulative distribution function (CDF) analysis to help inform interpretation of phase 3 data.

14. FDA recommended that the KCCQ instruments be culturally adapted and translated for all intended study populations and KCCQ TSS be assessed by country or region.

June 5, 2019, Written Responses to sponsor's Type B meeting request

The sponsor requested a Type B meeting to seek FDA guidance on the proposed content and format of a supplemental NDA submission based on the results of the DAPA-HF trial. Relevant FDA recommendations are as follows:

a. Please provide a random sample of adjudication packages for patients with a subject ID that ends in a 3.
b. FDA agreed with the sponsor's proposal to provide narratives for all deaths, SAEs, DAEs, and AEs of special interest (i.e., volume depletion, renal events, major hypoglycemic events, fractures, DKA, and AEs leading to amputation).
c. FDA agreed with the sponsor's proposal to provide case report forms (CRFs) for all deaths, SAEs, and DAEs.

September 9, 2019, Fast Track Designation

Fast Track Designation was granted to dapagliflozin development program for the following indication:

(b) (4)

based on the data you propose to collect in the DAPA-HF trial (IND 130631)

September 20, 2019, Type C Meeting / Top-Line Results

The sponsor presented the results of DAPA-HF trial. Highlights of the discussion are listed below:

a. FDA noted that the treatment effect in NYHA Class II patients appeared to be more favorable than the effect in NYHA Class III/IV patients (representing almost 1/3 of enrolled patients, nearly all Class III), and the p-value for the interaction for NYHA class was significant (p=0.0087). The sponsor believes the finding by NYHA class is likely to be play of chance given multiple comparisons.
a. Regarding the use of Win ratio to analyze KCCQ endpoint, FDA commented that win ratios can be difficult to interpret clinically and noted that there was

only a 2.8-point difference in KCCQ scores between treatment groups at 8 months. The Agency questioned whether the size of the treatment effect on the KCCQ (as reflected by the mean effect or responder analyses) was clinically relevant and recommended that the sponsor address this issue in the NDA submission.

12. Pharmacology Toxicology Assessments and Additional Information

Not applicable.

13. Clinical Pharmacology Assessment: Additional Information

Not applicable.

14. Trial Design: Additional Information and Assessment

Table 26 lists dates of key events during the DAPAHF Trial.

Table 26. Event Dates for DAPA-HF Trial (Source: Sponsor material)

Event	Date
First Subject In	10-February-2017
Last Subject In	17-July-2019
Interim Analysis	29-March-2019
Database Lock	11-August-2019

Protocol Amendments

The first Global Clinical Study Protocol Version 1 is dated 10/26/2016. There was only one amendment to the global clinical study protocol, dated 10/26/2017 and at the time of the amendment, 81 endpoint events had accrued. Additional amendments were made to the local documents in different countries. These amendments were not expected to impact subject safety or interpretation of efficacy.

Relevant changes in the amendment to the global study protocol dated 10/26/2017 are listed below:

- KCCQ clinical/overall symptom score was changed to total symptom score based on FDA feedback
- AEs leading to a risk for lower limb amputations were included as AE of interest based on FDA feedback
- Information related to the echocardiographic sub-study was added
- The requirement to adjudicate potential endpoints related to eGFR decline was removed
- The recording of AEs was limited to not include potential renal endpoints that are based on examination and tests, i.e., laboratory results only, unless fulfilling the serious adverse event (SAE) criteria or adverse event leading to discontinuation of IP (DAE) criteria, because the protocol already mandated laboratory values to be systematically analyzed
- Clarification was added that open label use of SGLT2 inhibitor in combination with the investigational product was prohibited and considered a protocol violation. It was not a protocol violation if the patient was off SGLT2 inhibitor
- Clarification was added that the Data Monitoring Committee (DMC) have the possibility to do more than one interim analysis of efficacy if they deem necessary, and that the stopping rule includes significance for the primary endpoint and CV Death

This amendment was submitted to DCRP under IND 130631, changes were reviewed, and no additional comments were conveyed to the sponsor.

Study Data Flow

The Rave Web Based Data Capture (WBDC) system was used for data collection and query handling. Study data were recorded in the electronic case report forms (eCRFs) in Rave.

Management of concomitant medications in DAPA-HF Trial

Use of medications known to cause hypoglycemia in patients with type 2 diabetes mellitus: The protocol allowed for lowering the dose of insulin or insulin secretagogues such as sulfonylurea to minimize the risk of hypoglycemia when used in combination with the study medication in patients with baseline HbA1c < 7%.

Concomitant treatment with open label SGLT2 inhibitors: Open label use of other SGLT2 inhibitors was prohibited, unless patients were off the IP and did not have any other treatment options.

Concomitant diuretic medications: The dose of diuretics could be proactively adjusted to minimize any deleterious effects on hypovolemia/volume depletion accentuated by the diuretic effects of the IP.

Concomitant medication doses: The protocol encouraged stable doses of concomitant medications during the trial to all assessment of incremental benefit with dapagliflozin.

Endpoint Reporting and Adjudication

Potential study endpoints were identified by using laboratory data, patient interview, and/or information obtained through standard medical practice. The following endpoints were centrally adjudicated using source documents and relevant eCRFs:

- All deaths
- All HF events (hospitalizations for HF or urgent HF visits)
- Potential renal endpoints:
  - eGFR declines ≥50% from baseline
  - eGFR values <15 mL/min/1.73m2
  - Dialysis
  - Kidney transplantation
  - Doubling of serum creatinine (since the most recent central laboratory measurement)
- Cardiac ischemic events (MI and unstable angina)
- Cerebrovascular events (stroke and TIA)
- DKA (not considered an efficacy variable but will be adjudicated as a safety variable)

Death was subclassified as CV or non-CV and renal primary cause (death due to ESRD when dialysis is not given)

Heart Failure Events: Clinical data interchange standards consortium (CDISC) definition for hospitalization for heart failure (HF) and urgent heart failure visit was used. A heart failure event included hospitalization for heart failure and urgent outpatient visits. **A heart failure hospitalization** was defined as an event that met all the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF
2. The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
   (a) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   (b) Decreased exercise tolerance
   (c) Fatigue
4. The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:
   (a) Physical examination findings considered to be due to heart failure, including new or worsened:

(i) Peripheral edema
(ii) Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
(iii) Pulmonary rales/crackles/crepitations
(iv) Increased jugular venous pressure and/or hepatojugular reflux
(v) S3 gallop
(vi) Clinically significant or rapid weight gain thought to be related to fluid retention

(b) Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

(i) Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT- proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
(ii) Radiological evidence of pulmonary congestion.
(iii) Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)).
OR
(iv) Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5. The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:
(a) Augmentation in oral diuretic therapy
(b) Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator)
(c) Mechanical or surgical intervention, including:

(v) Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

(vi) Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

An **urgent heart failure visit** was defined as an event that met all the following criteria:

1. The patient has an urgent, unscheduled office/practice or emergency department

visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2. All signs and symptoms for HF hospitalization (i.e., 3) symptoms, 4) physical examination findings/laboratory evidence of new or worsening HF, as indicated above) must be met.
3. The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

Cardiovascular death included deaths due to acute myocardial infarction, sudden cardiac death, heart failure or cardiogenic shock, stroke, CV procedure, CV hemorrhage, other CV causes (e.g., pulmonary embolism or peripheral arterial disease).

Renal Endpoints: eGFR baseline was defined as the mean central laboratory value from Visit 1 and Visit 2. Dialysis, renal transplantation, eGFR events (<15 mL/min/1.73m2, ≥50% decline in eGFR) and doubling of serum creatinine (compared with the most recent central laboratory measurement) were in the eCRF and submitted for adjudication.

Other events: Other than the study endpoints, the following events were also documented in the eCRF:

- evidence of worsening HF symptoms/signs leading to initiation of a new treatment for HF or augmentation of existing oral therapy for HF sustained for at least 4 weeks
- NYHA class
- New diagnosis of AF was recorded as an AE with additional information on a separate eCRF page
- New onset of T2D, post randomization, defined as reporting of new onset T2D necessitating initiation of anti-diabetic medication or HbA1c>6.5% measured by central lab at two consecutive study visits
- PROs: PGIS, PGIC, KCCQ, EQ-5D-5L

Clinical Event Adjudication

The following potential endpoints were adjudicated in the DAPA-HF trial:

1. All HF events (hospitalization for HF or urgent HF visits)
2. All deaths
3. Dialysis
4. Renal transplant
5. Doubling of serum creatinine*
6. Myocardial infarction
7. Stroke

*Initial CEA committee charter included doubling of serum creatinine as an endpoint to be adjudicated. According to global study protocol amendment dated 10/26/2017, the requirement to adjudicate potential endpoints related to eGFR decline was removed.

Adjudication was performed by Clinical Event Adjudication (CEA) committee at Uppsala Clinical Research Center. The CEA committee was independent of the sponsor, DMC, and Executive Committee. The CEA committee comprised of Clinical Faculty Leader (CEA Chair), CEA co-chair, scientific nephrology co-chair, CEA physician reviewers, CEA Coordinators and Endpoint Office staff (CEA monitors and CEA assistants). All potential endpoints were reviewed independently by two CEA physician reviewers (Phase I). For stroke, HF, or renal events, one of the CEA physician reviewer had to be a neurologist, cardiologist, or nephrologist, respectively. If the two CEA physician reviewer's adjudication decision matched, then the final results was saved in the CEA database. Minor disagreements were resolved by a consensus agreement between the two reviewers. Unresolved minor and major disagreements were reviewed by 3 CEA physician reviewers at a Phase II meeting and a final decision rendered by consensus agreement or when required, a majority vote.

Adjudication and DMC Meeting Minutes Review

According to the **DKA-AC** meeting minutes, the two CEC adjudicators for DKA events changed throughout the trial.

DMC meeting minutes: DMC for DAPA-HF trial is also monitoring the DAPA-CKD trial. Some key discussion points at the DMC meetings are listed below:

Meeting Date 04/04/2017

- HF event is defined differently in HF and chronic kidney disease (CKD) trials; therefore, the DMC will not combine HF events across the two trials
- Because dapagliflozin is insulin-independent and directly excretes glucose based on baseline glycaemia, it has a low propensity for causing hypoglycemia.
- The DMC asked how dapagliflozin reaches the target in the body; AZ discussed that dapagliflozin may reach the target through filtration.
- AZ acknowledged that patients who use Tes-Tape to detect glucose in their urine could unblind themselves; however, typically patients without T2DM do not use Tes-Tape.
- Patients with low baseline eGFR have a higher incidence of volume depletion on dapagliflozin and larger difference compared to placebo (1.5% in placebo group versus 3.2% on dapagliflozin).
- The canagliflozin label warns about increases in potassium in patients on drug, but this has not been seen with dapagliflozin.

- **Fracture**: after a two-year bone mineral density study, there was no significant difference in bone mineral density between the placebo and dapagliflozin groups. AZ does not have data on fractures for those with severe renal failure. In high risk patients, AZ found little evidence for fractures related to dapagliflozin. AZ saw more fractures in patients with moderate renal failure but has not found anything connecting these fractures to dapagliflozin.
- **Amputation**: AZ is not aware of evidence that suggests dapagliflozin is associated with an increased risk of amputation.

Meeting Date 02/06/2018

- DMC report included 3,017 randomized patients and recommended to continue the trial unmodified.
- AZ stopped enrollment in Brazil and Russia because the sites in these countries had enrollment rates exceeding expectations. In addition, AZ must ensure that countries which opened sites later, such as China and India, contribute a sufficient number of patients as required by local regulatory agencies. EC/AZ also wants 20% of the study population to come from North America or Western Europe for potential future subgroup analyses.
- Digoxin use at baseline in 17% of patients (much lower than in PARADIGM HF); this low result may be caused by incomplete or incorrect medication coding.

Meeting Date 06/12/2018

- DMC report included 4,302 randomized patients and recommended to continue the trial unmodified.
- DMC reviewed closed report by diabetic status, but did not share this information with AZ.

Meeting Date 03/29/2019

- DMC report included 4,744 randomized patients and recommended to continue the trial unmodified.
- Interim analysis and fifth safety review was conducted.
- The DMC reviewed the pooled (type 2 diabetes [T2D] and non-T2D) closed report. The interim efficacy results did not fulfill the following superiority stopping criteria: 1) the one-sided p-value of the primary composite endpoint comparison is <0.001 in favor of dapagliflozin, and 2) the one-sided p-value of the CV death comparison is <0.001 in favor of dapagliflozin. The primary composite endpoint reached the required significance level; however, CV death did not.

- Because the FDA considered necrotizing fasciitis of the perineum a potential safety concern for SGLT2 inhibitors, AZ performed a program-wide review; however, AZ has found no evidence of a causal relationship between dapagliflozin and Fournier's gangrene.
- AZ has yet to find evidence of a relationship between dapagliflozin and amputations.
- DMC informed AZ that DMC reviews data by diabetic status.
- **AZ presentation**:
    - Clinical trials communication on Fournier's gangrene -10/10/2018
        - August 2018, FDA communication considers necrotizing fasciitis of the perineum in patients treated with SGLT2 inhibitors to be "new safety information" and should be included in the labelling.
        - A review of post-marketing cases from AstraZeneca's global Patient Safety database up to 4 October 2018 retrieved 16 cases. Most patients had T2DM or other risk factors for Fournier's gangrene.
        - From AstraZeneca clinical studies completed before 30 August 2018 (7,000 patients exposed to dapagliflozin), no case of Fournier's gangrene was identified. DECLARE CVOT, 17,160 patients (total follow-up of approx. 67,000 patient-years) 6 events within the on-treatment analysis (1 in the dapagliflozin group and 5 in the placebo group).
        - In conclusion, the data and information retrieved, and the literature do not support a causal relationship between dapagliflozin and Fournier's gangrene. Therefore, AstraZeneca does not consider Fournier´s gangrene or necrotizing fasciitis of the perineum in patients treated with dapagliflozin to be "new safety information."
- **Closed Report**:
    - The study completed enrollment on August 17, 2018, with 8140 potential patients screened and 4744 patients randomized.

Table 27. The schedule of study visits and assessments in DAPA-HF Trial (Source: Sponsor material)

Activity	Enrolment	Randomi-zation	Site visits					PTDV	SCV	Reference CSP
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14 (±7)**	**0**	**14 (±3)**	**60 (±7)**	**120 (±7)**	**240 (±14)**	**Day 360 (±14 and every 4th month)**		**≤6 wks from SED**	
Sign Informed Consent Form (ICF)	X									
Local laboratory assessment of NT-proBNP[a]	X[a]									
Inclusion/exclusion criteria	X	X								3.1
Demography	X									
Medical/surgical history	X									
General physical examination	X							X	X	5.2.1.2
Targeted physical examination		X	X	X	X	X	X			5.2.1.2
Assessment of left ventricular function[b]	X									4.1.1
NYHA Functional Classification	X				X	X		X	X	5.1.6
Electrocardiogram (ECG)	X									5.2.2
Height	X									5.2.3.2
Vital signs *(BP, pulse and body weight)*	X	X	X	X	X	X	X	X	X	5.2.3
Pregnancy testing	X	X								4.1.1
Randomization in IxRS		X								3.5

Activity	Enrolment	Randomi-zation	Site visits					PTDV	SCV	Reference CSP
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7, 8, 9 etc.**	**PTDV**	**SCV**	
Day	**-14 (±7)**	**0**	**14 (±3)**	**60 (±7)**	**120 (±7)**	**240 (±14)**	**Day 360 (±14 and every 4th month)**		**≤6 wks from SED**	
Concomitant medication		X	X	X	X	X	X	X	X	7.7
Central laboratory assessments[c]	X	X	X	X	X	X	X	X	X	5.2.1
PK sampling (predose)[d]							X			5.4
ePRO questionnaires[e]		X			X	X	X[d]	X	X	5.1.9
Potential endpoint events, SAEs, DAEs, AEs of interest[f]	X	X	X	X	X	X	X	X	X	5.1.1
Dispense IP (including kit verification in IxRS)/Collect IP		X			X	X	X	X	X	7.2
IP compliance reminder		X	X	X	X	X	X			7.5
Sample for future biomarker research, optional[g]		X					X			5.7

[a] Local laboratory assessment is optional and may be used to assess eligibility (according to local routine) of NT-proBNP. If used, the ICF need to be signed before the optional assessment starts. The optional local laboratory assessment can be done up to 3 months prior to randomization.

[b] LV assessments only if no assessment has been performed within 12 months prior to enrolment.

[c] Central laboratory assessments include alkaline phosphatase (ALP), ALT, AST, bilirubin, blood urea nitrogen (BUN), creatinine (including eGFR assessment), haematocrit, haemoglobin (Hb), HbA1c, NT-proBNP, phosphate, potassium, and sodium, as specified in Table 2.

[d] PK samples will be collected at visit 7.

[e] PGIS, KCCQ, EQ-5D-5L will be filled in at visit 2,5,6,7 and every 12 months after visit 7, and at PTDV and SCV. PGIC will be filled in at the same visits, with exception of visit 2.

[f] SAEs will be collected from the time of informed consent throughout the study until and including the patient's last visit. Potential endpoints, DAEs, AEs leading to dose reduction and temporary interruptions and AEs of interest will be collected from randomization throughout the study until and including the patient's last visit.

[g] Blood samples for potential future biomarker research will be collected at visit 2 and visit 7 and may be analysed at the discretion of AstraZeneca. The biomarker sampling is subject to separate approval/consent by the patient and is optional.

15. Efficacy Assessment Additional Information and Assessment

Applicability of Foreign Data: Per sponsor, "*all US investigational sites were filed to IND 130631 and Form FDA 1572 were collected from US investigators; Non-US investigational sites were not filed and followed ICH-GCP guidelines, 21CFR312.120, appropriate AstraZeneca standards, and other relevant country regulations.*"

Regional Assessments

The number of patients randomized by country and geographical region are listed in Table 28. Tables 29 and 30 show the region-specific treatment effect and safety analysis, respectively. There were no significant differences between regions with regards to treatment effect, and the rate of adverse events.

Tables 31 shows the baseline use of medications and device therapies in different regions. Although differences are observed (ARNI use, MRA use, devices), a consistent treatment effect was observed with regards to CV death, hospitalization for HF, and urgent HF visit in the overall population, North America and ROW (Table 32).

Region-specific baseline characteristics, heart failure therapy, efficacy and safety findings in patients enrolled in DAPA-HF trial indicate that the overall trial findings are applicable to the US population.

Table 28. Number of randomized patients by country and region (FAS) (Source: Sponsor material)

US	North America		Rest of the world	
454 (9.6%)	North America	677 (14.3%)	Asia	1096 (23.1)
	US	454 (9.6%)	China	237 (5.0)
	Canada	223 (4.7%)	India	237 (5.0)
			Japan	343 (7.2)
			Taiwan	141 (3.0)
			Vietnam	138 (2.9)
			Eastern Europe	1604 (33.8)
			Bulgaria	266 (5.6)
			Czech Republic	210 (4.4)
			Hungary	250 (5.3)
			Poland	290 (6.1)
			Russia	422 (8.9)
			Slovakia	166 (3.5)
			Western Europe	550 (11.6)
			Denmark	99 (2.1)
			Germany	186 (3.9)
			Netherlands	135 (2.8)
			Sweden	68 (1.4)
			UK	62 (1.3)
			South America	817 (17.2)
			Argentina	297 (6.3)
			Brazil	520 (11.0)
	Total	677 (14.3%)	Total	4067 (85.7%)
		Total:	**North America + Rest of World = 4744 (100%)**	

Table 29. Region-specific Treatment Effect for Primary Endpoint in DAPA-HF Trial (Source: Reviewer Analysis)

Region	Number of patients (n)	Treatment Effect	P-value
Asia/Pacific	1096	0.66 (0.49, 0.87)	<0.01
Europe	2154	0.84 (0.69, 1.01)	0.069
Eastern Europe	1604	0.81 (0.66, 1.01)	0.063
Western Europe	550	0.92 (0.60, 1.41)	0.70
North America	677	0.73 (0.51, 1.03)	0.074
South America	817	0.64 (0.42, 0.88)	<0.01

Table 30. Region-specific Data from Safety Analysis Set in DAPA-HF Trial (Source: Reviewer analysis)

Variable	Treatment Arm	Overall n 4736	Asia/Pacific n 1092	Europe n 2153	Eastern Europe n 1604	Western Europe n 549	North America n 674	South America n 817
Mean Baseline NT-ProBNP* (pg/mL)	Dapa*	2317.4	2106.6	2296.1	2341.1	2164.6	2185.3	2768.7
	Placebo	2365.9	2205.2	2423.5	2485.5	2242.4	2282.8	2500.5
Baseline NYHA* Class II (% of patients)	Dapa*	67.6	75.6	58.0	51.5	77.6	73.6	78.1
	Placebo	67.4	75.2	58.2	52.7	74.1	72.4	76.2
Baseline Atrial Fibrillation Yes n (% of patients)	Dapa*	914 (38.6)	149 (27.6)	506 (46.3)	360 (44.2)	146 (52.3)	134 (40.2)	125 (31.2)
	Placebo	901 (38.1)	141 (25.5)	522 (49.3)	372 (47.2)	150 (55.6)	125 (31.2)	103 (24.8)
Baseline mean BMI* (kg/m^2)	Dapa*	28.2	24.1	29.2	29.4	28.7	30.6	28.9
	Placebo	28.1	24.2	29.3	29.3	29.1	30.4	28.6
Baseline DM* Yes n (% of patients)	Dapa*	991(41.9)	216 (40.0)	442 (40.4)	343 (42.1)	99 (35.5)	156 (46.9)	177 (44.1)
	Placebo	989 (41.8)	229 (41.5)	417 (39.4)	316 (40.1)	101 (37.4)	160 (46.9)	183 (44.0)
Mean actual exposure (days)	Dapa*	502.2	459 9	530.7	538.9	506 9	456.4	519.4
	Placebo	495.8	454 1	535.0	543.7	509 5	437.3	499.3
HHF* Yes n (% of patients)	Dapa*	229 (9.7)	40 (7.4)	117 (10.7)	91 (11.2)	26 (9.3)	39 (11.7)	33 (8.2)
	Placebo	317 (13.4)	74 (13.4)	135 (12.8)	106 (13.4)	29 (10.7)	57 (16.7)	51 (12.3)
Adverse Event Rate n (%)	Dapa*	902(38.1)	198 (36.7)	425 (38.9)	322 (39.5)	103 (36.9)	134 (40.2)	145 (36.2)
	Placebo	997(42.1)	222(40.2)	442 (41.7)	319 (40.4)	123 (45.6)	152 (44.6)	181 (43.5)

*Dapa: Dapagliflozin 10 mg, NT-ProBNP: N-terminal pro-B-type natriuretic peptide, NYHA: New York Heart Association, BMI: body mass index, DM: Diabetes mellitus, HHF: Hospitalization for Heart Failure

Table 31. Baseline therapy and device usage by region for patients in DAPA-HF (Source: Sponsor material)

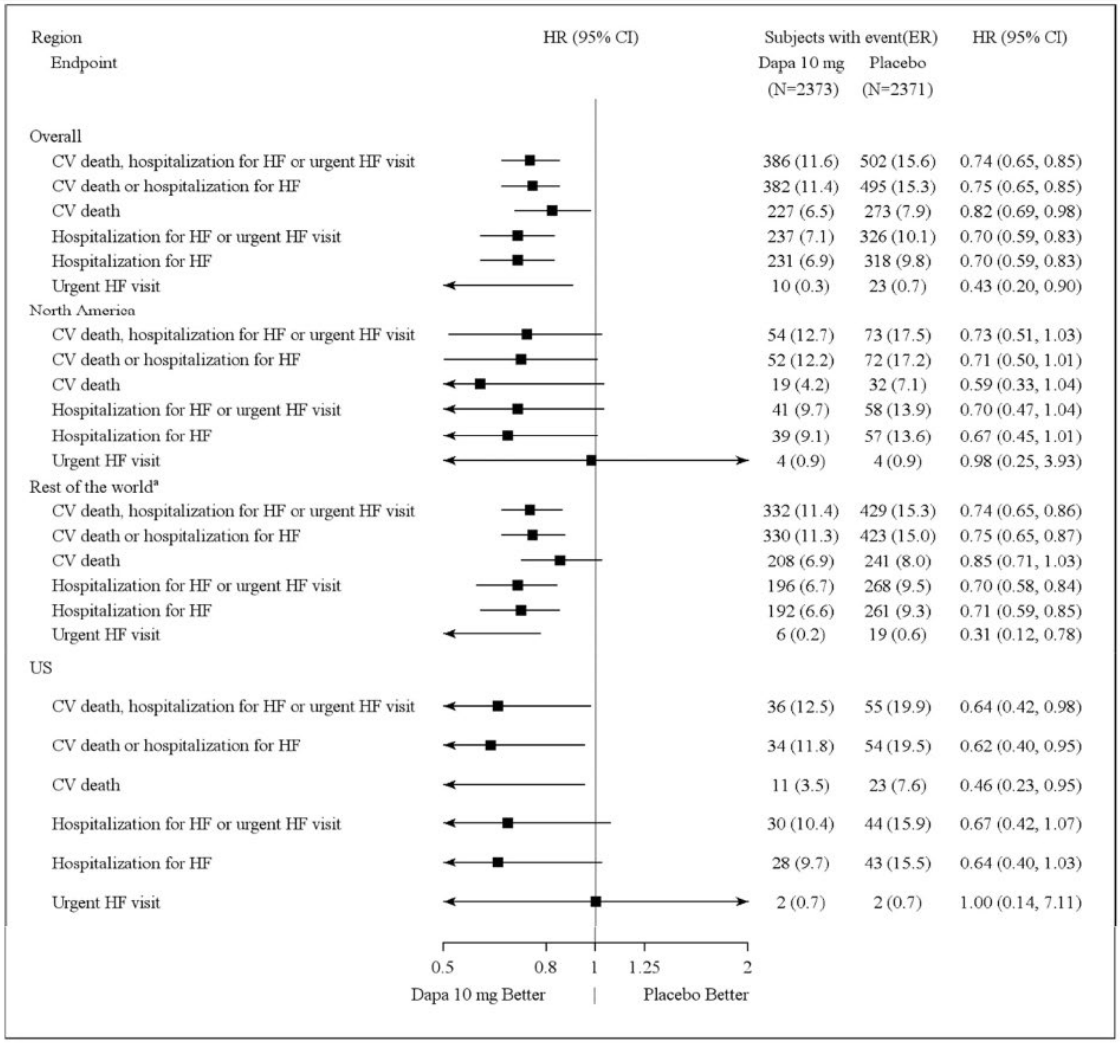
Baseline heart failure medication use

Treatments	Number (%) of subjects			
	US (N=454)	North America (N=677)	Rest of the world (N=4067)	Overall (N=4744)
ACE inhibitor (ACEi)	195 (43.0)	283 (41.8)	2378 (58.5)	2661 (56.1)
Angiotensin receptor blocker (ARB)	104 (22.9)	139 (20.5)	1168 (28.7)	1307 (27.6)
Neprilysin inhibitor/ARB (ARNI)	121 (26.7)	219 (32.3)	289 (7.1)	508 (10.7)
Beta Blocker	443 (97.6)	659 (97.3)	3899 (95.9)	4558 (96.1)
Mineralocorticoids/Aldosterone antagonists (MRA)	187 (41.2)	313 (46.2)	3057 (75.2)	3370 (71.0)
ACEi or ARB	297 (65.4)	417 (61.6)	3535 (86.9)	3952 (83.3)
ACEi, ARB or ARNI	410 (90.3)	626 (92.5)	3816 (93.8)	4442 (93.6)
(ACEI, ARB or ARNI) and Beta Blocker	401 (88.3)	611 (90.3)	3665 (90.1)	4276 (90.1)
(ACEI, ARB or ARNI) and Beta Blocker and MRA	168 (37.0)	290 (42.8)	2801 (68.9)	3091 (65.2)
Diuretics	386 (85.0)	578 (85.4)	3855 (94.8)	4433 (93.4)
Loop diuretics	353 (77.8)	508 (75.0)	3317 (81.6)	3825 (80.6)
Other diuretics[a]	211 (46.5)	344 (50.8)	3211 (79.0)	3555 (74.9)
Vasodilators	124 (27.3)	177 (26.1)	589 (14.5)	766 (16.1)
Digitalis glycosides	76 (16.7)	109 (16.1)	778 (19.1)	887 (18.7)
Ivabradine	2 (0.4)	6 (0.9)	222 (5.5)	228 (4.8)

Baseline cardiac device therapy use

Device		Number (%) of subjects			
		US (N=454)	North America (N=677)	Rest of the world (N=4067)	Overall (N=4744)
Cardiac pacemaker	n	454	677	4067	4744
	Yes	88 (19.4)	143 (21.1)	521 (12.8)	664 (14.0)
Pacemaker type	Conventional Pacemaker	37 (8.1)	59 (8.7)	250 (6.1)	309 (6.5)
	CRT-P	2 (0.4)	2 (0.3)	58 (1.4)	60 (1.3)
	CRT-D	49 (10.8)	82 (12.1)	212 (5.2)	294 (6.2)
	Type not recorded	0	0	1 (0.0)	1 (0.0)
CRT-D or CRT-P	n	454	677	4067	4744
	Yes	51 (11.2)	84 (12.4)	270 (6.6)	354 (7.5)
ICD	n	454	677	4067	4744
	Yes	247 (54.4)	303 (44.8)	650 (16.0)	953 (20.1)
ICD or CRT-D	n	454	677	4067	4744
	Yes	294 (64.8)	382 (56.4)	860 (21.1)	1242 (26.2)

Table 32. Forest plot of primary composite endpoint and components by geographic region (Full Analysis Set) (Source: Sponsor material)



[a] All countries except Canada and US

CI confidence interval. CV cardiovascular. ER event rate. FAS full analysis set. HF heart failure. HR hazard ratio. N number of patients in treatment group.

Study Drug Exposure

The mean duration of exposure to the study drug was 16.8 ± 6.3 and 16.6 ± 6.5 months in dapagliflozin versus placebo groups, respectively. The cumulative study drug exposure over time was ≥ 6 months for 90% and ≥ 12 months for 80% of the patients in each group. The total number of days on 5 mg dose of study drug per subject were 264.3 ± 192.1 and 214.6 ± 198.5 days in dapagliflozin and placebo arms, respectively. The number of patients who did not return

to 10 mg dose of the study drug were 37 (1.6%) and 30 (1.3%) in dapagliflozin and placebo arms.

Patient disposition

Patient disposition was analyzed by age, gender, race, and geographic region. No significant differences were noted.

Standard of Care for Heart Failure in DAPA-HF trial

One of the study eligibility criterion was that patients should be on stable standard of care therapy for HF according to local guidelines prior to randomization. The DMC was responsible for review of study participant concomitant medications. Current standard of care for patients with HFrEF includes use of ACEI/ARB/ARNI, beta-blocker, MRA, hydralazine with isosorbide dinitrate, ivabradine, digoxin, and ICD/CRT-D device therapy. The use of concomitant HF medications and their doses were well balanced between the two treatment arms at baseline and during the trial.

KCCQ

KCCQ Overall Summary (KCCQ-OS) score is a 23-item, patient-reported questionnaire used to evaluate HF- specific symptoms, function, and quality of life over a 2-week period. It has been validated in patients with heart failure with preserved ejection fraction (HFpEF) and HFrEF. [10] It covers the following five domains:

1) Total Symptoms (Symptom Frequency and Symptom Burden)
2) Physical Limitation
3) Quality of Life
4) Social Limitation
5) Self-Efficacy

The scores for each domain are transformed into values between 0 and 100, with higher scores representing better health status. A 5-point difference in KCCQ-OS score is known to be associated with increased risk for CV death and HF hospitalization in patients with HFpEF and HFrEF.[8] KCCQ Total Symptom score (KCCQ-TSS) includes symptom frequency and burden domains of KCCQ-OS score.

[10] Pokharel Y, Khariton Y, Tang Y, et al. Association of Serial Kansas City Cardiomyopathy Questionnaire Assessments With Death and Hospitalization in Patients With Heart Failure With Preserved and Reduced Ejection Fraction: A Secondary Analysis of 2 Randomized Clinical Trials [published correction appears in JAMA Cardiol. 2018 Feb 1;3(2):181]. *JAMA Cardiol*. 2017;2(12):1315–1321. doi:10 1001/jamacardio.2017.3983

KCCQ and Other Measures of Functional Capacity

Based on data from the Washington University Heart Failure Registry, Joseph et al 2013[11] have demonstrated that the mean KCCQ-OS score and KCCQ-TSS correlate with NYHA class in patients with HFrEF ($r = -0.55$, $p < 0.001$). Table 33 displays the mean KCCQ-OS and KCCQ-TSS by NYHA class in both HFrEF and HFpEF.[13] These data are limited, in that KCCQ was administered only at initial enrollment.[13] Hence, these data do not help to define a clinically meaningful change in KCCQ-TSS in patients with HFrEF. These data suggest that in patients with HFrEF, there is approximately a 20-point difference in mean KCCQ-TSS between each NYHA class.

Table 33. Mean KCCQ Overall Summary and Total Symptoms Score by NYHA class (Source: Joseph et al 2013)[13]

	KCCQ overall summary score		KCCQ symptoms score	
NYHA	HFrEF (EF≤40)	HFpEF (EF≥50)	HFrEF (EF≤40)	HFpEF (EF≥50)
I	81.3	91.3	89.9	94.1
II	66.1	68.4	73.2	72.3
III	45.3	43.0	52.8	44.2
IV	29.2	27.3	34.5	29.9
p-value	<.001	<.001	<.001	<.001

Green et al[12] conducted a study in patients with HFrEF to confirm the validity, reliability and responsiveness of KCCQ. The reliability cohort comprised stable HFrEF patients and the responsiveness cohort comprised HFrEF patients hospitalized with decompensated congestive heart failure who later improved. Both cohorts underwent KCCQ-OS measurement at baseline and at 3 months. In the reliability cohort, mean change in KCCQ-OS score was 0.8 to 4.0 points on a 100-point scale over three months of observation which was not statistically significant and similar reproducibility was noted for NYHA class. In the responsiveness cohort, mean change in KCCQ-OS score was 15.4 to 40.4, with a corresponding improvement in mean NYHA class from 3.2 to 2.4. The KCCQ TSS had the largest 'signal-to-noise' ratio (responsiveness statistic (observed change in responsiveness cohort/ standard deviation of change in reliability cohort) = 3.19), among all other KCCQ domains.

Spertus et al[13] demonstrated that in patients with HFrEF, KCCQ-OS decreased by -24.9±15.8, -16.8±13.8, and -5.4±10.8 points for patients experiencing large, moderate, and small

[11] Joseph SM, Novak E, Arnold SV, et al. Comparable performance of the Kansas City Cardiomyopathy Questionnaire in patients with heart failure with preserved and reduced ejection fraction. *Circ Heart Fail*. 2013;6(6):1139–1146. doi:10.1161/CIRCHEARTFAILURE.113.000359
[12] Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol. 2000 Apr; 35(5):1245-55.
[13] Spertus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, et al. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005;150(4):707-15.

deterioration, respectively; and improved by 5.7±16.1, 10.7±16.2, and 22.3±15.0 in patients with small, moderate, and large improvements in heart failure. The mean change in KCCQ scores was significantly different for all categories of change compared with the stable patients (1.3±11; P<0.01 for all comparisons). Changes in KCCQ Summary scores were symmetric with respect to improvement versus decline. There was a statistically significant improvement in 6-minute walk test in patients with moderate and large improvement in KCCQ-OS, but not for those with small improvement in KCCQ-OS. Dreyer et al[14] reported the sensitivity and specificity associated with a 5-point change in KCCQ TSS using patient reported clinically important improvement was 47 and 70%, respectively. Within the EPHESUS trial,[15] each 5-point decrement in TSS was associated with a 9.1% increased (decreased for improvement in scores) hazard for death and cardiovascular hospitalization.

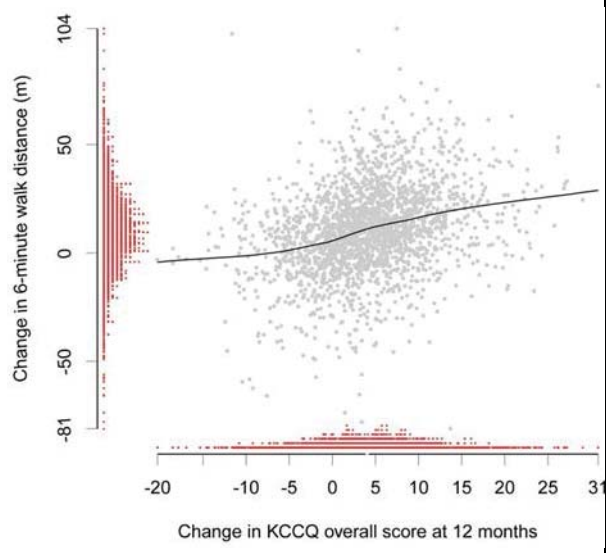
Flynn et al[16] examined the relationship between KCCQ-OS and changes in peak VO2 and 6-minute walk distance at 3 and 12 months, using data from Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) and concluded that KCCQ was not highly correlated with changes in functional capacity, including peak VO2 and 6-minute walk distance. Figure 18 displays the relationship between change in KCCQ-OS and change in peak VO2 and 6-minute walk distance.

Prognostic Value of KCCQ

Pokharel et al[12] conducted a retrospective analysis of data from two studies – TOPCAT and HF-ACTION to evaluate the prognostic value of current, prior, or change in KCCQ-OS score and found that the most recent score has the strongest association with risk for CV death and HF hospitalization. In this study, each 5-point difference in prior or current KCCQ-OS scores was associated with a 6% (95% CI, 4%-9%; $P < 0.001$) to 8% (95% CI, 5%-10%; $P < .001$) lower risk for subsequent CV death/first HF hospitalization in patients with HFrEF in unadjusted analyses. An increase in KCCQ-OS score from prior to current visit was associated with lower risk of CV death or first HF hospitalization (HR, 0.94; 95% CI, 0.91-0.97 and HR, 0.95; 95% CI, 0.91-0.99 in patients with HFpEF and HFrEF, respectively, per 5-point change in KCCQ-OS. However, when the current visit KCCQ-OS was included in the model with either the prior visit score or the change from prior to current score, only the current KCCQ-OS was significantly associated with CV death or first HF hospitalization, indicating that the most recent KCCQ-OS was the most prognostically important assessment. Results were similar in fully adjusted models.

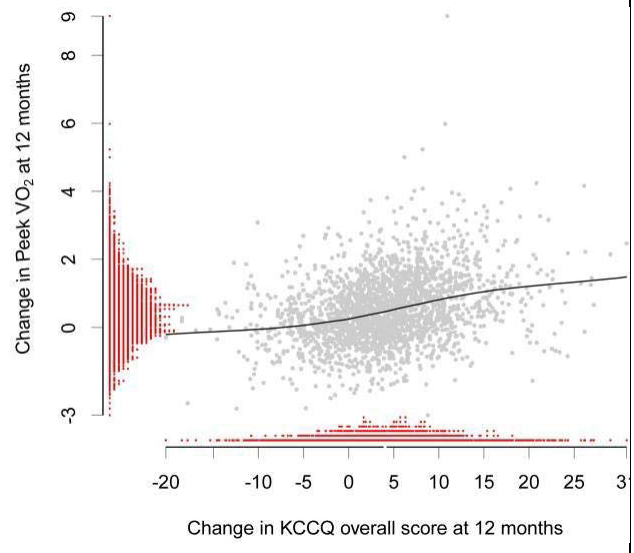
[14] Dreyer RP, Jones PG, Kutty S, Spertus JA. Quantifying clinical change: discrepancies between patients' and providers' perspectives. Qual Life Res (2016) 25:2213–2220.
[15] FDA KCCQ qualification package.
[16] Flynn KE, Lin L, Moe GW, et al. Relationships between changes in patient reported health status and functional capacity in outpatients with heart failure. Am Heart J 2012; 163:88-94 e3

Figure 16. Relationship between change in KCCQ-OS and change in peak VO2 / 6-minute walk distance, HF-ACTION Data Analysis, Flynn et al[18]



A 5-point change in KCCQ overall score was associated with a 111.69-meter change in 6-minute walk distance (95% CI, 95.91–133.67); correlation coefficient r = 0.31 (95% CI, 0.26 to 0.38)

Coefficient of determination 0.10 implying that 10% change in KCCQ is accounted for by change in 6-minute walk distance (reviewer analysis)



A 5-point change in KCCQ overall score was associated with a 2.50-ml/kg/min change in peak VO_2 (95% CI, 2.21–2.86); correlation coefficient r = 0.31 (95% CI, 0.24 to 0.39)

Coefficient of determination 0.10 implying that 10% change in KCCQ is accounted for by change in Peak VO_2 (reviewer analysis)

KCCQ-OS: Kansas City Cardiomyopathy Questionnaire Overall Score, HF-ACTION: Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training, CI: Confidence Interval

Changes in KCCQ Domains at 8 Months in DAPA-HF

In DAPA-HF, median change in KCCQ score by various domains (Table 35) indicated that the domains of physical limitation, symptom frequency, and social limitation showed a slight improvement (about 4 points) in dapagliflozin arm compared to placebo.

Table 34. Summary of KCCQ scores Change at 8 Months from Baseline by Domain in DAPA-HF (Source: Reviewer Compilation)

Domain	Change from Baseline			
	Dapagliflozin Mean (SD)	Placebo Mean (SD)	Dapagliflozin Median (Min, Max)	Placebo Median (Min, Max)
Physical Limitation	4.31 (21.21)	2.29 (21.85)	4.2 (-100, 91.7)	0 (-100, 100)
Symptom Stability	3.24 (25.06)	2.69 (24.95)	0 (-100, 100)	0 (-100, 100)
Symptom Frequency	6.41 (19.88)	3.39 (20.61)	4.2 (-68.8, 95.8)	0 (-100, 81.3)
Symptom Burden	5.81 (20.33)	3.21 (20.62)	0 (-75.0, 100)	0 (-100, 91.7)
Total Symptom Score	6.11 (18.65)	3.30 (19.24)	4.2 (-71.9, 90.6)	2.1 (-100, 82.3)
Self-Efficacy	4.96 (21.98)	4.26 (22.90)	0 (-100, 100)	0 (-87.5, 100)
Quality of Life	7.85 (21.94)	5.78 (22.05)	8.3 (-91.7, 100)	8.3 (-91.7, 100)
Social Limitation	6.35 (24.93)	4.71 (25.21)	4.2 (-100, 100)	0 (-91.7, 100)
Overall Summary Score	6.17 (18.83)	3.87 (17.42)	5.0 (-73.3, 85.3)	2.9 (-66.5, 82.1)
Clinical Summary Score	5.50 (17.04)	2.92 (17.70)	4.2 (-70.7, 83.8)	1.4 (-74.3, 86.8)

Patient Global Impression of Severity (PGIS) Based Analyses to Define Clinically Meaningful Change in KCCQ-TSS in DAPA-HF

DAPA-HF employed PGIS as a PRO to help understand a clinically meaningful change in KCCQ-TSS. PGIS was scored in response to a single question – overall, how would you rate the severity of your heart failure symptoms today? The patient could respond in one of the 6 ways with the corresponding numeric score - No symptoms (1), Very mild (2), Mild (3), Moderate (4), Severe (5), Very Severe (6). Change in PGIS was measured as a difference in the numeric value of PGIS at 8 months from baseline, which was then categorized as small, moderate or large improvement/deterioration or stable. Table 36 illustrates the categorization of change in PGIS in DAPA-HF. Table 37 summarizes the timepoints of measurement of NYHA class, KCCQ-TSS, and PGIS in DAPA-HF.

The applicant conducted the following analyses to derive meaningful change thresholds on the FAS population, on blinded study data across both treatment arms and only included patients with complete data on all corresponding variables at baseline and 8 months:

- Calculate Spearman correlation coefficient between change in KCCQ-TSS and PGIS to ensure adequacy of PGIS as an anchor for the KCCQ-TSS endpoint
- Construct empirical cumulative distribution function (eCDF) complemented by the probability density function (PDF) of a category
- Receiver operating characteristic (ROC) curve analysis using logistic regression analyses for each cut-off in change from baseline KCCQ-TSS to characterize CMWPC
- Responder analysis using CMWPC from baseline KCCQ-TSS from anchor-based analyses

Table 35. Categories of change from baseline PGIS at 8 months in DAPA-HF (Source: Sponsor Material)

		PGIS at 8 months					
		No symp-toms	Very mild	Mild	Mode-rate	Severe	Very Severe
PGIS at baseline		**1**	**2**	**3**	**4**	**5**	**6**
No symptoms	**1**	0 Stable	+1 SD	+2 MD	+3 LD	+4 LD	+5 LD
Very mild	**2**	-1 SI	0 Stable	+1 SD	+2 MD	+3 LD	+4 LD
Mild	**3**	-2 MI	-1 SI	0 Stable	+1 SD	+2 MD	+3 LD
Moderate	**4**	-3 LI	-2 MI	-1 SI	0 Stable	+1 SD	+2 MD
Severe	**5**	-4 LI	-3 LI	-2 MI	-1 SI	0 Stable	+1 SD
Very severe	**6**	-5 LI	-4 LI	-3 LI	-2 MI	-1 SI	0 Stable

LD Large deterioration. MD Moderate deterioration. SD Small deterioration. SI Small improvement. Moderate improvement. LI Large improvement.

PGIS Patient Global Impression of Severity

Table 36. Timepoints of measurement of NYHA class, KCCQ, and PGIS in DAPA-HF trial (Source: Reviewer compilation)

Activity	Enrolment	Randomization	Month 4	Month 8	Month 12	Month 24	PTDV	SCV
Visit number	1	2	5	6	7			
NYHA class	x		x	x			x	x
KCCQ		x	x	x	x	X	x	x
PGIS		x	x	x	x	X	x	x

PTDV: Premature Treatment Discontinuation Visit, SCV: Study Closure Visit, NYHA: New York Heart Association, KCCQ: Kansas City Cardiomyopathy Questionnaire, PGIS: Patient global impression of severity

Table 38 displays the distribution of change in KCCQ-TSS by change in PGIS categories at 8 months. These descriptive statistics suggest that a median change in KCCQ-TSS of approximately, 8 and 15 correlated with small/moderate and large improvement in PGIS, respectively. The Spearman correlation coefficient between KCCQ TSS and PGIS change was 0.34 (for the 5 categories) and 0.35 (for the 7 categories). Figure 17 displays the empirical cumulative distribution function (eCDF) for change from baseline KCCQ-TSS at 8 months versus change from baseline PGIS at 8 months with 7 categories, that demonstrated the following:

- Curves for large, moderate and small deterioration are separated from the curve for no change, between KCCQ-TSS change from approximately -40 to 20
- Curves for moderate and small deterioration are separated from each other between KCCQ-TSS change from -40 to 0 and overlap for KCCQ-TSS change of ≥ 0
- Curves for small and moderate improvement overlap
- Curves for large improvement and small/moderate improvement are clearly separated from each other and from curve for no change between KCCQ-TSS change from approximately -20 to 40.

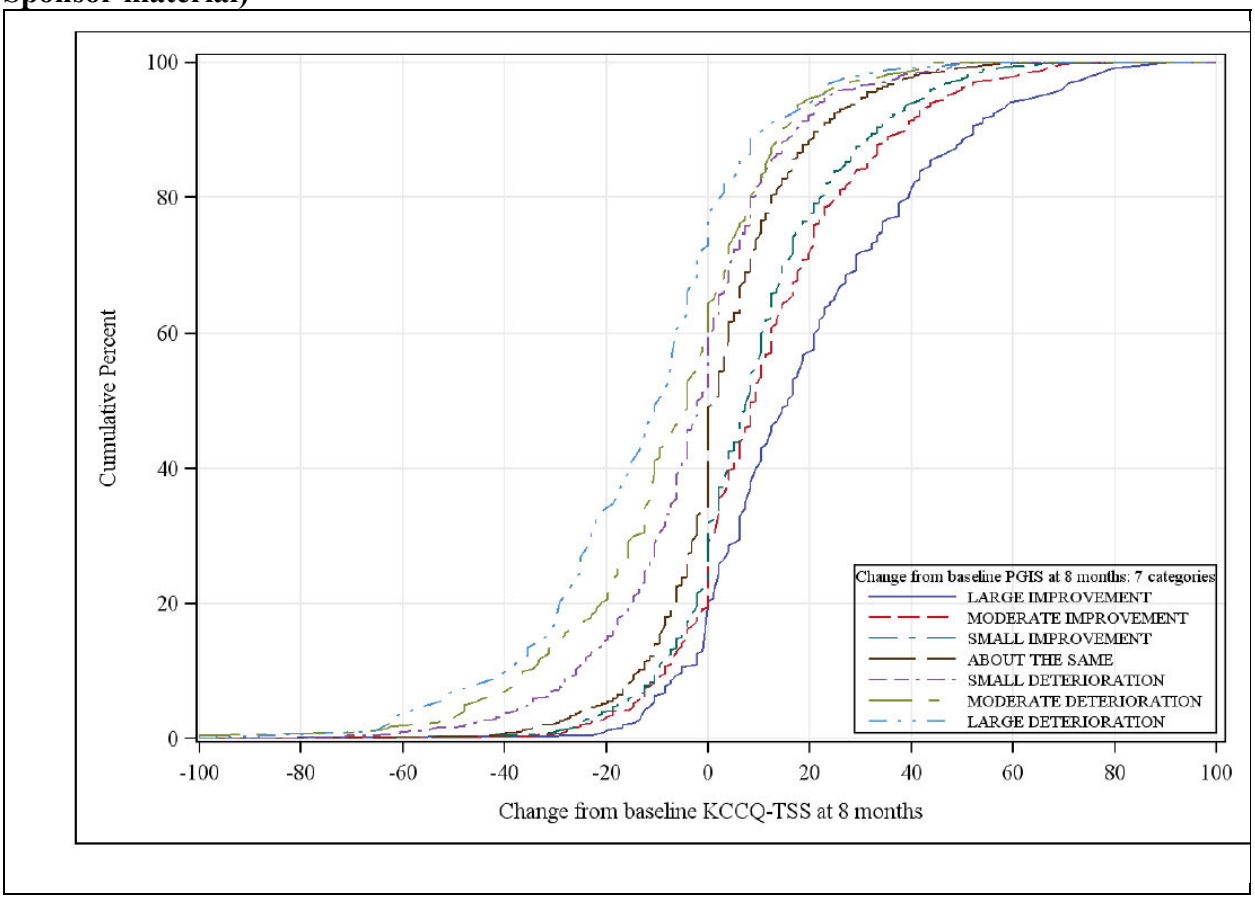
Based on ROC analysis, the KCCQ-TSS change cut-off points of 9 and -2 for large improvement and deterioration, respectively had a low sensitivity and specificity of 62 to 72% and 65 to 69%, respectively. Hence, the applicant considered more stringent cut-off points to define CMWPC.

Table 37. Distribution of change from baseline KCCQ-TSS at 8 months by change from baseline PGIS at 8 months, blinded analyses of DAPA-HF (Source: Sponsor material)

	N	(%)	Mean	SD	Min	Q1	Median	Q3	Max	Correlation[a]
PGIS at 8 Months: 7 Categories										0.35
Large Improvement	255	(7)	20.0	22.7	-22.9	2.1	15.6	34.4	90.6	
Moderate Improvement	402	(10)	11.9	18.7	-35.4	0.0	9.4	20.8	72.9	
Small Improvement	831	(21)	9.6	17.4	-49.0	0.0	8.3	17.7	80.2	
Stable	1522	(39)	3.2	15.5	-63.5	-4.2	1.0	10.4	82.3	
Small Deterioration	561	(14)	-3.0	18.2	-71.9	-11.5	-2.1	7.3	50.0	
Moderate Deterioration	223	(6)	-6.9	20.8	-100.0	-17.7	-4.2	6.3	43.7	
Large Deterioration	89	(2)	-11.9	21.6	-65.6	-25.0	-8.3	0.0	54.2	
PGIS at 8 Months: 5 Categories (Version A)										0.34
Moderate or Large Improvement	657	(17)	15.0	20.7	-35.4	0.0	10.4	26.0	90.6	
Small Improvement	831	(21)	9.6	17.4	-49.0	0.0	8.3	17.7	80.2	
Stable	1522	(39)	3.2	15.5	-63.5	-4.2	1.0	10.4	82.3	
Small Deterioration	561	(14)	-3.0	18.2	-71.9	-11.5	-2.1	7.3	50.0	
Moderate or Large Deterioration	312	(8)	-8.4	21.1	-100.0	-19.3	-6.3	4.2	54.2	
PGIS at 8 Months: 5 Categories (Version B)										0.34
Large Improvement	255	(7)	20.0	22.7	-22.9	2.1	15.6	34.4	90.6	
Small or Moderate Improvement	1233	(32)	10.3	17.9	-49.0	0.0	8.3	19.8	80.2	
Stable	1522	(39)	3.2	15.5	-63.5	-4.2	1.0	10.4	82.3	
Small or Moderate Deterioration	784	(20)	-4.1	19.0	-100.0	-12.5	-2.1	6.8	50.0	
Large Deterioration	89	(2)	-11.9	21.6	-65.6	-25.0	-8.3	0.0	54.2	

[a] Absolute value of the Spearman correlation coefficient for change from baseline KCCQ-TSS at 8 months and change from baseline PGIS at 8 months with each categorization

Figure 177. Empirical cumulative distribution function for change from baseline KCCQ-TSS at 8 months versus change from baseline PGIS at 8 months with 7 categories (Source: Sponsor material)



From these anchor-based analyses, the applicant determined the following:

- CMWPC is 5 to10 points in KCCQ-TSS at 8 months
- An improvement of ≥15 points is moderate or large improvement
- A deterioration of ≥10 points is a large deterioration

Responder analyses were conducted with the following considerations:

- Number and percentage of patients who achieved a CMWPC, as defined by the applicant, were summarized and analyzed using logistic regression
- Deaths prior to the 8-month assessment were counted as not improved, in comparisons of improvement from baseline, and were counted as deteriorated in comparisons of deterioration from baseline
- The baseline KCCQ-TSS can be too close to the end of the scale (0 or 100) to show a pre-specified change; for example, a patient with a score of 97 at baseline cannot have a 5-point increase. Such patients were defined as responders if they remained too high for improvement, or too low in the analysis of deterioration.

The handling of these cases affects the proportion of responders in each group but should not affect the comparison between groups

Reviewer comments:

1. *In the study by Green et al[11], the mean change in KCCQ in the reliability cohort comprised of stable HFrEF ranged from 0.8 to 4.0. In the study by Flynn et al, a 5-point change in KCCQ-OS was associated with some improvement in Peak VO2 and 6-minute walk test, but the association was weak. Spertus et al. demonstrated that patients who experienced small improvement in HFrEF, improved their KCCQ-OS by 5.7±16.1 without a statistically significant improvement in 6 minute-walk test. Hence, published literature indicate that a change of 5 points in KCCQ-OS is a small/minimal change in how a patients with HFrEF feels. The applicant used anchor-based analysis within DAPA-HF to define a clinically meaningful change in KCCQ-TSS, a component of KCCQ-OS and selected a change in KCCQ-TSS at 8 months of 5 to 10 as CMWPC that correlates with only a small improvement in PGIS.*
2. *The sensitivity and specificity of the applicant defined CMWPC is low. Hence, it is not a robust measure to discriminate between responder and non-responder.*
3. *The eCDF curves* of *change from baseline at 8 months for KCCQ versus PGIS (7 categories) suggest that, for a change in KCCQ-TSS ranging between -20 and 40, PGIS change categories – no change, large improvement, and small/moderate improvement can be distinguished. For a change in KCCQ-TSS ranging between -40 to 20, PGIS change categories – no change, large, moderate, and small deterioration can be distinguished.*

Analysis of Change from Baseline at 8 months in the KCCQ-TSS

The applicant transformed the raw scores for change in KCCQ-TSS at 8 months from baseline by using fractional ranks as follows:

- deaths prior to the 8-month assessment were assigned the worst ranks within each stratum
- of the patients who died, the relative ranking was based on their last value of change from baseline in TSS while alive before deriving fractional ranks
- mean method was used for ties and stratified by T2DM status at randomization
- composite endpoint was then analyzed using the rank ANCOVA method (Stokes et al 2012), adjusted for ranked baseline TSS value, to test the null hypothesis of no differences in the distributions of ranked outcomes between the 2 treatment groups.
- Cochran Mantel Haenszel (CMH) test, stratified for the T2DM status at randomization, was used to compare treatment groups. The p-value from the CMH test of treatment effect at 8 months was used for the confirmatory statistical testing of this secondary endpoint.
- Win ratio and the corresponding 95% confidence interval (Wang and Pocock 2016) adjusted for baseline KCCQ-TSS and stratified by T2DM were reported as

a summary statistic using the same ranking approach as in the KCCQ TSS hypothesis test. This was accomplished by creating all possible pairs of patients across arms and labelling patients on dapagliflozin 10 mg in each pair as "winner", "loser" or "tied", based on their ranks. The crude win ratio is defined as the ratio of the number of "winner" pairs divided by the number of "loser" pairs and an estimated win ratio greater than 1 favored dapagliflozin.

Link to DAPA-HF protocol: https://clinicaltrials.gov/ct2/show/NCT03036124
Link to DAPA-HF published results:
https://www.nejm.org/doi/pdf/10.1056/NEJMoa1911303?articleTools=true

16. Clinical Safety Assessment Additional Information and Assessment

None.

17. Mechanism of Action/Drug Resistance Additional Information and Assessment

None.

18. Other Drug Development Considerations Additional Information

None.

19. Data Integrity-Related Consults (OSI, Other Inspections)

No inspections were performed.

20. Labeling Summary of Considerations and Key Additional Information

Based on the findings of change in KCCQ-TSS in DAPA-HF, the sponsor proposed an indication for [redacted] (b) (4) with dapagliflozin. Detailed discussion of KCCQ-TSS

findings in DAPA-HF is presented in section 5.7.1. Although the difference in change in KCCQ-TSS at 8 months between dapagliflozin and placebo was statistically significant favoring dapagliflozin, the degree of change in KCCQ-TSS was lower than the clinically meaningful threshold. (b) (4)

Dosing recommendations for patients with HFrEF based on renal function were considered. DAPA-HF excluded patients with eGFR < 30 ml/min/1.73m2 (CKD-EPI). Nevertheless, 24 patients with an eGFR <30 mL/min/1.73 m2 at randomization were randomized. Additionally, an initial decrease in eGFR to <30 mL/min/1.73 m2 was observed for more patients in the dapagliflozin arm: 2.9% and 3.0% of patients had an eGFR <30 mL/min/1.73 m2 at days 14 and 60 in the dapagliflozin treatment group compared to 2.0% and 2.0% in the placebo group for the "on treatment" period. By day 240 there was no difference observed between treatment groups, and at day 360 more patients in the placebo arm had an eGFR <30 mL/min/1.73 m2 (3.6%) compared with the dapagliflozin treatment arm (3.3%). The same pattern was seen for the "on and off" treatment period. There were no discontinuation criteria for patients with an eGFR decline to below 30 mL/min/m2. Overall safety and efficacy findings are similar regardless of eGFR. Hence, no dose adjustment for dapagliflozin in patients with HFrEF is recommended. Dapagliflozin is contraindicated in patients with end stage renal disease and those on dialysis.

As discussed in section 6.6, AKI, currently described in the warnings and precautions section of labeling for Farxiga, was not observed more frequently in the dapagliflozin arm of DAPA-HF. The incidence of AEs related to volume depletion was slightly higher in the dapagliflozin arm (7.2%) vs. the placebo arm (6.5%) with the most common reported AEs of hypotension and hypovolemia. Hence, we recommend that the warning and precaution of AKI be deleted. As there have been some post marketing reports of AKI with dapagliflozin, this can be stated under the subheading of volume depletion (which replaces the heading of "hypotension" in the warnings section as it is a more accurate description of the adverse reaction). .

21. Financial Disclosure

Table 38. Covered Clinical Studies: DAPA-HF

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2233		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
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: 2 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
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[a] ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 2		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

[a] Note: Steps taken to minimize bias: While not specifically stated for the 4 investigators with disclosable financial interests, DAPA-HF was a randomized, double blinded trial, and the results were not driven by any single site. Hence, we do not believe that the stated financial interests were a source of bias in DAPA-HF.

22. Review Team Acknowledgements

Table 39. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	John Koerner
Nonclinical Team Leader	Jean Wu
Office of Clinical Pharmacology Reviewer(s)	NA
Office of Clinical Pharmacology Team Leader(s)	NA
Clinical Reviewer	Charu Gandotra / Tzu-Yun Mcdowell
Clinical Team Leader	Fortunato Senatore
Statistical Reviewer	Fanhui Kong
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Mary Ross Southworth
Division Director (signatory)	Norman Stockbridge

Table 40. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Pallaiah Thammana
Microbiology	NA
OPDP/DMPP	Zarna Patel/ Morgan Walker
OSI	NA
OSE/DEPI	NA
OSE/DMEPA	NA
OSE/DRISK	NA
COA	Onyekachokwu Illoh

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary.

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/s/

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TZU-YUN C MCDOWELL
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FANHUI KONG
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JIALU ZHANG
04/22/2020 06:02:32 PM

MARY R SOUTHWORTH
04/22/2020 06:16:45 PM

NORMAN L STOCKBRIDGE
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s020

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202293
Supporting document/s:	1740
Applicant's letter date:	11/06/2019
CDER stamp date:	11/06/2019
Product:	Dapagliflozin
Indication:	Heart Failure
Applicant:	AstraZeneca
Review Division:	Division of Cardiology and Nephrology
Reviewer:	John Koerner, Ph.D.
Supervisor/Team Leader:	Jean Wu MD, Ph.D.
Division Director:	Norman Stockbridge MD, Ph.D.
Project Manager:	Alexis Childers

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 202293 are owned by AstraZeneca or are data for which AstraZeneca has obtained a written right of reference. Any information or data necessary for approval of NDA 202293 that AstraZeneca does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 202293.

TABLE OF CONTENTS

Executive Summary

1.1 Introduction

Dapagliflozin is a sodium glucose co-transporter 2 (SGLT2) inhibitor approved for the treatment of type-2 diabetes. Nonclinical data and relevant labeling sections were reviewed under original NDA submission by Dr. Mukesh Summan, Ph.D., DABT (dated 12/09/2013). A post-marketing review for rodent bladder tumor risk was reviewed by Huiqing Hao (dated 03/29/2018).

In the current NDA efficacy supplement, the sponsor is requesting approval for use of dapagliflozin in adults with heart failure with reduced ejection fraction. To this purpose, the sponsor submitted nonclinical proof of concept studies in mouse models of type 2 diabetes.

1.2 Brief Discussion of Nonclinical Findings

The sponsor submitted three non-GLP studies to evaluate dapagliflozin's effects on cardiac structure and function in mouse models of type 2 diabetes. Study results were consistent with a dapagliflozin-induced improvement in cardiac structure and function in diabetic animals. These studies did not address cardiac effects in healthy animals.

1.3 Recommendations

1.3.1 Approvability

This drug is approvable from a nonclinical perspective based on data provided in the original application and FDA reviews for treatment of diabetes.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

No labeling changes are recommended based on the submitted pharmacology studies.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 960404-48-2

Generic Name: Dapagliflozin

Code Name: BMS-512148

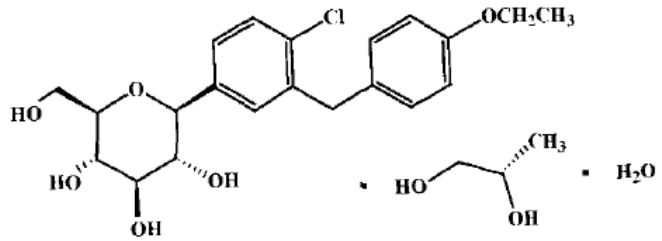
Chemical Name
1S)-1,5-Anhydro-1- C-[4-chloro-3-[(4- ethoxyphenyl)methyl]-pheny1]-D-g1ucitol, (S)-propylene glycol, monohydrate

Molecular Formula/Molecular Weight

$C_{21}H_{25}ClO_6.C_3H_8O_2.H_2O$ / MW = 502.98 (*S*-Propylene glycol monohydrate);

MW= 408.87 (Non-solvated, non-hydrated form)

Structure or Biochemical Description



Pharmacologic Class

Sodium glucose co-transporter 2 (SGLT2) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 68652

2.3 Drug Formulation

Dapagliflozin film-coated tablets are manufactured as 5 mg or 10 mg strengths.

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Patients with heart failure and reduced ejection fraction will be administered dapagliflozin orally at 5 or 10 mg/day.

2.7 Regulatory Background

Dapagliflozin was approved on January 8, 2014 for the treatment of type 2 diabetes under NDA 202293. The approved oral dosage is 5 or 10 mg/day.

A post-marketing review for rodent bladder tumor risk was reviewed by Huiqing Hao, Ph.D. on 03/29/2018. In that study, the effect of dapagliflozin on the incidence of urinary bladder tumors was evaluated in a rat model of bladder tumor promotion, which uses N-Butyl-N- (4-hydroxybutyl)-nitrosamine (BBN, 100 and 400 mg/kg) as tumor initiator.

Dapagliflozin (0.5 mg/kg) did not enhance the incidence of transitional cell carcinoma (TCC) in rats pretreated with BBN. A slight increase in the incidences of urothelial papilloma and hyperplasia was noted with dapagliflozin but did not reach statistical significance. The reviewer considered the post-marketing requirement #2121-3 to be fulfilled.

3 Studies Submitted

3.1 Studies Reviewed

1. Dapagliflozin improves the coronary microvascular function and cardiac contractility in prediabetic ob/ob−/− mice

2. Dapagliflozin attenuates the activation of the Nlrp3/ASC inflammasome and ameliorates the development of diabetic cardiomyopathy in mice with T2DM

3. Dapagliflozin Attenuates the Activation of NLRP3/ASC Inflammasome in Cardiofibroblasts from Mice with T2DM

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

- NDA 202293 was reviewed under the original NDA submission by Dr. Mukesh Summan, Ph.D., DABT (dated 12/09/2013).
- A post-marketing review for rodent bladder tumor risk under NDA 202293 was reviewed by Huiqing Hao, Ph.D. (dated 03/29/2018).

4 Pharmacology

4.1 Primary Pharmacology

Nonclinical Pharmacology Report AstraZeneca
Nonclinical HF 001

Dapagliflozin improves the coronary microvascular function and cardiac contractility in prediabetic ob/ob−/− mice

In this non-GLP study, dapagliflozin given at dosages of 1.5 and 4.0 mg/kg/day in drinking water to obese, insulin resistant homozygous male C57BL/6J-lepob mice (ob/ob−/− mice) for 10 weeks increased coronary flow velocity reserve (CFVR) and fractional area change (FAC) of left ventricle, an index of left ventricular contractility. Dapagliflozin also increased urinary glucose excretion and reduced HbA1c in this model.

Nonclinical Pharmacology Report AstraZeneca
Nonclinical HF 002

Dapagliflozin attenuates the activation of the Nlrp3/ASC inflammasome and ameliorates the development of diabetic cardiomyopathy in mice with T2DM

In this non-GLP study, dapagliflozin reversed the left ventricular structural and functional defects in a mouse model of type 2 diabetes {BTBR.Cg-Lepob/WiscJ} (BTBR ob/ob−/−)). In this mouse model, significant structural defects are manifested by the increases in the end-diastolic volume (EDV) of left ventricle (LV), in the end-systolic volume (ESV) of left ventricle, in the interventricular septum thickness at end-diastole (IVSd) and in the interventricular septum thickness at end-systole (IVSs), as compared to those in healthy wild-type control mice of the same age. Those effects were associated with the attenuation of NLRP3 (NOD-like receptor 3) inflammasome activation in the heart tissues, as assessed by gene expression level or immunoreactivity of key components of the inflammasome.

Administration of dapagliflozin at 1 mg/kg/day for 8 weeks restored the LV EDV, LV ESV, IVSd and IVSs to the levels observed in the healthy wild-type mouse. Treatment with dapagliflozin also decreased the cardiac fibrosis and apoptosis observed in this mouse model. Attenuation of the NLRP3-mediated inflammasome activation by dapagliflozin suggests a mechanistic explanation of those cardiac benefits.

Nonclinical Report AstraZeneca
Dapagliflozin – Nonclinical HF 003

Dapagliflozin Attenuates the Activation of NLRP3/ASC Inflammasome in Cardiofibroblasts from Mice with T2DM

In this non-GLP study using cells from a diabetic mouse model {BTBR.Cg-Lepob/WiscJ} (BTBR ob/ob−/−)), the sponsor assessed whether dapagliflozin directly attenuates diabetes-induced activation of the NLRP3 inflammasome in mouse cardiofibroblasts, and what molecular pathways are involved in this process using cardiofibroblasts isolated from wild type and BTBR ob/ ob−/− mice. Results showed that dapagliflozin at concentrations between 0.3 and 0.5 μM attenuated the activation of the inflammasome induced by LPS. Dapagliflozin (0.4 μM) augmented AMPK phosphorylation in cardiofibroblasts stimulated with LPS. This effect of dapagliflozin on the LPS-induced inflammasome activation was completely blocked with compound C, an AMPK inhibitor, and could be replicated with the compound A769662, an AMPK activator. These results are consistent with the AMPK pathway playing an important role in the dapagliflozin-mediated inhibition of NLRP3 inflammasome activation in cardiofibroblasts. However, the dapagliflozin concentration used in these in vitro experiments is more than 30-fold higher than the free drug concentration in human or mouse plasma at the pharmacologically relevant dose. The sponsor concluded that the molecular

mechanisms for the dapagliflozin-induced attenuation of inflammasome activity are likely dissimilar between the in vivo and in vitro conditions.

11 Nonclinical Discussion

Study results in mouse models of type 2 diabetes were consistent with a dapagliflozin-induced improvement in cardiac structure and function in diabetic animals. These nonclinical studies do not address cardiac effects in healthy animals.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202293Orig1s020

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

PATIENT LABELING REVIEW

Date:	April 17, 2020
To:	Alexis Childers **Division of Cardiovascular and Renal Products (DCaRP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	FARXIGA (dapagliflozin)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 202293
Supplement Number:	S-020
Applicant:	AstraZeneca

1 INTRODUCTION

On November 6, 2019, AstraZeneca submitted for the Agency's review an Efficacy Supplement to their New Drug Application (NDA) 202293/S-020 for FARXIGA (dapagliflozin) tablets. This supplement proposes a new indication for the use of FARXIGA in adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and (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 Cardiovascular and Renal Products (DCaRP) on January 3, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG), for FARXIGA (dapagliflozin) tablets.

2 MATERIAL REVIEWED

- Draft FARXIGA (dapagliflozin) tablets MG received on November 6, 2019, and received by DMPP and OPDP on April 13, 2020.
- Draft FARXIGA (dapagliflozin) tablets Prescribing Information (PI) received on November 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 13, 2020.

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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

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ZARNA PATEL
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LASHAWN M GRIFFITHS
04/17/2020 04:40:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring MD 20993

CLINICAL OUTCOME ASSESSMENT (COA) REVIEW MEMORANDUM

RE: NDA 202293/S-020 – Dapagliflozin (Farxiga)

FROM: Onyeka Illoh
Clinical Outcome Assessment (COA) Reviewer
Division of Clinical Outcome Assessment (DCOA)

Elektra Papadopoulos
Director (Acting)
DCOA

SUBJECT: Division of Cardiology and Nephrology consult to DCOA requesting input on the adequacy of data based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) to support labeling claims
(DARRTS Reference ID: 4521200)

SPONSOR: AstraZeneca

Please check all that apply:

☐ Rare Disease/Orphan Designation
☐ Pediatric

A. EXECUTIVE SUMMARY

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of Cardiology and Nephrology [DCN] (formerly Division of Cardiovascular and Renal Products), on November 18, 2019 for NDA 202293 regarding dapagliflozin (Farxiga). This COA consult is related to the review of the adequacy of data based on the Kansas City Cardiomyopathy Questionnaire (KCCQ) Total Symptom Score (TSS) (b) (4) (b) (4)

The applicant submitted an efficacy supplement (S-020) for dapagliflozin for treatment in adults with heart failure with reduced ejection fraction (HFrEF) seeking an indication to "reduce the risk of cardiovascular death and (b) (4) . The sponsor submitted a pivotal multinational, multicenter, parallel group, event driven, randomized, double-blind, placebo-controlled, phase 3 clinical trial [Study D1699C00001 (DAPA-HF)] conducted among patients aged ≥18 years with HFrEF who were treated with standard of care. The primary efficacy endpoint is time to first occurrence of any of the components of this composite: (1) cardiovascular death, (2) hospitalization for heart failure,

(3) an urgent heart failure visit. The key secondary endpoint is change from baseline measured at 8 months in the KCCQ-TSS (see description in Appendix 2 of this review).

Review Conclusions:

This review concludes that the DCOA has significant concerns about the clinical meaningfulness of the observed results, which demonstrated exceedingly small between-group differences.

This review concludes the following:

- While the change in KCCQ-TSS at Month 8 showed a statistically significant between-group difference, the result appears to be driven by the large sample size as the magnitude of the between-group change was quite small as demonstrated by nearly overlapping empirical cumulative distribution function (eCDF) curves and probability density function (PDF) curves for dapagliflozin vs. placebo. The between-group separation is slight throughout the entire distribution including at the clinically meaningful responder thresholds (i.e., ≥15 points). [Of note, a threshold of ≥15 points for improvement in the KCCQ-TSS is the most appropriate cut-off (as opposed to 5 or 10 points) for clinically meaningful within-patient change as it more clearly distinguishes itself based on curves for eCDF from the anchor-based analyses.]
- (b) (4)
- (b) (4)

Additional Comments:

- Of note, the item content of the KCCQ-TSS does not precisely reflect symptom frequency, as the name would imply, but rather the frequency of certain patient-reported, symptom-related limitations and impacts. Additionally, the "Symptom Burden Domain" more precisely reflects the concept of symptom bother, which may not reflect the true occurrence of symptoms, particularly in patients who have adjusted to living with chronic heart failure symptoms.

Please refer to Section B for more details on the interpretation of the KCCQ-TSS results.

Background:

(b) (4)

Table 15: (b) (4)

(b) (4)	***FARXIGA 10 mg*** ***N*=*** (b) (4)	***Placebo*** ***N*=*** (b) (4)	(b) (4) ***p-value§***
(b) (4)			

Reviewer's comments: *It is important to note that* (b) (4)

(b) (4)

Materials reviewed:

- Written Responses dated May 4, 2017 (DARRTS Reference ID: 4093696) and November 9, 2018 (DARRTS Reference ID: 4347871)
- Clinical Study Report (CSR) for Study D1699C00001 (DAPA-HF)
- PRO Evidence Dossier
- Draft Label
- Applicant's responses to Agency's information request for additional PRO data (i.e., item-level analyses, anchor-based analyses, eCDF and PDF plots, information on how the proposed threshold translate into category changes for the items that constitute the

KCCQ-TSS) submitted on February 13, 2020 (SDN 1799), March 4, 2020 (SDN 1810) and March 18, 2020 (SDN 1818).

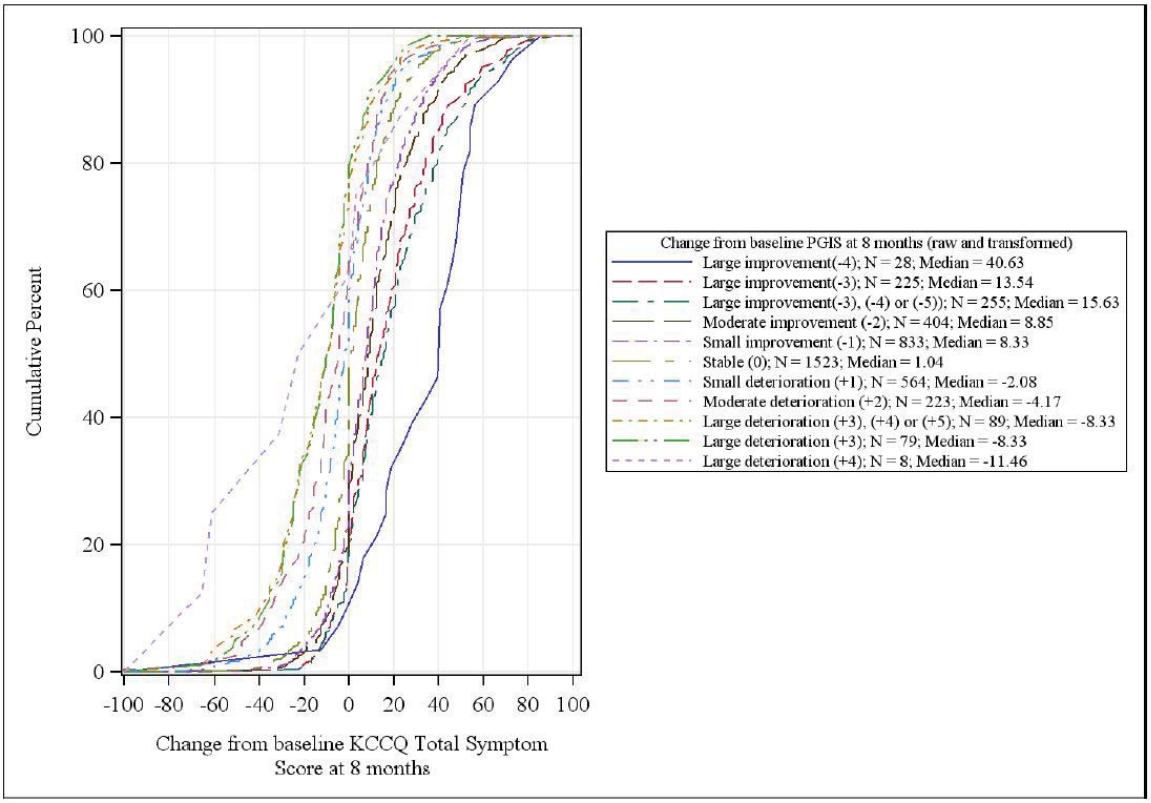
B. INTERPRETATION OF SCORES

To date, the following information has been submitted:

- ☒ Anchor-based analyses
- ☒ Anchor-based empirical cumulative distribution function (eCDF) curves
- ☒ eCDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☒ Anchor-based probability density function (PDF) curves
- ☒ PDF study arm curves (Treatment vs. Placebo/Active Comparator)
- ☐ Qualitative support for meaningful change (e.g., patient input)

The applicant provided the following Patient Global Impression of Severity/Change (PGI-S/C) anchor-based eCDF and PDF curves for the KCCQ Total Symptom Score (Figures 1 – 4).

Figure 1. eCDF for change from baseline KCCQ Total Symptom Score at 8 months versus change from baseline score on PGIS for HF symptoms at 8 months



Reviewer's comments: *In line with the Agency guidance, the PGIS was used as the primary anchor in the estimation of meaningful within-patient change threshold(s) as it is less likely to be subject to recall error than PGIC. See Appendix 3 and 4 for copies of the PGIS and PGIC anchor scales.*

The applicant proposed thresholds for improvement (5, 10 and 15 points, corresponding to "small improvement", "moderate improvement" and "large improvement", respectively) and deterioration (5 and 10 points, corresponding to "small or moderate deterioration" and "large deterioration", respectively). Based on this eCDF plot, it appears that a threshold of ≥15 points for improvement in the KCCQ-TSS is the most appropriate cut-off (as opposed to 5 or 10 points) for clinically meaningful within-patient change as the eCDF curves demonstrated a clear separation between large improvement and no change in the interval between 15 points and greater increase in KCCQ-TSS at 8 months, but the distinction was not as clear between small and moderate improvement.

Figure 3. PDF for change from baseline KCCQ Total Symptom Score at 8 months versus change from baseline score on PGIS for HF symptoms at 8 months

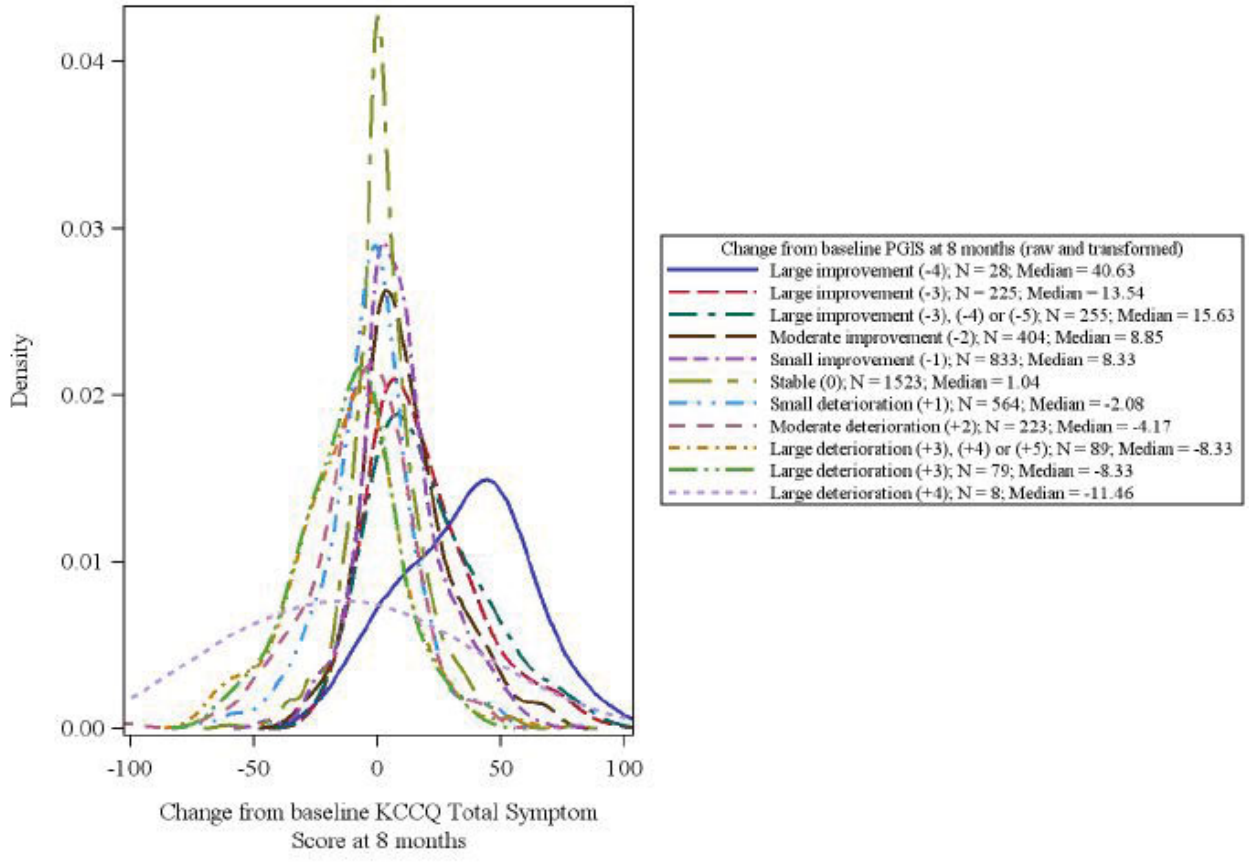


Figure 3. eCDF for change from baseline KCCQ Total Symptom Score at 8 months versus PGIC for HF symptoms at 8 months

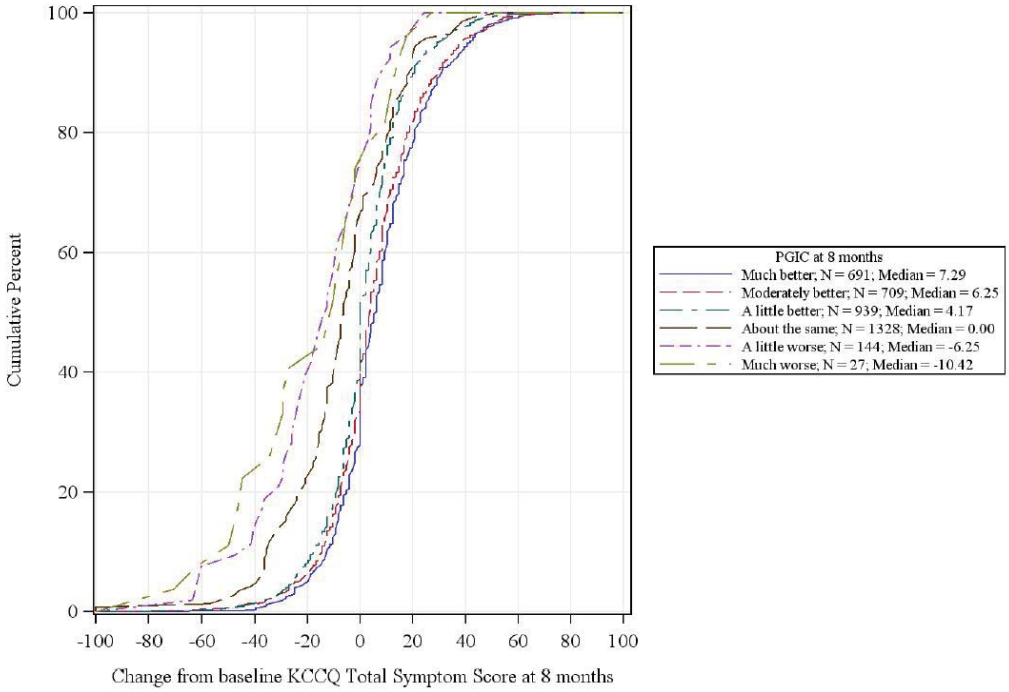


Figure 4. PDF for change from baseline KCCQ Total Symptom Score at 8 months versus PGIC for HF symptoms at 8 months

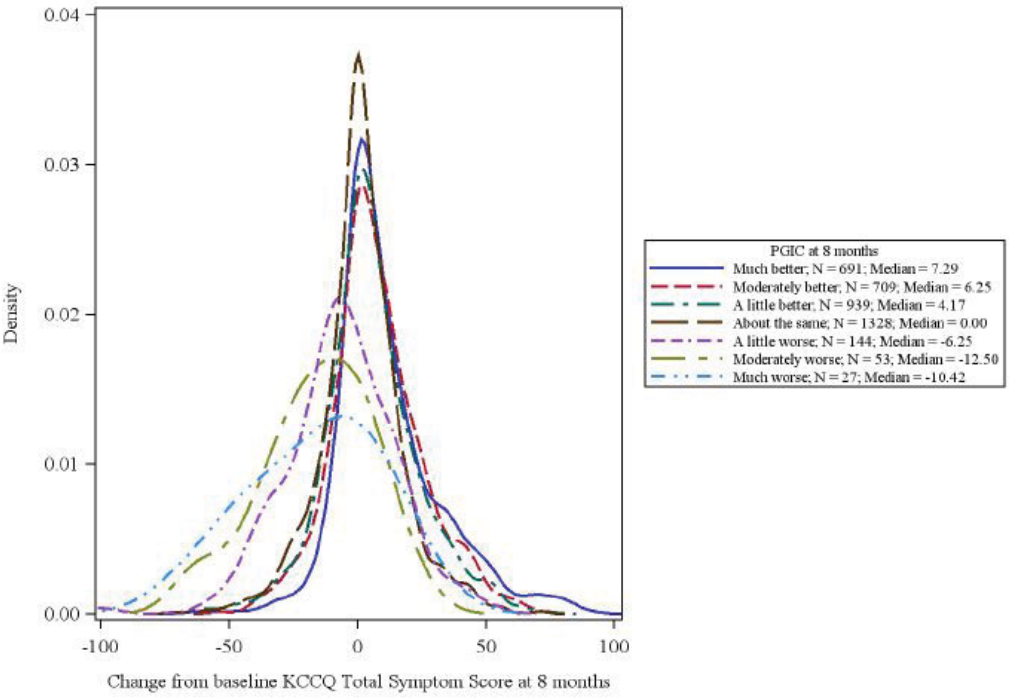


Table 1 documents the adequacy of the score interpretability of the KCCQ-TSS.

Table 1. Review of Score Interpretability for the KCCQ-TSS

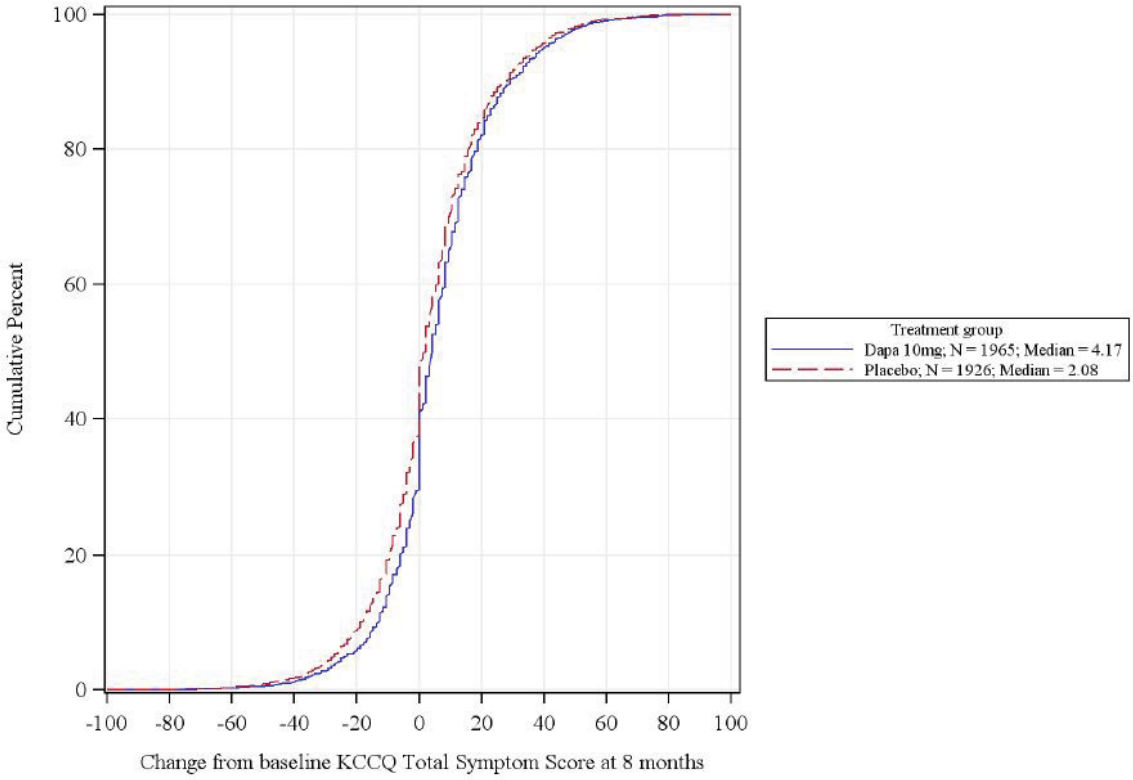
COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Appropriate global anchor scales were included for anchor-based analyses ☒ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☒ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer's comments)	Response to Information Request (SDN 1799, 1810, and 1818)

Reviewer's comments: *In the DAPA-HF NDA submission documents, the sponsor presented a 5-point threshold (based on data from the literature), as well as 10-point and 15-point thresholds (derived using blinded anchor-based analyses of data from the DAPA-HF study) for identifying clinically meaningful within-patient change. The anchor-based analyses of data from the DAPA-HF study does not support a 5-point threshold. In the applicant's response to the Information Request (IR) dated March 18, 2020 (SDN 1818), the applicant acknowledged that the 5-point threshold is not appropriate for clinically meaningful within-patient change in the KCCQ-TSS and stated that higher thresholds such as the proposed 10 and 15 points are more appropriate. Based on the eCDF and PDF plots provided in the applicant's response to the IR dated March 4, 2020 (SDN 1810), it appears that a threshold of ≥15 points for improvement in the KCCQ-TSS is a more appropriate cut-off compared to a 10-point threshold for clinically meaningful within-patient change as the eCDF curves demonstrated a clear separation between large improvement and no change in the interval between 15 points and greater increase in KCCQ-TSS at 8 months, but the distinction was not as clear between small and moderate improvement.*

The applicant also proposed responder analyses based on the 5, 10, and 15 points thresholds. Given the conflicting evidence in the NDA submission on what constitutes a responder threshold, the proposed responder analyses do not appear reasonable.

The applicant provided the following eCDF and PDF study arm curves for the KCCQ Total symptom score:

Figure 5. eCDF for change from baseline KCCQ Total symptom score at 8 months, Dapagliflozin versus Placebo



Reviewer's comments: *This eCDF plot shows a very slight separation (nearly overlapping curves) between the treatment and placebo arms at all points along the curve, including the clinically meaningful responder thresholds (i.e., ≥15 points), which does not support the interpretation of a clinically meaningful between-group difference.*

Figure 6. PDF for change from baseline KCCQ Total Symptom Score at 8 months, Dapagliflozin versus Placebo

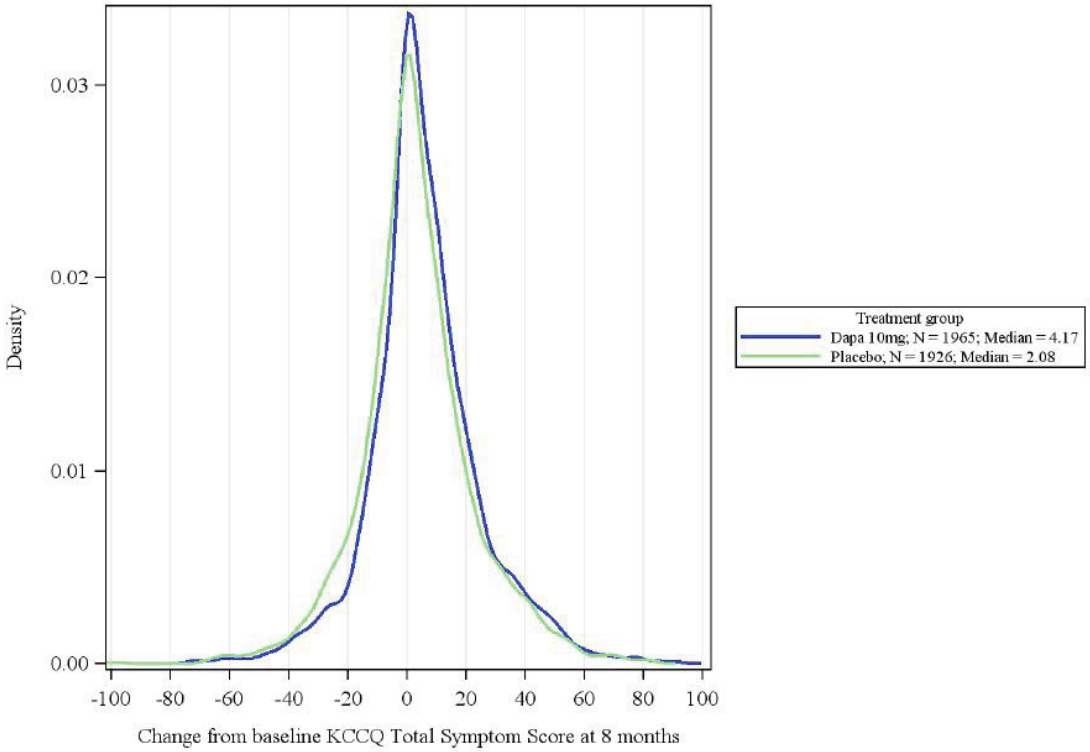


Table 2 shows the distribution of change from baseline in the items included in the KCCQ-TSS across raw and transformed change from baseline scores in PGIS at 8 months for the full analysis set.

Table 2. Change from baseline in the KCCQ-TSS individual items across raw and transformed change from baseline scores in PGIS at 8 months

			Change from baseline KCCQ-TSS Item					
KCCQ-TSS Item	Change from baseline PGIS	N	Mean	SD	95% CI for Mean	Min	Median	Max
Item 3: Have Swelling in Feet/Ankles/Legs	Large improvement (-3), (-4) or (-5)	255	0.51	1.41	(-2.2 - 3.3)	-4.0	0.0	4.0
	Large improvement (-3)	225	0.41	1.35	(-2.2 - 3.1)	-4.0	0.0	4.0
Item 4: Bothered by Swelling in Feet/Ankles/Legs	Large improvement (-3), (-4) or (-5)	255	0.45	1.16	(-1.8 - 2.7)	-3.0	0.0	4.0
	Large improvement (-3)	225	0.39	1.14	(-1.9 - 2.6)	-3.0	0.0	4.0
Item 5: Times Fatigue Limited Ability	Large improvement (-3), (-4) or (-5)	255	1.61	1.99	(-2.3 - 5.5)	-3.0	1.0	6.0
	Large improvement (-3)	225	1.48	1.92	(-2.3 - 5.2)	-3.0	1.0	6.0
Item 6: Bothered by Fatigue	Large improvement (-3), (-4) or (-5)	255	1.00	1.31	(-1.6 - 3.6)	-2.0	1.0	4.0
	Large improvement (-3)	225	0.89	1.25	(-1.6 - 3.3)	-2.0	1.0	4.0
Item 7: Times Shortness of Breath Limit Ability	Large improvement (-3), (-4) or (-5)	255	1.47	1.86	(-2.2 - 5.1)	-3.0	1.0	6.0
	Large improvement (-3)	225	1.40	1.80	(-2.1 - 4.9)	-3.0	1.0	6.0
Item 8: Bothered by Shortness of Breath	Large improvement (-3), (-4) or (-5)	255	0.96	1.31	(-1.6 - 3.5)	-4.0	1.0	4.0
	Large improvement (-3)	225	0.86	1.26	(-1.6 - 3.3)	-4.0	1.0	4.0
Item 9: Times Shortness of Breath Limit Sleep	Large improvement (-3), (-4) or (-5)	255	0.61	1.49	(-2.3 - 3.5)	-4.0	0.0	4.0
	Large improvement (-3)	225	0.57	1.39	(-2.2 - 3.3)	-4.0	0.0	4.0

Reviewer's comment(s): *Table 2 was reproduced by this reviewer to showcase median change-scores in the KCCQ-TSS items across large improvement change-scores in the PGIS (corresponds to ≥15 points responder threshold).*

The change in KCCQ-TSS at Month 8 showed a statistically significant between-group difference (Win ratio 1.18; 95% CI 1.11, 1.26). However, the effect size is exceedingly small and is driven (as shown in Table 2) by change in a subset of the KCCQ-TSS component items (Items 5 – 8), while other items (Items 3, 4, and 9) were unchanged.

C. APPENDICES

Appendix 1: Kansas City Cardiomyopathy Questionnaire (KCCQ)
Appendix 2: Overview of the KCCQ and Description of the Total Symptom Score
Appendix 3: Patient Global Impression of Severity (PGIS) for Heart Failure Symptoms
Appendix 4: Patient Global Impression of Change (PGIC) for Heart Failure Symptoms

Appendix 1: Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your heart failure and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. Heart failure affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue, or ankle swelling) changed?
My symptoms of heart failure have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?
It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all Bothersome	I've had no swelling
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your fatigue bothered you?
It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no fatigue
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

8. Over the past 2 weeks, how much has your shortness of breath bothered you? It has been ...

Extremely bothersome	Quite a bit bothersome	Moderately bothersome	Slightly bothersome	Not at all bothersome	I've had no shortness of breath
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?

Not at all sure	Not very sure	Somewhat sure	Mostly sure	Completely sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your heart failure limited you enjoyment of life?

It has extremely limited my enjoyment of life	It has limited my enjoyment of life quite a bit	It has moderately limited my enjoyment of life	It has slightly limited my enjoyment of life	It has not limited my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?

I felt that way all of the time	I felt that way most of the time	I occasionally felt that way	I rarely felt that way	I never felt that way
☐	☐	☐	☐	☐

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 week?

Place an X in one box on each line

Activity	Severely Limited	Limited quite a bit	Moderately Limited	Slightly Limited	Did not limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationship with loved ones	☐	☐	☐	☐	☐	☐

Appendix 2 KCCQ-TSS Scoring Algorithm and Scoring of Item Response Options and Domains Included in the TSS

The KCCQ-TSS is calculated as the average of the symptom frequency and symptom burden scores (see below). Scores are transformed to a range of 0-100. Higher scores represent a better outcome.

KCCQ Domain Score	Symptom / Sign	KCCQ Items	Response options	Derivation of Domain Score
Symptom frequency Score	Edema	Item 3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?	Every morning = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5	If at least two of Questions 3, 5, 7 and 9 are not missing, then compute: S3 = [(Question 3) – 1]/4 S5 = [(Question 5) – 1]/6 S7 = [(Question 7) – 1]/6 S9 = [(Question 9) – 1]/4 Symptom frequency score = 100*(mean of S3, S5, S7 and S9)
	Fatigue	Item 5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?	All of the time= 1 Several times a day = 2 At least once a day = 3 3 or more times a week but not every day = 4 1-2 times a week = 5 Less than once a week = 6 Never over the past 2 weeks = 7	
	Dyspnea	Item 7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?		
	Orthopnea	Item 9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of shortness of breath?	Every night = 1 3 or more times a week but not every day = 2 1-2 times a week = 3 Less than once a week = 4 Never over the past 2 weeks = 5	
Symptom burden score	Edema	Item 4. Over the past 2 weeks, how much has swelling in your feet, ankles or legs bothered you?	Extremely bothersome = 1 Quite a bit bothersome = 2 Moderately bothersome = 3 Slightly bothersome = 4 Not at all bothersome = 5 I've had no swelling/fatigue/shortness of breath = 5	If at least one of Questions 4, 6 and 8 is not missing then compute: Symptom burden score = 100*[(mean of Questions 4, 6 and 8 actually answered)-1]/4
	Fatigue	Item 6. Over the past 2 weeks, how much has your fatigue bothered you?		
	Dyspnea	Item 8. Over the past 2 weeks, how much has your shortness of breath bothered you?		
Total Symptom Score:				Average of the symptom frequency score and symptom burden score

Appendix 3: Patient Global Impression of Severity (PGIS) for Heart Failure Symptoms

Overall, how would you rate the severity of your heart failure symptoms today?

- ☐ No symptoms
- ☐ Very mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

Appendix 4: Patient Global Impression of Change (PGIC) for Heart Failure Symptoms

Overall, how would you rate the change in your heart failure symptoms since starting this study?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

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ELEKTRA J PAPADOPOULOS
04/14/2020 10:26:50 AM

LABEL AND 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:	March 17, 2020
Requesting Office or Division:	Division of Cardiovascular and Renal Products (DCRP)
Application Type and Number:	NDA 202293/S-20
Product Name, Dosage Form, and Strength:	Farxiga (Dapagliflozin) tablets, 5 mg and 10 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca AB (AZ)
FDA Received Date:	November 6, 2019
OSE RCM #:	2019-2293
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

As a part of the NDA efficacy supplement review process, this review evaluates the proposed Farxiga prescribing information (PI) for areas of vulnerability that could lead to medication errors.

AstraZeneca seeks the proposed indication to allow the use of Farxiga in adults with heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and (b) (4) (b) (4).

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	C - N/A
ISMP Newsletters*	D - N/A
FDA Adverse Event Reporting System (FAERS)*	E - N/A
Other	F - N/A
Labels and Labeling	G

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

We note AZ did not propose any renal dose adjustment in patients with heart failure, however, Farxiga is contraindicated in type 2 diabetes mellitus patients with eGFR less than 30 mL/min/1.73m^2. In email communication with the Review Team, we learned heart failure patients with eGFR less than 30 mL/min/1.73m^2 were not included in the DAPA-HF clinical trial, thus, no renal dose adjustment data was submitted for FDA review. We recommend the PI be revised to clearly communicate that Farxiga was not studied in heart failure patients with eGFR less than 30 mL/min/1.73m^2 to prevent inadvertent inappropriate dosing in this patient population.

Our review of the proposed PI also identified other areas that may be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Farxiga PI may be improved to promote the safe use of this product from a medication error perspective. We provide specific recommendations in Section 4.1 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS (DCRP)

A. Prescribing Information

1. Consider including the route of administration "orally" after the dose throughout Section 2 of the PI. For example, revise the statement "To improve glycemic control,…" in section 2.2 so it reads "To improve glycemic control, the recommended starting dose of FARXIGA is 5 mg orally once daily, taken in the morning, with or without food."
2. We recommend adding information on the maximum daily dose for each of the indications if such data is submitted for the Agency's review.
3. We recommend spelling out each abbreviation upon first use in Section 2 of the PI so that the reader does not have to search for the abbreviation's definition in other sections of the PI when trying to dose a patient, thus improving readability of the PI.
4. In section 2.4 Patients with Renal Impairment, (b) (4) [redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Farxiga received on November 6, 2019 from AstraZeneca AB (AZ).

Table 2. Relevant Product Information for Farxiga	
Initial Approval Date	01/08/2014
Active Ingredient	Dapagliflozin
Indication	(Current) In adults with type 2 diabetes mellitus: • as an adjunct to diet and exercise to improve glycemic control. • 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. **(Proposed)** In adults with heart failure with reduced ejection fraction (HFrEF) to reduce the risk of cardiovascular death and [redacted] (b) (4)
Route of Administration	Oral
Dosage Form	Tablets
Strength	5 mg and 10 mg
Dose and Frequency	(Current) 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. To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus, the recommended dose is 10 mg once daily. **(Proposed)** To reduce the risk of CV death and [redacted] (b) (4) in patients with HFrEF, the recommended dose is 10 mg once daily.
How Supplied	Yellow biconvex diamond shaped tablet
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].
Container Closure	Bottles of 30 tablets

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 17, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, dapagliflozin. Our search identified 3 previous reviews[a,b,c] , 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.

[b] Conrad A. Labeling Review for Farxiga, NDA 202293/ (b) (4) . Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Feb 15. RCM No.: 2018-2089.

[c] Conrad A. Label and Labeling Review for Farxiga and Xigduo XR, NDA 202293/S-018 and NDA 205649/S-011. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Jun 07. RCM No.: 2018-2812.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with post-market medication error data, we reviewed the following Farxiga labels and labeling submitted by AstraZeneca AB (AZ).

- Prescribing Information (Image not shown) received on November 6, 2019, available from \\cdsesub1\evsprod\nda202293\0654\m1\us\annotated-draft-label-hfref.pdf

G.2 Label and Labeling Images

N/A

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MARIETTE A AIDOO
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